CORRESPONDENCE

Endocrine flexibility

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Two tools reflect fairly well how glucocorticoids (GCs) could help vertebrates cope with stressors: a Ginsu knife and a Swiss army knife. The Ginsu is the pinnacle of a specific function: cutting. No tool surpasses its ability to transform whole foods into smaller pieces. By contrast, a Swiss army knife is among one's last choices to prepare a meal, but it is among the first choices one takes on a trip into the unknown. Which tool reflects better the manner by which GCs resolve stressors? To us, it's the Swiss army knife because stress is not a carrot. All stressors are different, so no single hormonal solution will be viable for every challenge an organism faces. GCs and their regulatory elements must instantiate information from the brain about the adversity of stressors, so if we are to understand how endocrine systems function and evolve, we must account for how they encode and transduce information (Zimmer et al., 2022). In other words, we must understand what hormones do, not just describe and investigate quantitative variation in them.

In endocrinology, there has been recent verve to study endocrine flexibility (Taff and Vitousek, 2016; Hau et al., 2016; Grindstaff et al., 2022; Zimmer et al., 2022): how organisms variably use hormones to adjust their phenotypes to prevailing conditions (Lema and Kitano, 2013; Martin et al., 2011). The concept of endocrine flexibility implies that hormones encode information; if they produce organismal-level effects, they are by definition difference makers. However, prevailing approaches to describing endocrine flexibility effectively disregard what work it is that hormones do (Zimmer et al., 2022). For decades, we have known that circulating GC concentrations functionally vary over two distinct time scales (Hau et al., 2016). When they vary modestly and rhythmically over days or seasons, they tend to regulate energy metabolism and growth. However, when they spike and diminish over very short time scales (minutes to hours), they tend to help animals avoid or endure stressors (Fig. 1A). It is this latter role of GCs that has garnered the most attention regarding endocrine flexibility to date.

In a recent paper in *Journal of Experimental Biology*, Grindstaff et al. (2022) defined endocrine flexibility as how individuals modulate hormone levels in response to the environment. This definition is consistent with others (Taff and Vitousek, 2016), but it is so broad that it is hard to use as an empirical guide. However, it does explain why the currently most popular approach to describing endocrine flexibility is to generate reaction norms for hormone concentrations measured repeatedly in one animal, typically what are called (i) baseline, (ii) post-stressor and (iii) after negative feedback samples (Fig. 1B; Hau et al., 2016; Taff and Vitousek, 2016). This approach is particularly tractable, but its pragmatism supersedes its conceptual validity. One can describe variation in hormone concentrations with reaction norms, but why expect such reaction norms to reflect the range of possible endocrine phenotypes achievable by an individual, true endocrine flexibility?

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The first questionable aspect of the 'concentration reaction norm as flexibility' approach is that it artificially decomposes GC responses into assumedly unrelated parts. If flexibility is the trait of interest, why parse it? True, there can be inferential and statistical problems in focusing on some composite traits (e.g. area under a curve of hormone concentrations over an arbitrary time period; Hau et al., 2016). However, endocrine flexibility is by nature a composite trait; it is necessarily complex and not sensibly decomposed. The current emphasis on reaction norms seems to derive from a drive to assess repeatability (Reed et al., 2019). If hormone traits are not repeatable, the rationale goes, they must not be (sufficiently) heritable and thus are of questionable evolutionary relevance (Hau et al., 2016; Grindstaff et al., 2022). Whereas this argument is largely valid (notwithstanding non-genetic heritable factors), what do we expect about repeatability of traits that function by being flexible? How high can or should repeatability be for such a trait be?

The second questionable aspect of using reaction norms to describe endocrine flexibility is that it elevates hormone concentrations to an indefensible position in the regulatory hierarchy. Recently, we defined endocrine flexibility for GCs in stress responses as 'within-individual rapid and reversible change in HPA regulation in response to unpredictable challenges' (Zimmer et al., 2021). We favor this definition because it is eco-evolutionarily appropriate (i.e. the individual that encodes salient information about stressors fastest and/or most accurately, subsequently best matches its phenotype to prevailing adversity or opportunity; Zimmer et al., 2022), it is agnostic about the particular relationship between hormone concentrations and information, and it implicates a particular measurable form of GC flexibility, the root-mean square of successive differences (RMSSD) of GC stress responses (Zimmer et al., 2021; Fig. 1C). RMSSD, borrowed from studies of heart rate flexibility, enumerates the diversity of hormonal responses to stressors achievable by a given individual in a particular window of time. It, too, involves concentration measurements, but it describes variation in those measurements in a manner much more commensurate with the information content of hormones (Zimmer et al., 2022). Moreover, in one population of house sparrows (*Passer domesticus*), it was related to behavioral differences among birds: some birds had Swiss army knife GC flexibility whereas others used a Ginsu approach (Zimmer et al., 2021).

Going forward, we advocate for consensus in how endocrine flexibility can be effectively studied. We concur that classic reaction norm frameworks can be powerful to quantify the joint contributions of genetic and environmental forces on traits including endocrine flexibility (Fig. 1C; Grindstaff et al., 2022; Hau et al., 2016). However, we think that measures such as RMSSD (or perhaps residual within-individual variance in a mixed-model framework) get us closer to endocrine flexibility. Ultimately, our goal is not to describe hormone variation associated with different contexts, as reaction norms do. We seek to understand the ability of

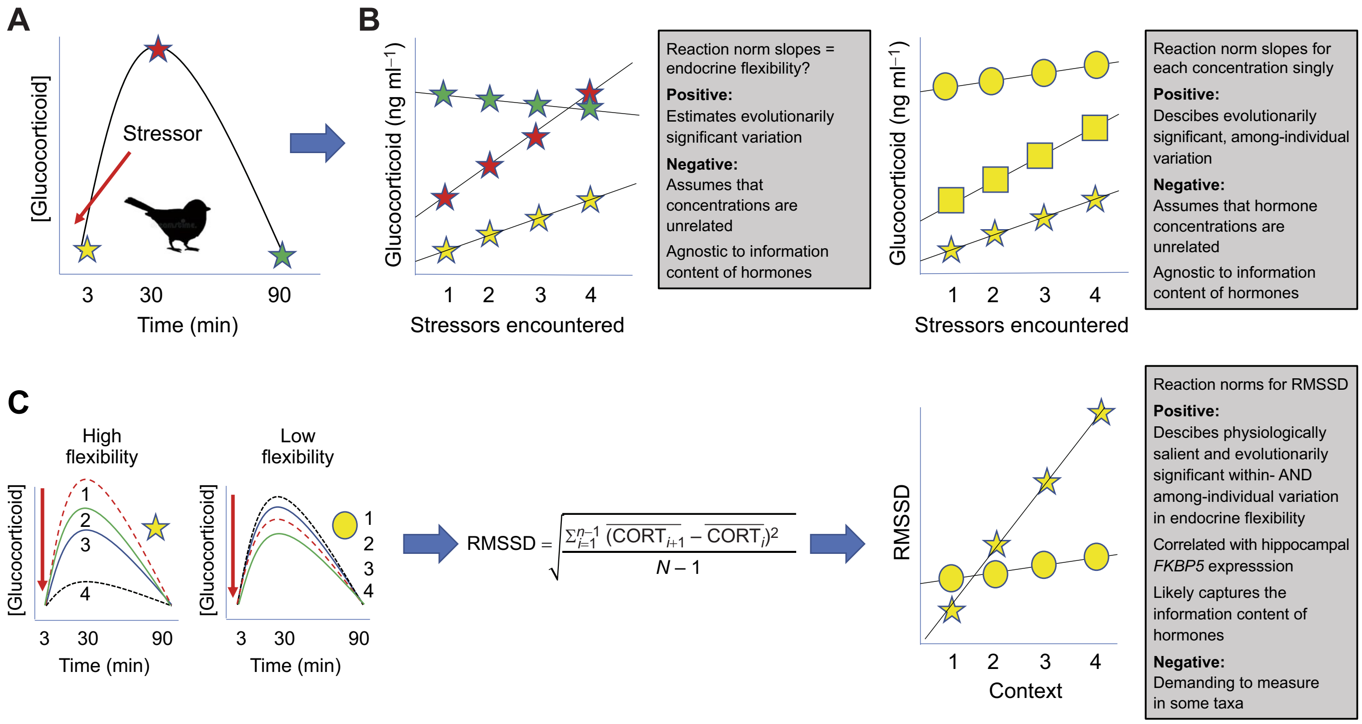

Fig. 1. Alternatives to studying endocrine flexibility. (A) An idealized glucocorticoid (GC) stress response, depicting the tendency for GCs to increase soon after exposure to some adverse, unpredicted stimulus (red arrow), peak later then decline to pre-stressor levels. Stars figure depict typically measured hormone concentrations from blood: baseline (<3 min from stressor exposure; yellow), peak (30 min after stressor; red) and after negative feedback [90 min after stressor or more often dexamethasone (DEX) exposure; DEX strongly binds GR receptors in the brain; green]. (B) Left: one alternative to describing GC flexibility entails a reaction norm framework whereby baseline, peak and/or post-DEX concentrations are measured in the same individual repeatedly across contexts. Resultant slopes for each type of concentration measured along environmental gradients (or repeatedly in individuals) are intended to describe evolutionarily relevant within-individual variation and perhaps endocrine flexibility. Right: comparisons of such slopes for different concentration types among individuals (represented by different symbols), separately, describe plastic variation among individuals/genotypes. (C) An alternative to describing GC flexibility involves measurement of several stress responses (1–4, colored curves) in one animal, followed by quantification of root-mean square of successive differences (RMSSD), for all stress responses of said individual (Zimmer et al., 2021) [in this case measured as corticosterone (CORT) levels]. RMSSD is a measurement common in heart rate flexibility research, and explicitly describes flexibility in a trait. Critically, RMSSD itself is amenable to a reaction norm framework, making it suitable for traditional evolutionary analyses.

individuals to adjust their endocrine systems to respond to different stressors, with the expectation that prevailing environmental conditions, prior experience and internal contexts will require different stress responses (Taborsky et al., 2021).

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Competing interests
The authors declare no competing or financial interests.

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