FKBP5: A Key Mediator of How Vertebrates Flexibly Cope with Adversity

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Flexibility in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis is an important mediator of stress resilience as it helps organisms adjust to, avoid, or compensate for acute and chronic challenges across changing environmental contexts. Glucocorticoids remain the favorite metric from medicine to conservation biology to attempt to quantify stress resilience despite the skepticism around their consistency in relation to individual health, welfare, and fitness. We suggest that a cochaperone molecule related to heat shock proteins and involved in glucocorticoid receptor activity, FKBP5*, may mediate HPA flexibility and therefore stress resilience because it affects how individuals can regulate glucocorticoids and therefore capacitates their abilities to adjust phenotypes appropriately to prevailing, adverse conditions. Although the molecule is well studied in the biomedical literature,* FKBP5 *research in wild vertebrates is limited. In the present article, we highlight the potential major role of* FKBP5 *as mediator of HPA axis flexibility in response to adversity in humans and lab rodents.*

Keywords: plasticity, glucocorticoids, stress, epigenetic, resilience

Since Hans Seyle introduced the term to physiology (Selye 1950), stress has been a major research subject but also a subject of much debate. Indeed, there remains no universally accepted definition of stress (Romero 2004, Romero et al. 2009, Del Giudice et al. 2018, Harris 2020). Nevertheless, responding to stressors (box 1) by mounting appropriate physiological stress responses is crucial for health, welfare, and fitness (Ralph and Tilbrook 2016, Taff and Vitousek 2016, McCormick and Romero 2017, Caulfield and Cavigelli 2020). Such stress responses are highly conserved across species, but in vertebrates, many culminate in the activation of the hypothalamic–pituitary–adrenal (HPA) axis (Romero 2004, Vitousek et al. 2019a). The HPA axis acts as an interface between an individual and changes in its internal and external environments, primarily by regulating the secretion and release of glucocorticoids, which are important mediators of homeostasis (Wingfield et al. 1998, Sapolsky et al. 2000, McEwen and Wingfield 2003, Hau et al. 2016, Gray et al. 2017). Unsurprisingly, because they are so easy to measure, glucocorticoids have become a favorite metric from medicine to conservation biology to attempt to quantify stress. To an extent, this approach has been fruitful, because differences in glucocorticoid regulation in response to and in resilience from stressors can be associated with differences in health and fitness (Schoenle et al. 2018, Caulfield and Cavigelli 2020). However, extensive and important disparities remain, probably because of the regulatory complexity of the HPA axis.

Recently, there has been a concerted movement toward better descriptions of within-individual dynamics of the HPA—namely, efforts to describe stress resilience (box 1; Romero et al. 2009, Taff and Vitousek 2016, Rao and Androulakis 2019, Vitousek et al. 2019b). Stress resilience connotes the propensity of an individual to use glucocorticoids to cope with adversity, which, in many cases, equates to HPA flexibility. We define HPA flexibility as rapid (over the course of minutes to days), reversible plasticity in HPA axis function that occurs within individuals in response to unpredictable changes in the environment. Such flexibility enables rapid mobilization of hormones to match current environmental conditions or resolve or escape stressors, but it also includes the ability of individuals to metabolize or otherwise dampen the effects of glucocorticoids on other physiological and behavioral traits. The HPA axis is by nature plastic, so we expect that it is HPA flexibility, or plasticity in the plastic regulation of the HPA, which connects individual variation in this endocrine process to organismal performance and ultimately fitness.

HPA flexibility is likely critical because it enables animals to respond appropriately to dynamic and unpredictable changes in the environment by facilitating rapid realization of optimal phenotypes (Taff and Vitousek 2016). As an

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Box 1. Glossary.

Band-pass filter: In electronics, a band-pass filter is a device that discards sound frequencies outside a particular size window. In the present article, we portray *FKBP5* as a band-pass filter for glucocorticoids access to GR, thus making it a proxy for the semiotic information (or functional) fraction of glucocorticoid concentrations.

Cytosine–phosphate–Guanine (CpG) methylation: Chemical alteration of DNA structure (but not sequence) where a methyl group is added to a cytosine followed by a guanine. DNA methylation predominantly occurs at cytosines followed by guanines, or CpG sites and can alter gene expression by affecting the interaction of DNA with regulatory molecules such as transcription factors.

Semiotic information: The meaning and quality of information carried by syntactic information. Semiotic information represents the part of syntactic information that is interpreted (i.e., it is the functional information encoded in a signal), the difference that makes a difference.

Stress resilience: the ability of an individual to recover from exposure to a stressor or to maintain normal processes or activities despite the presence of a stressor through active coping mechanisms. It is important to note that this term describes one occurrence and does not, by itself, indicate flexibility. An individual may differ in its ability to recover or adapt to same or different stressors across its lifespan.

Stressor: Unpredictable internal or external stimuli that threaten homeostasis and trigger physiological stress responses.

Syntactic information: Reduction in uncertainty of a system on the basis of the difference between two states of the system, i.e., information increases predictability. Syntactic differs from semiotic information in that the former does not involve the meaning or interpretation of the signal.

example, consider two individuals: one with high and one with low HPA flexibility living in fairly stable, nonthreatening conditions under which the appropriate response to an acute stressor is to elevate glucocorticoid concentrations moderately and return to baseline quickly. In these mild conditions, both individuals would be able to express suitable responses. However, if environmental conditions changed in an extreme and unexpected way (e.g., a major cold snap or the incursion of a novel predator), the individual with high HPA flexibility should outcompete the low HPA flexibility conspecific. In the case of a major cold snap, high HPA flexibility would represent the most appropriate phenotype, because it would facilitate the mobilization of glucose to fuel locomotion away from the area and enhance foraging, followed by strong negative feedback to limit the costs of sustained, elevated levels of glucocorticoids, as soon as an alternative foraging area was reached. Whereas the high-flexibility individual is primed to be able to achieve the new appropriate phenotype, the low-flexibility individual could not adjust its phenotype sufficiently or the challenge might subside before the appropriate phenotype could be achieved.

In a way, a focus on HPA flexibility is consistent with existing frameworks in stress biology; glucocorticoid concentrations measured over time (i.e., prior to and after stressors) have been used before as readouts for HPA flexibility, and they are sometimes linked to health and fitness (Romero and Wikelski 2010, Taff et al. 2018, Vitousek et al. 2019b, Zimmer et al. 2019, Caulfield and Cavigelli 2020). However, it is rare that negative feedback be measured as an aspect of flexibility, and it is even rarer that within-individual changes in HPA inductions and returns to baseline are quantified. Whereas some aspects of HPA axis regulation (e.g., stress-induced glucocorticoid level) might be consistent across stressors, it is equally plausible that their regulation flexibly changes across different stressor exposures. For these reasons, skepticism endures as to what measures sufficiently capture HPA flexibility (Schoenle et al. 2018, Wada 2019, Caulfield and Cavigelli 2020).

Information theory and *FKBP5*

Phenotypic modifications associated with variation in glucocorticoid concentrations under adverse conditions are mainly mediated through glucocorticoid receptors (GR; de Kloet et al. 1998, de Kloet 2004, Romero 2004, Joëls et al. 2008), so HPA flexibility must involve GR signaling. Because GR function depends largely on *FKBP51*, (the gene encoding the FK506 binding protein 51; hereafter, *FKBP5*; figure 1), it is imperative to understand the interplay among hormones, receptors, and cofactors to predict variation in whole-organism phenotypes. A promising perspective to take to make our case involves information theory. To date, several concepts (e.g., allostasis, reactive scope, the damage-fitness hypothesis) have been offered to explain how stress hormones mediate performance and fitness (McEwen and Wingfield 2003, Romero et al. 2009, Wada 2019). However, most of these ideas are based on physiological trade-offs, tend to be difficult to measure, and tend to focus on circulating hormones themselves as the variables to be predicted by the framework. If we envision glucocorticoid concentrations as capacitors of information, however, some new inroads are revealed.

To make this case, it is important to first distinguish the two major forms of information relevant to HPA flexibility and its effects on phenotypes: syntactic and semiotic information (box 1; O'Connor et al. 2019). Hormones inherently

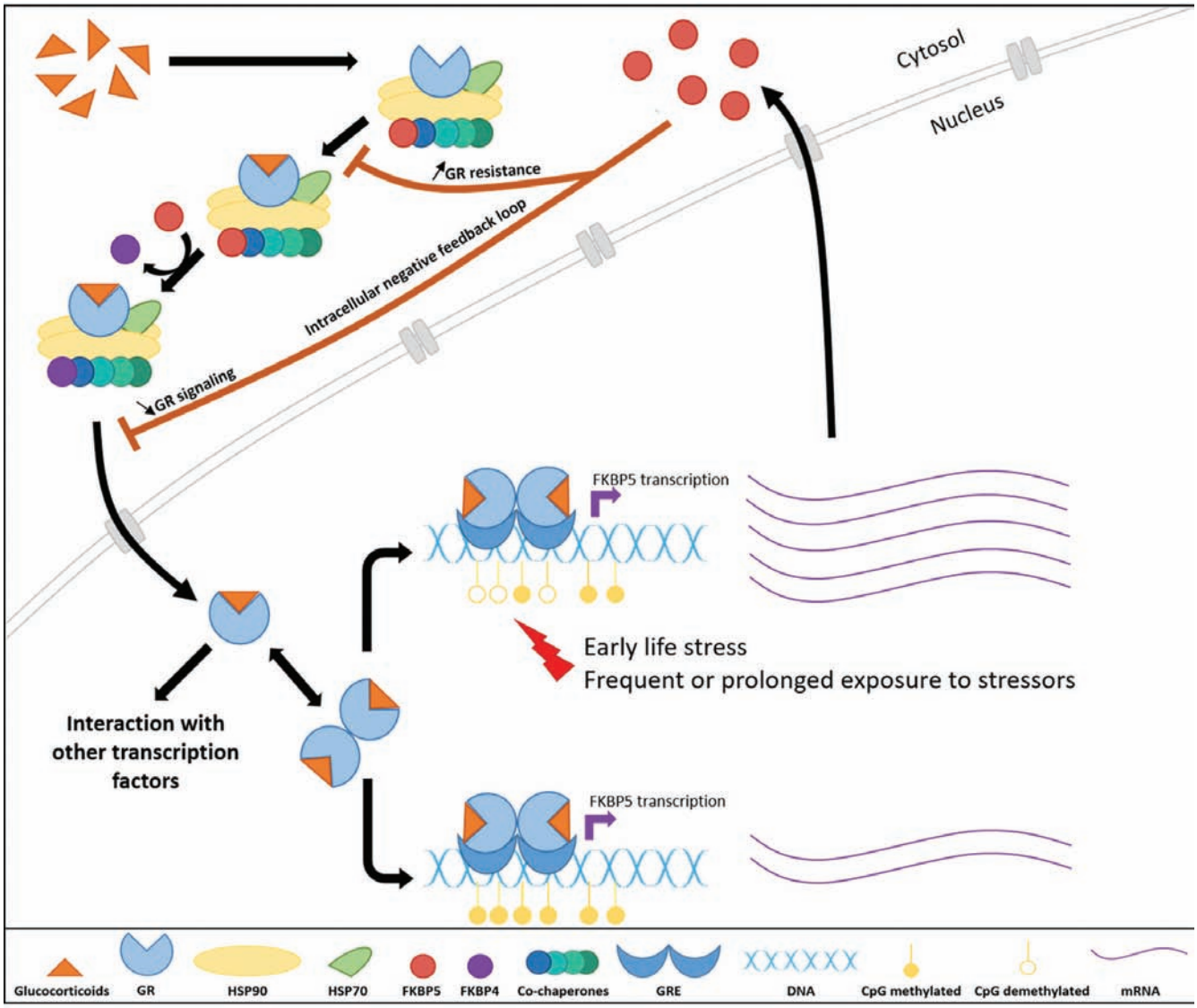

Figure 1. A schematic representation of* FKBP5 *regulation after GR activation by glucocorticoids. Glucocorticoids enter the cytoplasm and bind to the glucocorticoid receptor (GR) complex.* FKBP5 *reduces glucocorticoid binding affinity and the subsequent nuclear translocation of the GR complex; the exchange of* FKBP5 *for* FKBP4 *allows GR translocation to the nucleus. Two GRs dimerize and bind to DNA at glucocorticoid response elements (GRE), but monomeric GR can interact with other transcription factors. In both cases, GR activation affects the expression of many genes but also rapid induction of* FKBP5 *transcription. Transcription sensitivity depends, however, on GRE methylation status: High methylation at specific CpG sites within particular GREs of the* FKBP5 *locus reduces the transcript number. By contrast, low methylation (e.g., due to early life or chronic stress) increases the transcript number.* FKBP5 *mRNA translocates to the cytoplasm, where it is translated into* FKBP5 *protein. High levels of* FKBP5 *in the cytoplasm form an ultrashort, intracellular negative feedback loop that increases GR resistance by decreasing GR affinity for glucocorticoids or inhibiting GR translocation to the nucleus. Source: Adapted from Zannas and colleagues (2016) with permission.

carry syntactic information by coordinating the actions of a target system relative to other systems and other states of the target system. However, what typically interests endocrinologists is the semiotic information content (O'Connor et al. 2019) of glucocorticoids, the fraction that encodes the information that can be interpreted and transduced to the rest of the body via GR. We can quantify the amounts of glucocorticoids in circulation (syntactic) but only a fraction of this variation will interact with receptors and will affect host performance and fitness (semiotic). The semiotic fraction of hormones is usually obscure because concentrations tell us nothing about receptors and other aspects of HPA

regulation, even though it tends to be this semiotic fraction that most likely links to organismal function and fitness. A focus on the semiotic content of glucocorticoids is just what attention to *FKBP5* provides.

In a sense, the free hormone hypothesis and the reservoir hormone hypothesis represent prior attempts to focus on the semiotic fraction of glucocorticoid concentrations. These hypotheses highlighted that only free glucocorticoids, unbound to the corticosteroid-binding globulin, can leave circulation and bind to GR in target tissues (for a review, see Breuner et al. 2013). These free hormones get us closer to the semiotic information content of glucocorticoids, but it remains unclear whether bound or free glucocorticoids are biologically active. Other factors, too, affect glucocorticoid access to target tissues and cells such as 11β-hydroxysteroid dehydrogenase enzymes, 21-hydroxylase, p-glycoprotein, or serine/threonine-protein kinase. These HPA elements may affect the semiotic content of glucocorticoid concentrations. Ultimately, however, to focus attention on the semiotic information content of glucocorticoids, we need to know more about GR—in particular, how GR binding varies temporally and therefore underlies HPA flexibility.

We propose that *FKBP5* expression, in effect, encodes much of the semiotic information content of glucocorticoids, because it regulates GR affinity for glucocorticoids and therefore the signaling propensity of this hormone (Binder 2009, Zannas et al. 2016). *FKBP5* is expressed in many tissues (including areas involved in HPA axis regulation such as the pituitary and adrenal glands), but its expression in the region of the brain in which glucocorticoid regulation is controlled (hypothalamus, hippocampus, amygdala) seems most important to understand. In an information theoretic context, *FKBP5* in the HPA regulatory centers probably acts as a band-pass filter (box 1) that excises the semiotic signal from glucocorticoid concentrations, representing exactly the aspect of glucocorticoids that interests most biologists studying stress. Because *FKBP5* determines how hormone concentrations and GRs interact as well as how GR functions vary over the lifetime of individuals (see below), we predict that *FKBP5* expression effectively represents the semiotic information content of circulating glucocorticoids that enable HPA flexibility.

In the present article, we develop these ideas—in particular, discussing how *FKBP5* might be a particularly valuable proxy for HPA flexibility. *FKBP5* plays a crucial role in flexibly regulating GR function and subsequent responses to stressors of various duration and intensity in humans and lab model organisms. Our goal in the present article is to summarize how this particular gene might mediate phenotypic responses to and recovery from variation in glucocorticoid concentrations at the organismal level in all vertebrates that rely on it in the context of coping with adversity.

HPA axis regulation and response to adversity

In the absence of stressors, circulating concentrations of glucocorticoids are usually low to support basic life processes (Sapolsky et al. 2000, Landys et al. 2006), and unsurprisingly, baseline concentrations vary daily, seasonally, and with life-history stage (Sapolsky et al. 2000, Romero 2002, Landys et al. 2006). When facing a stressor, a cascade of reactions is triggered, beginning with the perception of the stressor in higher brain areas (hippocampus or amygdala) signaling the hypothalamus to secrete corticotropin-releasing hormone. Surges in this hormone induce the release of adrenocorticotropic hormone from the pituitary gland, leading to the rapid release of glucocorticoids (within 3 minutes) by the adrenal glands. The semiotic information content carried by these glucocorticoid surges promotes a suite of physiological and behavioral changes that mediate the response to and the recovery from the stressor, temporarily redirecting resources from inessential activities (e.g., reproduction, digestion, and growth) toward immediate survival (Wingfield et al. 1998, Sapolsky et al. 2000, Breuner et al. 2008). This stress response is fundamental to coping with stressors, because individuals that do not increase glucocorticoids when exposed to stressors often suffer or die (Darlington et al. 1990, Thaker et al. 2010).

A crucial aspect of these stress responses is that they must eventually be resolved via negative feedback, a return of glucocorticoids to baseline concentrations (Dallman and Bhatnagar 2001, Romero 2004, Vitousek et al. 2019b). Impairment of negative feedback can result in sustained tissue exposure to glucocorticoids (i.e., information overload; figure 3 in Martin et al. 2016), which can result in myriad pathologies such as depression or anxiety disorders in humans (Checkley 1996, Holsboer 2000, Pariante and Lightman 2008) and low survival or reproductive success in wildlife (Romero and Wikelski 2010, Zimmer et al. 2019, Zimmer et al. 2020). Indeed, dysfunctional negative feedback (via a reduction in the number or affinity of glucocorticoid receptors—in particular, brain regions such as the hypothalamus, the hippocampus, and the anterior pituitary) underlies many of the detrimental consequences of chronic stress for health, welfare, and fitness emphasized in the literature (Dallman and Bhatnagar 2001, Romero 2004, Dickens and Romero 2013, Ralph and Tilbrook 2016).

All effects of glucocorticoids are mediated through the binding of corticosterone or cortisol (depending on the taxon) to either membrane-associated or intracellular mineralocorticoid receptors (MR) and glucocorticoid receptors (GR; de Kloet et al. 1998, Breuner and Orchinik 2001, de Kloet 2004, Romero 2004, Tasker et al. 2006, Groeneweg et al. 2012, Gray et al. 2017). Membrane-associated receptors mediate nongenomic effects of glucocorticoids (Tasker et al. 2006, Groeneweg et al. 2011). Intracellular receptors translocate to the nucleus after binding to glucocorticoids, where they act as transcription factors at glucocorticoid responsive elements (GRE), causing major changes in the expression of thousands of genes (Sapolsky et al. 2000, Datson et al. 2008, Juszczak and Stankiewicz 2018). Because MR has a tenfold higher affinity for glucocorticoids than GR, a two-tiered system for regulation also exists; whereas MRs are activated at low to moderate hormone concentrations, GRs

are additionally activated by relatively high concentrations. Consequently, MR mediates the integrity, stability, and sensitivity of the HPA axis to stressors, whereas GR mediates phenotypic modifications associated with stress responses, as well as negative feedback to terminate the stress responses (de Kloet et al. 1998, de Kloet 2004, Romero 2004, Joëls et al. 2008).

At the organismal level, semiotic information encoded by glucocorticoids helps adjust phenotypes to predictable challenges (e.g., seasons, reproductive needs) but also unpredictable stressors (Sapolsky et al. 2000, Hau et al. 2016, Taff and Vitousek 2016). Animals face myriad natural stressors such as failed predation events, storms, intra- and interspecific competition, infections, and food shortages that can elicit stress responses (Wingfield and Romero 2001, Wingfield and Ramenofsky 2011, Schoenle et al. 2018). In recent times, animals are also exposed to new regimes (more frequent or higher intensity) of anthropogenic stressors including habitat destruction or alteration, pollution, introduced species, and historically atypical climates (Angelier and Wingfield 2013, Sih 2013, Wingfield 2013, Dantzer et al. 2014, Schoenle et al. 2018). In these situations, the activation of the HPA axis may not allow the mounting of an efficient response to cope with the challenge or may result in dysregulation of the HPA axis, leading to chronic stress (Dickens and Romero 2013, Dantzer et al. 2014, Schoenle et al. 2018). In addition, differences in glucocorticoid concentrations among individuals or populations can be associated with differences in health and fitness but these relationships show high levels of inconsistency and variation, are often context dependent, and can be hard to identify due solely to natural, diel variation in glucocorticoid concentrations (Breuner et al. 1999, Schoenle et al. 2018, Vitousek et al. 2019a, Caulfield and Cavigelli 2020). Therefore, it is unsurprising that single glucocorticoid measurements are unreliable predictors of health, welfare and fitness (Ralph and Tilbrook 2016, Schoenle et al. 2018, Wada 2019, Caulfield and Cavigelli 2020). Arguably, we might learn more about the ecology and health implications of stressors by focusing on the integral characteristic of glucocorticoid physiology, HPA flexibility.

FKBP5 a central regulator of HPA axis

Extensive biomedical research has recently implicated *FKBP5* as a crucial determinant of HPA flexibility (Lee 2016, Rein 2016, Zannas et al. 2016). *FKBP5* is a cochaperone associated with heat shock protein 90. This molecule is both integral to the GR complex and is strongly upregulated in response to stressors or elevated glucocorticoid concentrations (Binder 2009, Zannas and Binder 2014, Zannas et al. 2016). *FKBP5* expression can be induced by glucocorticoids and has been shown to be a very accurate measure of GR regulation and signaling and is therefore an appropriate marker of HPA flexibility (Lee et al. 2011, Menke et al. 2012, Zannas and Binder 2014, Rein 2016, Zannas et al. 2016). These effects of *FKBP5* stem from its potent inhibitory activity on GR signaling and GR activity with intracellular and systemic consequences for response to stressors (Rein 2016, Zannas et al. 2016).

The inhibitory effect of *FKBP5* on GR arises via two pathways. After glucocorticoids enter the cytoplasm, they bind to the GR-chaperone complex, then the exchange of *FKBP5* for *FKBP4* allows GR translocation to the nucleus, affecting transcriptional regulation of many genes (figure 1; Davies et al. 2002, Wochnik et al. 2005). Increases in intracellular *FKBP5* levels prevent this exchange, sequestering GR and decreasing GR-dependent transcriptional activity. Increases in *FKBP5* also decrease GR binding affinity for glucocorticoids (figure 1; Binder 2009, Rein 2016, Zannas et al. 2016, Li et al. 2020). A crucial point in *FKBP5* regulation is that its expression is also induced by glucocorticoids when GR binds an intronic GRE (glucocorticoid response element) of the *FKBP5* locus (figure 1; Binder 2009, Jääskeläinen et al. 2011, Klengel et al. 2013, Zannas and Binder 2014, Rein 2016, Zannas et al. 2016). *FKBP5* mRNA translocates to the cytoplasm, where it is translated into *FKBP5* protein.

Given the inhibitory effect of *FKBP5* on GR signaling and activity, increased expression of *FKBP5* mediated by glucocorticoids constitutes an ultrashort, intracellular negative feedback loop that regulates intracellular GR sensitivity (figure 1; Zannas and Binder 2014, Rein 2016, Zannas et al. 2016). *FKBP5* expression can also affect negative feedback via a second, less direct pathway, in essence, increasing GR resistance by acting as a molecular amplifier of stress responses (Zannas and Binder 2014, Lee 2016, Rein 2016). By modulating central GR sensitivity and resistance, and access to glucocorticoids semiotic information content, which are likely important mediators of HPA flexibility, *FKBP5* regulation and expression represent integral elements of HPA flexibility (figure 1).

FKBP5 as mediator of HPA flexibility

By modulating GR signaling in response to stressor exposure and increased glucocorticoid concentrations, we propose that *FKBP5* is a major mediator of HPA flexibility. We expect that higher HPA flexibility would be associated with greater stress resilience, because it would allow finer tuning of the HPA axis to adversity. Studies using *FKBP5* knockout mice showed no obvious effects on physiology and behavior under typical housing conditions but differences in stress-coping capacity after mice were exposed to acute or chronic stressors (Touma et al. 2011, Hartmann et al. 2012, Hoeijmakers et al. 2014). At a physiological level, *FKBP5* knockout is usually associated with an attenuated stress response and stronger HPA axis negative feedback, all indicating higher GR sensitivity (Touma et al. 2011, Hartmann et al. 2012, Hoeijmakers et al. 2014). At a behavioral level, knocking out *FKBP5* enhances stress-coping behaviors with more swimming and less floating in a forced-swim test after exposure to an acute stressor and increased exploration in stressful environments (Touma et al. 2011, Hartmann et al. 2012, Hoeijmakers et al. 2014). These results suggest that low baseline *FKBP5* expression, or modest increases in

FKBP5 expression in response to stressors, is associated with high HPA flexibility.

Because *FKBP5* is a potent inhibitor of GR function and GR dysregulation has been linked to stress-related behavioral disorders, changes in *FKBP5* expression are implicated in the development of stress-related disease in humans (Binder et al. 2004, Rein 2016, Zannas et al. 2016). Since the seminal study by Binder and colleagues (2004), which showed that a haplotype of *FKBP5* (characterized by increased *FKBP5* expression) in humans was associated with hyperactive HPA axis affecting the response to antidepressants and recurrence of depressive episodes, much mental health research has focused on *FKBP5* regulation (for a review, see Zannas et al. 2016, Criado-Marrero et al. 2018, Matosin et al. 2018). This particular haplotype contains a specific single nucleotide polymorphism (SNP) located in an enhancer region close to an intronic GRE is associated with an increased expression of *FKBP5* in response to GR activation (Binder et al. 2004). The up-regulation of *FKBP5* in risk T allele carriers results in a stronger GR resistance, weakening HPA axis negative feedback and sustaining circulating glucocorticoid at high concentrations, which can ultimately lead to stress-related mental disorders (Zannas and Binder 2014, Matosin et al. 2018, Zannas et al. 2016). This SNP has also been associated with structural and functional alterations in the hippocampus and amygdala associated with consequences for cognition, emotionality regulation, and inhibition (Zannas et al. 2016, Matosin et al. 2018). Polymorphisms in *FKBP5* (including the risk T allele and other SNPs) are associated with differences in its regulation after exposure to adverse conditions resulting in differences in HPA axis function and in the risk of PTSD (posttraumatic stress disorder; Binder et al. 2008, Yehuda et al. 2009, Hawn et al. 2019, Li et al. 2020), bipolar disorder (Willour et al. 2009, Seifuddin et al. 2013), impaired cognitive function (Sabbagh et al. 2014, Blair et al. 2019), and increased anxiety (Criado-Marrero et al. 2019, Touma et al. 2011). However, it is worth noting that only a few studies have reported a main effect of *FKBP5* genotype on risk of mental health disorders, and results are inconsistent (Zannas et al. 2016, Matosin et al. 2018). Nevertheless, available data suggest that different *FKBP5* genotypes are associated with differences in HPA axis flexibility ultimately affecting health.

Stronger evidence for links between *FKBP5* genotype and mental health is found when considering the interaction between *FKBP5* and early life adversity (Zannas and Binder 2014, Zannas et al. 2016, Matosin et al. 2018). For instance, studies focusing on the risk T allele showed that carriers have high *FKBP5* expression and, therefore, GR resistance when exposed to adversity during childhood. This association, although related to a higher risk of developing mental health disorders, was not observed when considering exposure to adverse conditions during adulthood (for a review, see Zannas and Binder 2014, Zannas et al. 2016, Matosin et al. 2018). *FKBP5* genotype–environment (GxE) interaction studies have several limitations (Zannas et al. 2016, Matosin et al. 2018), but GxE interactions involving *FKBP5* seem to influence HPA axis flexibility and risk of developing stress-related mental health disorders.

FKBP5 epigenetic regulation and HPA flexibility

FKBP5 expression regulation by glucocorticoids during stress responses strongly depends on GRE DNA methylation status that generally occurs at specific cytosine–phosphate–guanine (CpG) sites (box 1). High methylation at specific CpG sites within or proximal to particular GREs of the *FKBP5* locus reduces its expression, but low methylation (e.g., due to early life adversity) increases transcript abundance (figure 1; Lee et al. 2010, Zannas et al. 2016, Wiechmann et al. 2019). Importantly too, glucocorticoids can directly alter methylation of specific CpG sites within GREs of *FKBP5*. In mice, chronic exposure to glucocorticoids decreased methylation at specific CpG sites in *FKBP5* intron regions in hippocampus, hypothalamus and blood (Lee et al. 2010). In addition, DNA methylation at specific CpG sites in GREs is dynamic and highly responsive to acute GR activation (Sawamura et al. 2016, Wiechmann et al. 2019). Importantly, changes in *FKBP5* expression were inversely correlated with DNA methylation changes at these specific CpG sites (Wiechmann et al. 2019). It is worth noting that the GREs for which DNA methylation status affects *FKPB5* expression are located on different intronic regions in humans (intron 7) and rodents (intron 5).

Enduring effects of environmental conditions on gene expression can depend on epigenetic regulation of gene transcription. Differential methylation of *FKBP5* GREs appears to mediate some GxE interactions affecting the risk of developing psychiatric disorders. In some risk T allele studies, exposure to adverse conditions during childhood was associated with low methylation at specific CpG sites in the *FKBP5* intron 7 GRE (Klengel et al. 2013). This low DNA methylation was only detected in individuals exposed to adversity during childhood, not adulthood, and was not observed in those carrying the alternate genotype (Klengel et al. 2013). This result was also confirmed in hippocampal progenitor cells, where treatment with dexamethasone induced demethylation of the same CpG sites in *FKBP5* (intron 7). This demethylation occurred only when the treatment was applied at proliferation and early differentiation stages, not later (Klengel et al. 2013). CpG sites that dynamically respond to acute GR activation in intron 7 are the same those that are demethylated in response to childhood stressor exposures (Wiechmann et al. 2019).

Whereas acute stressors result in transient demethylation, permanent lower methylation in *FKBP5* GREs in response to adverse conditions during early life or to chronic stressors could result from sustained GR activation (figure 1; Zannas et al. 2016, Wiechmann et al. 2019). Therefore, *FKBP5* GRE methylation status could enduringly amplify or limit HPA flexibility in the face of adversity. In addition, transgenerational effects of adverse conditions on *FKBP5* DNA methylation have been reported. Holocaust survivors and

their children showed altered DNA methylation at the CpG sites in *FKBP5* intron 7 GRE (Yehuda et al. 2015). In female rats, prenatal exposure to predator odor was associated with permanent reduction of DNA methylation of specific CpG sites of *FKBP5* intron 5 in the amygdala, resulting in higher *FKBP5* expression and sustained HPA activation. Lower methylation was also accompanied by an increase in anxiety-like behaviors in stressful situations (St-Cyr et al. 2017). These results suggest that *FKBP5* may be a primary target for long-term epigenetic programming of HPA flexibility, altering the semiotic content of glucocorticoids depending on the environments experienced by individuals or even their parents (figure 2).

FKBP5 as a marker of HPA flexibility in wildlife

Despite the growing recognition of the major role that *FKBP5* plays in response to stressors in human health (Lee et al. 2011, Menke et al. 2012, Ewald et al. 2014, Lee 2016, Rein 2016, Zannas et al. 2016, Zannas et al. 2019), research on *FKBP5* in wildlife is rare. Encouragingly, a few studies have already measured *FKBP5* expression in a few bird species, showing that expression increases in the brain and multiple peripheral tissues in response to stressors or glucocorticoid treatments (Park et al. 2007, Løtvedt et al. 2017, George et al. 2019, Rensel and Schlinger 2020). We expect that *FKBP5* will have utility as a proxy for HPA flexibility in wildlife because it captures the capacity of an individual to adjust its phenotype appropriately to prevailing, adverse conditions, again because it encodes the semiotic information content of glucocorticoid concentrations and by extension HPA flexibility.

Variation in *FKBP5* regulation and therefore HPA flexibility could influence the absolute capacity of individuals to match optimal phenotypic response across diverse conditions (scope of flexibility, *sensu* Taff and Vitousek 2016), or the speed of changes in response to adverse conditions (speed of flexibility, *sensu* Taff and Vitousek 2016). In support from lab model organisms, individual differences in *FKBP5* regulation affect the strength of the acute stress response and the efficacy of negative feedback; individuals with lower *FKBP5* expression show lower glucocorticoid stress responses and stronger negative feedback (O'Leary et al. 2011, Touma et al. 2011, Hoeijmakers et al. 2014). Moreover, variation in *FKBP5* regulation is also associated with downstream effects that could impinge on wildlife fitness such as differences in sleep architecture, anxiety-associated behaviors, and cognitive flexibility under challenging conditions (Attwood et al. 2011, Albu et al. 2014, Sabbagh et al. 2014, Hartmann et al. 2015, Blair et al. 2019). In figure 2, we juxtapose how variation in *FKBP5* expression (in the present article, driven by DNA methylation) could affect individual access to the semiotic information content of glucocorticoids and therefore HPA flexibility and capacity to cope with adversity.

Variation in *FKBP5* regulation and its effect on HPA flexibility may be at least partly mediated by DNA methylation of specific CpG sites in or proximal to specific GREs that likely differ across taxa. Individuals exposed to adverse conditions during early life have been shown to have modified DNA methylation at specific CpG site in or near GREs usually resulting in permanently lower level of DNA methylation than individuals exposed to low adversity during early development (figure 2a; Klengel et al. 2013, St-Cyr et al. 2017). During adulthood, exposure to adverse conditions results in dynamic changes in DNA methylation at specific GREs in the *FKBP5* locus. DNA methylation at specific CpGs in these GREs quickly decreases in response to increases in glucocorticoids, transiently increasing expression of *FKBP5* (figure 2a; Sawamura et al. 2016, Wiechmann et al. 2019). Generally, effects of methylation kinetics when facing adversity on *FKBP5* expression could underpin most HPA flexibility by regulating access to glucocorticoid semiotic content. Methylation kinetics are also apt to vary among and within populations and species, contingent on the genetic variants (i.e., SNP predominance) that exist in nature.

We also expect that high baseline expression of *FKBP5* or strong increases in *FKBP5* expression in response to adversity via low methylation will be associated with low HPA axis flexibility (figure 2b). By contrast, higher CpG methylation should allow tighter regulation of *FKBP5* expression (figure 2a) and therefore high HPA flexibility (figure 2b). This higher HPA flexibility would result from a greater transduction of glucocorticoid semiotic information, giving access to a greater fraction of the HPA phenotypic space and consequently increasing the number of phenotype that can be reached (figure 2b). Therefore, tighter regulation of *FKBP5* would increase the scope of HPA flexibility, allowing better or faster matching to local conditions. Although studies on endocrine flexibility are limited (Taff and Vitousek 2016), we expect that HPA flexibility will be associated with fitness in most contexts. However, *FKBP5* relationships with fitness might not be linear such that fitness may be maximized at intermediate levels of flexibility or even reduced at extremes level of HPA flexibility (figure 2c).

A final critical point for the use of *FKBP5* as a measure of HPA flexibility is that its expression in peripheral tissues of mice seems to correlate with expression in the brain. Chronic exposure of mice to glucocorticoids for 4 weeks increased *FKBP5* expression in the hippocampus and blood (Lee et al. 2010). This increase in *FKBP5* expression resulted from a decrease in methylation at four CpG sites in GRE of intron 5 in the hippocampus and at two CpG sites in GRE of intron 1 in the blood. *FKBP5* expression and methylation levels at these CpG sites and tissues also correlated with the average level of circulating glucocorticoid over the 4 weeks of treatment. In the blood, after 4 weeks of exposure to two different concentrations of glucocorticoids, *FKBP5* expression was dose dependent. There was also a strong dose dependence between the decrease in methylation at two CpG sites of intron 1 and glucocorticoid exposure. These decreases were transient as CpG methylation levels returned to baseline level within 2 weeks

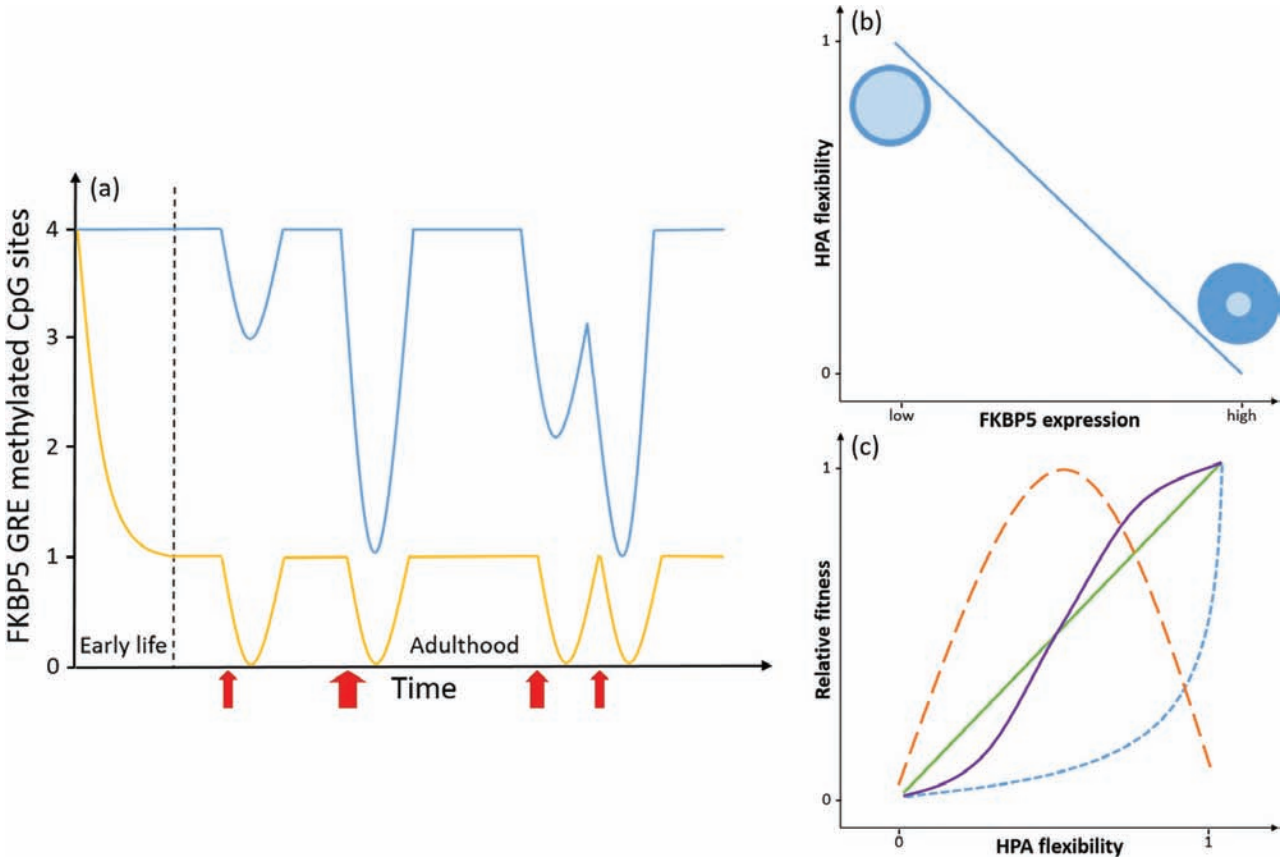

Figure 2. The epigenetic regulation of FKBP5 *and its implications for HPA flexibility and fitness. The two lines in panel (a) depict the organizational (early life, left of the dotted line) and acute effects in adulthood of stress on changes in DNA methylation (the troughs of various depths) for two genetically identical individuals. These hypothetical scenarios are based on known dynamism in methylation status of four CpG sites in intron 7 of the glucocorticoid response element (GRE) of the human* FKBP5 *gene driven by stressor exposures (note that the important factor is the presence of a GRE and that the genomic region in which the GRE epigenetic regulation occurs might differ between species as seen between humans and rodents; Klengel et al. 2013, Matosin et al. 2018, Wiechmann et al. 2019). Exposure to stressors during early life may result in permanent demethylation of some CpG sites (the yellow line) and therefore high* FKBP5 *expression (and low methylation) throughout life. This trajectory contrasts with an individual exposed to little adversity during early life (the blue line); this individual maintains high methylation at the same CpG sites. During adulthood, exposure to stressors (the red arrows, thickness of the arrow indicates intensity) causes transient demethylation of some CpG sites, which increases* FKBP5 *expression. Stronger or longer stressors should result in more demethylation, resulting in higher* FKBP5 *expression. Likewise, exposure to new stressors before full recovery from a previous one might further reduce methylation and increase* FKBP5 *expression. Generally, individual baseline levels of methylation and demethylation or remethylation kinetics in response to stressors will contribute to the capacity for HPA axis flexibility (i.e., in panel (a), changes in lines over time). Importantly, too, it is likely (but not depicted in the present figure) that genetic variation can also contribute to* FKBP5 *expression. (b) Expected relationship between* FKBP5 *expression, semiotic information content, and HPA flexibility. The blue line depicts the expected inverse relationship between* FKBP5 *expression and HPA flexibility. The dark blue circle represents the HPA phenotypic space (i.e., the pool of all available HPA regulatory space available to an individual). The light blue circle represents the fraction of the semiotic information from the total pool carried by glucocorticoids represented by the dark blue circle to which an individual has access and that can be transduced by GRs. In theory, the light blue circle can occupy the whole dark blue area. High* FKBP5 *expression creates an ultrashort, negative feedback loop reducing GR signaling (as is detailed in figure 1). Such GR resistance is associated with a limited access to semiotic information carried by glucocorticoids (the bottom right circles). This limited transduction of the semiotic information gives access to a limited amount of HPA regulatory space (i.e., low HPA flexibility). Conversely, low* FKBP5 *expression (or reduced increase in* FKBP5 *expression in response to a stressor) gives access to more HPA regulatory space, more semiotic information in glucocorticoids (i.e., high HPA flexibility). (c) Potential relationships between HPA flexibility and fitness. We expect that high HPA flexibility will typically be associated with fitness, but the shapes of these relationships could vary. Generally, we expect fitness and HPA flexibility to positively covary, because this relationship would enable an organism to mobilize and deactivate this integral endocrine pathway efficiently, particularly in rapidly changing or novel environments. However, whether the effects of HPA flexibility saturate or take quadratic forms in some environments warrants investigation, because flexibility could become detrimental if it prevents organisms from tracking environmental changes or if environments are predictable and benign.*

Box 2. Outstanding questions.

Are *FKBP5* expression and methylation correlated between peripheral tissues (e.g., blood, saliva) and regulatory regions of the HPA axis (hypothalamus, hippocampus, amygdala, prefrontal cortex, anterior pituitary, adrenal glands) in wildlife?

Is *FKBP5* expression consistent over time (e.g., seasons, life-history stage, aging) and across stressors? How does *FKBP5* regulation relate to HPA flexibility in wildlife? If it does, are baseline and stressor-induced levels of *FKBP5* tightly correlated, and if it does not, is the former or latter a better proxy of HPA flexibility?

Does *FKBP5* epigenetic status influence its regulation in wildlife? At which CpG sites does methylation occur and affect *FKBP5* regulation?

Does early life adversity affect *FKBP5* expression and methylation in wildlife? If so, are expression differences more often related to lower fitness (the silver-spoon hypothesis; Monaghan 2008) or higher fitness on maturation (the environmental matching hypothesis; Monaghan 2008)?

Can methylation status of *FKBP5* be transmitted reliably across generations, independently of genetic variation?

Is individual variation in HPA flexibility associated with differences in fitness? Could differences between individuals in *FKBP5* regulation influence the ability of individuals to adapt to novel, challenging, or dynamic environments? Can measures of *FKBP5* regulation be used as proxies of HPA flexibility and fitness?

(Lee et al. 2011, Ewald et al. 2014). Importantly, methylation level in blood also correlated with methylation level and expression changes in the hippocampus (Ewald et al. 2014). These results suggest that *FKBP5* expression and methylation in blood might serve as a proxy of expression and methylation in the hippocampus (Ewald et al. 2014, Lee 2016). Nevertheless, in order to be able to implement blood-monitoring techniques for *FKBP5* expression and methylation in wildlife, it will be necessary to check for correlations between blood and the different regulatory regions of the HPA axis (i.e., hippocampus, hypothalamus, amygdala, prefrontal cortex, anterior pituitary and adrenal glands) prior to and during stress responses and negative feedback (box 2). For each species, relationship strength could vary, and only with this information in hand will *FKBP5* measurements be useful in ecoevolutionary and conservation studies. In the best cases, measurements of *FKBP5* expression in the appropriate contexts and tissues could do for the field what years of effort to measure glucocorticoids have not really yielded.

Conclusions

Our goal in the present article was to highlight the potential role that *FKBP5* might play in HPA flexibility and therefore understanding how many vertebrate species handle adversity within and across generations. We also suggest that *FKBP5*, by regulating access to the semiotic information content of glucocorticoids, may be useful proxy for HPA flexibility, what most of us aspire to capture when we measure glucocorticoids in wild animals in regards to stressors. In humans, *FKBP5* appears to be an exemplary marker of GR signaling and particularly HPA flexibility (Yehuda et al. 2015, Lee 2016, Rein 2016, Zannas et al. 2016, Matosin et al. 2018). Moreover, *FKBP5* methylation and expression correlate between peripheral and HPA axis central tissues in mice, which allows measures of expression from peripheral tissues to be used as proxies of central expression (Ewald et al. 2014, Lee 2016). This relationship is critical to the use of *FKBP5* in wildlife but could also be of use to resource managers, captive breeding and translocation programs. Furthermore, it has been recently highlighted that transgenerational plasticity and epigenetic mechanisms involving glucocorticoids can have far-reaching effects at the population level and influence adaptation to global changes through their effects on physiology (Seebacher and Krause 2019, Donelan et al. 2020). We expect that the effects of *FKBP5* regulation on HPA flexibility and its potential transgenerational effects will influence adaptation to changing environments when relevant environmental conditions change on an appropriate timescale for HPA axis response. *FKBP5* responses to rapid changes in environmental conditions may be particularly important for adaptation to global changes, which often involve novel or more frequent stressors (e.g., food resources, predators, pathogens).

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