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Energetics of stress: linking plasma cortisol levels to metabolic rate in mammals

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Physiological stress may result in short-term benefits to organismal performance, but also long-term costs to health or longevity. Yet, we lack an understanding of the variation in stress hormone levels (i.e. glucocorticoids) that exist within and across species. Here, we present comparative analyses that link the primary stress hormone in most mammals (i.e. cortisol) to metabolic rate. We show that baseline concentrations of plasma cortisol vary with mass-specific metabolic rate among cortisol-dominant mammals, and both baseline and elevated concentrations scale predictably with body mass. The results quantitatively link a classical measure of physiological stress to whole-organism energetics, providing a point of departure for cross-species comparisons of stress levels among mammals.

1. Background

Studies on physiological stress have provided insights into how animals cope with environmental conditions and respond to disturbance. We have learned how short-term stress may benefit organismal performance [1], and how chronic or high-intensity stress may be detrimental to the behaviour, ecology and physiology of species [2–4]. Over the longer term, factors that cause stress (e.g. social structure, predation; [5,6]) may negatively impact species' health, reproduction and longevity [2,7].

Physiological stress is typically characterized in vertebrates by the concentration of glucocorticoid (GC) hormones (cortisol and/or corticosterone), which are produced by the adrenal cortex along the hypothalamic–pituitary–adrenal axis [8,9]. These hormones serve an important role in the stress response in all major classes of vertebrates [10,11] by signalling the upregulation or downregulation of relevant physiological systems (e.g. immune, metabolic; [7–9,12]). Stress is often assessed by comparing 'baseline' to 'elevated' concentrations of GC hormones among individuals of a species. The difference in these levels may be as much as an order of magnitude within species and two to three orders of magnitude across species, for reasons that remain unclear [13,14].

Here, we examine the relationship between the dominant GC hormone in mammals, cortisol, and a more general feature of their physiology, metabolic rate. As with cortisol, we know mammals increase metabolic rates (i.e. energy use) upon disturbance or exertion. But unlike cortisol, we have a better understanding of the factors that govern variation in metabolic rates within species at different levels of activity (i.e. metabolic scope) and across species differing in body size [15,16]. Establishing a general relationship between cortisol concentrations and metabolic rate in mammals could therefore serve as a point of departure for understanding intra- and interspecific differences in stress levels.

We hypothesize that cortisol concentration varies proportionally (i.e. linearly) with mass-specific metabolic rate across species, and thus exhibits the

Table 1. Outputs from Bayesian generalized linear mixed-models relating plasma cortisol concentrations (ng ml^{-1}) to body mass (g) and resting mass-specific metabolic rate (mW g^{-1}). DIC and conditional R^2 are reported, as well as the slopes and intercepts of the relationships with 95% CI.

model	DIC	slope (95% CI)	intercept (95% CI)	R^2
baseline cortisol versus resting metabolic rate				
metabolic rate + phylogeny	86.86	0.97 (0.36, 1.56)	3.30 (2.50, 4.18)	0.55
metabolic rate only	98.34	1.28 (0.75, 1.80)	3.07 (2.52, 3.62)	0.49
metabolic rate + covariates	130.62	1.53 (0.63, 2.52)	5.25 (−0.46, 1.18)	0.49
baseline cortisol versus body mass				
mass + phylogeny	162.47	−0.22 (−0.40, −0.05)	6.12 (4.19, 7.98)	0.54
mass only	164.53	−0.29 (−0.41, −0.17)	6.77 (5.56, 8.04)	0.57
mass + covariates	185.32	−0.35 (−0.53, −0.21)	8.16 (2.45, 10.35)	0.61
elevated cortisol versus body mass				
mass + phylogeny	204.74	−0.22 (−0.32, −0.12)	7.26 (6.02, 8.36)	0.63
mass + covariates	219.70	−0.25 (−0.33, −0.18)	7.72 (5.57, 9.62)	0.64
mass only	223.90	−0.24 (−0.38, −0.15)	6.99 (4.42, 9.31)	0.63
elevated cortisol versus baseline cortisol				
cortisol + phylogeny	69.39	0.57 (0.37, 0.75)	3.01 (2.04, 3.95)	0.53
cortisol only	79.75	0.61 (0.53, 0.77)	2.53 (2.02, 3.02)	0.47

same body mass-dependence. We hypothesize that cortisol concentration is related to mass-specific metabolic rate (B/M, in mW g^{-1}) and body mass (M, in g) as:

$$[\text{cortisol}] = a\frac{B}{M} = ab\,M^{-0.25}, \qquad (1.1)$$

where a is a constant that relates cortisol concentration to the flux of metabolic energy per gram of tissue (ng cortisol (ml plasma)$^{-1}$ mW^{-1} (g tissue)$^{-1}$, and b is a metabolic normalization constant that describes the mass-independent rate of energy flux per gram of tissue (mW g$^{0.25}$). The above equation predicts cortisol concentrations will scale to the −0.25 power of body mass (i.e. $B/M \propto M^{-0.25}$) across species, the same way as mass-specific metabolic rate [17]. We evaluate this model for plasma cortisol levels among mammal species that inhabit different environments, vary by orders of magnitude in mass and exhibit considerable taxonomic diversity (see the electronic supplementary material). Note that to the extent baseline cortisol levels correspond to resting metabolic rate, and elevated levels correspond to active metabolic rate, we expect the two levels to be linearly related to each other and vary similarly with body mass. This is because active metabolic rates are linearly related to resting rates, and both show similar body mass-dependencies [17,18].

2. Methodology

We compiled published data on total plasma cortisol concentrations for placental mammals considered 'cortisol-dominant' [13]. We categorized data as representing 'baseline' or 'elevated' cortisol concentrations based on the original author(s)' classification or descriptions. Cortisol measures from faecal or saliva samples were not included as these may differ from plasma measures [19].

We evaluated possible relationships of baseline cortisol concentration with metabolic rate and both baseline and elevated concentrations with body mass using Bayesian generalized linear mixed-models (see the electronic supplementary material). In performing these analyses, we explicitly considered the

possible effects of six additional factors on cortisol levels (i.e. cortisol collection method, sex, anaesthesia, stressor type, captivity and season) and any non-independence due to shared evolutionary history. The six factors were included as covariates in the models, and a recent phylogeny of mammals was included as a random effect [20]. We then used deviance information criteria (DIC) to select the best models [21].

3. Results

Baseline cortisol concentration was linearly related to resting mass-specific metabolic rate based on the 95% CI of the slope (0.97 (0.36, 1.56); table 1 and figure 1*a*). Metabolic rate explained 55% of the variation in baseline plasma cortisol concentrations across species of mammals. Elevated cortisol was highly correlated with baseline cortisol, though the slope was significantly less than 1 (slope = 0.57 (0.37, 0.75); table 1 and figure 1*b*). The best models for these relationships included phylogeny, but excluded covariates.
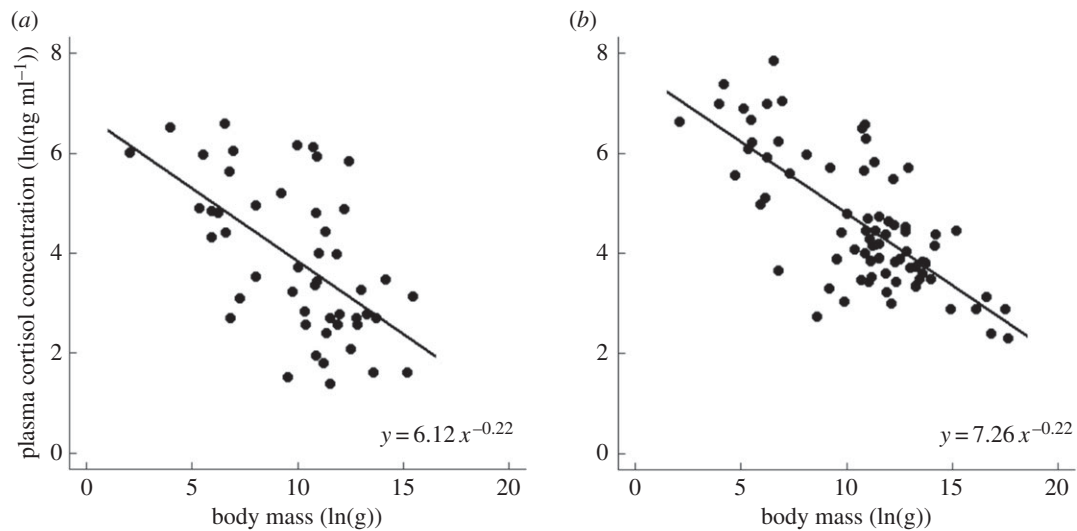
Baseline and elevated cortisol concentrations both showed relationships with body mass that are similar to those observed for mass-specific metabolic rate (table 1 and figure 2), though elevated levels were approximately three-fold higher than baseline levels on average. Consistent with equation (1.1), these relationships were well described by power laws, with scaling exponents that were not significantly different from the −0.25 value (i.e. −0.25 fell within CIs; table 1). Body mass explained 54% and 63% of the variation in baseline and elevated cortisol concentrations, respectively. Here, too, the best models included phylogeny, but excluded covariates (table 1).

4. Discussion

These results provide an *a priori* expectation for how plasma cortisol concentration should vary across species of mammals
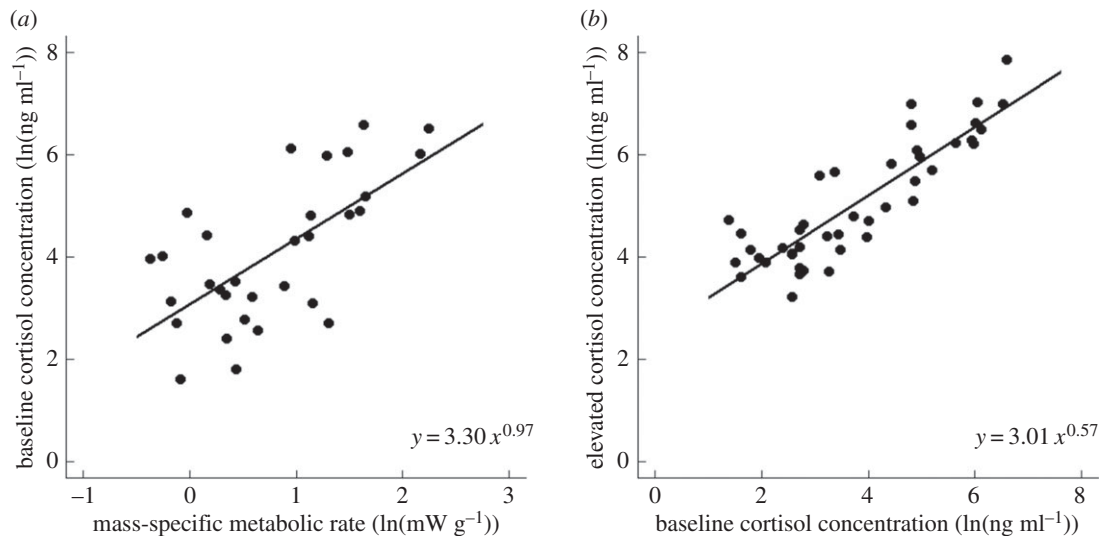
Figure 1. Relationships in cortisol-dominant mammals (a) between baseline plasma cortisol concentrations (ng ml^{-1}) and resting mass-specific metabolic rate (mW g^{-1}; $N = 49$) and (b) between elevated plasma cortisol concentrations and baseline cortisol concentrations ($N = 43$). Data are natural-log transformed.

Figure 2. Relationships in cortisol-dominant mammals of (a) baseline ($N = 49$) and (b) elevated plasma cortisol concentrations (ng ml^{-1}) ($N = 78$) to body mass (g). Data are natural-log transformed.

based on the observed relationships between cortisol, mass-specific metabolic rate and body mass (equation (1.1)). While it has long been understood that GCs play a role in metabolic function by helping to maintain blood glucose concentrations [22], it is still perhaps surprising to observe that the concentration of cortisol is proportional to mass-specific metabolic rate as opposed to production rates of this hormone. This could be achieved if cortisol production showed similar relationships with body mass and metabolic rate, but the turnover of individual molecules of cortisol was independent of these factors.

Perhaps more surprising is our observation that the slopes of the relationships with body mass are similar for both baseline and elevated levels of cortisol, given potential differences in GC-binding proteins and receptor density of stressed animals [22,23]. It is also noteworthy that elevated levels of cortisol were on average threefold greater than baseline levels for a given body mass (table 1), a difference that (perhaps coincidentally) corresponds to the average difference in resting and active metabolic rates reported for mammals [18]. If baseline and elevated levels of cortisol correspond to resting and active metabolic rates, respectively, it would suggest that

there exists an approximately constant relationship between cortisol concentration and energy flux across activity levels. It is unclear, however, how such a relationship would correspond to the coordinated activities of GC and mineralocorticoid (MR) receptors during stress. High-affinity MR receptors are thought to play a primary role at low stress levels, or early in the stress response, while low-affinity GC receptors become more important at higher levels of stress, or later in the stress response, as MR receptors become saturated [24].

Unexplained variation about the fitted lines shown in figures 1 and 2 is perhaps explained by the following: first, we did not attempt to account for all of the many factors that may influence cortisol concentration (e.g. environment), including intra-individual variation at baseline or elevated levels [25,26]. Still, at the scale of our analyses, the six covariates we did consider (i.e. cortisol collection method, sex, anaesthesia, stressor type, captivity and season) were not statistically significant. Second, criteria used to categorize cortisol concentrations as 'baseline' or 'elevated' are more subjective than those used to categorize metabolic rate because they were primarily designed for intraspecific comparisons [27]. Finally, while cortisol was the primary GC hormone considered here, corticosterone may

still play a significant role. At present, we lack a clear understanding of how relative concentrations of cortisol and corticosterone vary across species [13,14].

Considering stress in terms of individual energetics may provide insights into the trade-off between its short-term benefits and long-term costs [9]. Assuming that species possess a finite lifetime energy budget, an observation that forms the basis of the 'rate of living' hypothesis [28], increases in metabolic rate as part of the acute stress response may result in greater oxidative damage, which affects long-term health or longevity [29,30]. The relationship between stress and individual energetics may also explain why many basic attributes of organisms related to health and longevity have been shown to be negatively correlated with both cortisol concentration and mass-specific metabolic rate (e.g. lifespan; [31]). In this context, chronically high stress hormone levels in smaller mammals should perhaps not be viewed as negatively impacting evolutionary fitness, but rather as reflecting a different rate of living. Future work that relates measures of stress to metabolic energy expenditure may provide further insights into the relationship between the short- and long-term effects of stress.

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