OXFORD UNIVERSITY PRESS | Integrative and Comparative Biology

# Does hormonal pleiotropy shape the evolution of performance and life history traits?



| | |
|---|---|
| Journal: | *Integrative and Comparative Biology* |
| Manuscript ID | ICB-2017-0086 |
| Manuscript Type: | Symposium article |
| Date Submitted by the Author: | 31-Mar-2017 |
| Complete List of Authors: | Dantzer, Ben; University of Michigan, Psychology; University of Michigan, Ecology and Evolutionary Biology<br>Swanson, Eli; University of Minnesota, Ecology, Evolution and Behavior |
| Keywords: | Evolutionary endocrinology, Performance, Life history, Hormonal pleiotropy, Quantitative genetics |
| | |

# *Does hormonal pleiotropy shape the evolution of performance and life history traits?*

Ben Dantzer[a,b*], Eli M. Swanson[c]

[a]Department of Psychology, University of Michigan, Ann Arbor, MI 48109, USA,

[b]Department of Ecology and Evolutionary Biology, University of Michigan, Ann Arbor, MI 48109, USA

[c]Department of Ecology, Evolution and Behavior, University of Minnesota, St. Paul, MN 55108

[*]*Corresponding author (B. Dantzer); email: dantzer@umich.edu; phone: 1-734-615-2352*

Word count (including abstract, references, and figure legends): 7776

**Abstract**

Hormonal pleiotropy occurs when the concentrations of a single hormone influences the expression of two phenotypes and it may have similar evolutionary consequences as genetic pleiotropy. To date, most conceptual and empirical work on the putative evolutionary consequences of hormonal pleiotropy has focused on identifying if the different components of an endocrine axis (titer, receptor expression, etc.) that affect trait expression are themselves able to evolve independently from one another. This is an important focus because if these different components evolve together, the expression of two traits affected by the same hormone may be yoked and evolve non-independently. Here, we first focus on methodological approaches to identifying how hormonal pleiotropy could constrain the independent evolution of performance and life history traits. We then focus on a similar but less studied concept about how hormonal pleiotropy can constrain or facilitate adaptive phenotypic responses to selection. If the expression of two traits is affected by the same hormone, the magnitude of the phenotypic response to selection may be exacerbated or retarded compared to the absence of this hormonal pleiotropy. We use classical concepts from quantitative genetics to discuss an approach for identifying if hormonal pleiotropy has such evolutionary consequences using data collected from longitudinal studies of wild animals. We develop a simple quantitative genetics model to derive predictions about the conditions under which hormonal pleiotropy would constrain or facilitate the response to selection. We focus on performance and life history traits and how the effects of hormonal pleiotropy on the evolution of these traits depends upon the genetic correlations between the hormone and traits as well as the direction and strength of selection on the two traits. Finally, we review the literature for examples that have estimated these model parameters to characterize the studies that have or have not found support for these model predictions.

## Introduction

Genetic pleiotropy occurs when a single gene or locus affects two or more phenotypic traits. Genetic pleiotropy has long interested evolutionary biologists because selection upon one trait may cause a correlated or indirect response in other traits. As such, genetic pleiotropy may facilitate or retard the phenotypic response to selection as well as influence whether two or more traits evolve independently from one another (Cheverud, 1984; Falconer and Mackay, 1996; Lynch and Walsh, 1998). For example, if phenotype A and phenotype B are affected by the same gene but selection gradients on phenotypes A and B are opposite in sign (e.g., favoring large values of phenotype A but low values of phenotype B), the optimal response to selection in each trait may be constrained by selection acting on the other trait in the opposite direction. Additionally, phenotypes A and B may have non-independent evolutionary trajectories if they are linked together through genetic pleiotropy. Despite the theoretical possibility of genetic pleiotropy shaping phenotypic evolution, a few empirical studies indicate that genetic pleiotropy seems to rarely constrain the independent evolution of traits or the rate of adaptation (e.g., Agrawal and Stinchcombe, 2009; Conner et al. 2011; but see Morrissey et al., 2012).

Evolutionary physiologists and endocrinologists naturally have a position to play in our understanding of the role of pleiotropy in phenotypic evolution because hormones often have pleiotropic effects (Stearns, 1989; Ketterson and Nolan, 1992; Finch and Rose, 1995; Ketterson et al., 2005) and they may act as the functional mediators of genetic pleiotropy. Hormonal pleiotropy, where a single hormone affects multiple traits, has largely been studied in the context of trade-offs between behavioral or life history traits (Stearns, 1989; Ketterson and Nolan, 1992; Sinervo and Svensson, 1998; Ketterson et al. 2005). For example, elevated levels of the steroid hormone testosterone acting as a cause of antagonistic pleiotropy between parental and mating

behavior (Ketterson and Nolan, 1992). More recently, the field has expanded to focus more on the broader evolutionary implications of hormonal pleiotropy such as whether it constrains the independent evolution of any hormonally-mediated trait (Hau, 2007; McGlothlin and Ketterson, 2008; Adkins-Regan, 2008; Ketterson et al. 2009; Dantzer and Swanson, 2012). However, unlike genetic pleiotropy, less attention has been paid to how hormonal pleiotropy may constrain or facilitate the phenotypic response to selection acting on two phenotypes influenced by the same hormone (but see Ketterson et al. 2005; McGlothlin and Ketterson, 2008; Ketterson et al. 2009).

Our aims here are to 1) discuss the evolutionary consequences of hormonal pleiotropy (affecting whether two traits evolve independently and influencing the phenotypic response to selection), 2) describe the different approaches that can be used to examine whether hormonal pleiotropy constrains the independent evolution of phenotypes, and 3) to develop a simple quantitative genetics approach to testing whether hormonal pleiotropy constrains or facilitates responses to selection to spur future research on this latter topic especially in studies of the association between performance and life history traits. We introduce a simple quantitative genetics model to illustrate how hormonal pleiotropy may influence the phenotypic response to selection and use it to describe how data gathered from longitudinal studies of wild animals (selection gradients on phenotypes, genetic correlations between a hormone and different phenotypes) could be used to test some of the predictions. We then obtain estimates of these parameters (selection gradients, genetic correlations between hormones and life history or performance traits) from the literature to provide some indication of how often the conditions where hormonal pleiotropy constrains or facilitates phenotypic responses to selection. Our focus is specifically on performance and life history traits to better integrate concepts regarding the evolutionary consequences of hormonal pleiotropy into the study of performance and life history

trade-offs. However, the approaches described could easily be transferred to the study of other traits.

**Hormonal pleiotropy and the independent evolution of phenotypes**

Studies about the evolutionary consequences of hormonal pleiotropy have mostly focused on identifying whether the independent evolution of two behavioral traits are constrained due to the pleiotropic effects of hormones. For example, whether two traits that negatively co-vary (e.g., mating and parental behavior in male birds) exhibit such patterns because of the pleiotropic effects of a hormone acting on both traits. Two specific hypotheses have been formulated about the consequences of hormonal pleiotropy for the independent evolution of traits (Hau, 2007; Ketterson et al., 2009; Swanson and Dantzer, 2014). Similar to genetic pleiotropy, hormonal pleiotropy could constrain the independent evolution of traits whereby the optimal combination of traits favored by natural selection is not expressed because a hormone elevates the expression of one trait but decreases another (hypotheses labeled "evolutionary constraint", "phenotypic integration", or "evolutionary conservation of hormone effects": Hau, 2007; Ketterson et al., 2009; Swanson and Dantzer, 2014). For example, increased testosterone levels of may reduce parental behavior but elevate territorial or mating behavior in birds (Ketterson and Nolan, 1992; McGlothlin et al., 2007) or increased insulin-signaling may increase growth, development, and reproduction but reduce lifespan (Dantzer and Swanson, 2012; Swanson and Dantzer, 2014). On the other hand, hormonal pleiotropy could facilitate adaptive phenotypic integration by enabling the expression of adaptive suites of traits (Ketterson et al., 2009; Dantzer and Swanson, 2012). For example, increased insulin-signaling that depresses lifespan but increases growth and

reproductive output may be an adaptive combination of traits for environments in which there is high extrinsic mortality (Dantzer and Swanson, 2012).

The alternative hypothesis is that two phenotypes affected by the same hormone can evolve independently from one another because the levels of a circulating hormone are not the only factor determining trait expression (hypotheses labeled "evolutionary potential", "phenotypic independence", or "no evolutionary conservation of hormone effects": Hau, 2007; Ketterson et al., 2009; Swanson and Dantzer, 2014). Instead, the many components of an endocrine axis that translate into changes in the phenotypes that may be influenced by changes in hormone concentrations can also affect trait expression (Adkins-Regan, 2008). This is largely an issue of whether signal (hormone) production that influences trait expression can evolve independently from the receptivity of the tissues also affecting trait expression (Hau, 2007). For instance, increased insulin signaling or circulating testosterone levels could increase the expression of morphological trait 1 but not to the same degree as morphological trait 2 because trait 1 is hyper-responsive to the signal perhaps because of increased receptor expression for that signal in the tissue affecting or responsible for trait 1 (Emlen et al. 2012). If the multiple components of the endocrine axis can evolve independently, it is likely that any pleiotropic effects of a hormone can be overcome through the evolution of differential tissue expression or other mechanisms that facilitate a decoupling between the hormone concentration and phenotypic expression. Consequently, even if hormonal pleiotropy exists, it does not have to constrain the independent evolution of two phenotypes. Selection instead could favor individuals that have enhanced sensitivity to the hormonal signal for phenotype 1 but reduced sensitivity for phenotype 2. On the other hand, if the different component parts cannot evolve together, this

suggests that the two traits will be yoked due to hormonal pleiotropy, which may or may not be adaptive depending upon what combination of traits selection favors.

*How to test hypotheses about consequences of hormonal pleiotropy for the independent evolution of performance and life history traits?*

To address the evolutionary consequences of hormonal pleiotropy, it is crucial to address whether the many components of different endocrine systems/axes evolve together or separately, but how do you do this? One way is to ask whether patterns of phenotypic divergence between two individuals or two species are due to differences in circulating hormone levels or some other endocrine mechanism such as local differences in receptor expression. For example, hyper-allometric traits may be due to increased receptor expression for growth hormones that impact the growth or expression of those traits rather than a general overall increase in the hormone (Warren et al. 2013). In some organisms, receptor expression can be experimentally manipulated in different tissues and variation in receptor expression among different tissues affecting different traits can be documented (Emlen et al., 2012). These studies where there is tissue-specific variation in receptor expression and experimental manipulations in receptor activity show that increases or decreases in tissue receptor expression can manipulate phenotypes independently of one another would support the evolutionary potential or phenotypic independence hypothesis.

A second useful approach is to assess what causes variation in a phenotype by measuring variation in several different parts of the endocrine system rather than just circulating hormone levels and assessing what factors best explain variation in the phenotype of interest. For example, Rosvall et al. (2012) measured aggression in dark-eyed juncos (*Junco hyemalis*) and circulating

plasma testosterone levels and the abundance of androgen and aromatase receptor and estrogen receptor alpha mRNA in specific areas of the avian brain thought to affect aggressive behavior. They found that plasma testosterone levels were only positively associated with aggression in males but not females but that in both sexes, the abundance of androgen and aromatase receptor and estrogen receptor alpha receptor mRNA were positively associated with aggression. Although it would be useful to assess the proportion of variation in the behavior explained by each endocrine trait relative to the others, these data provide some support for the evolutionary potential or phenotypic independence hypothesis. They suggest that the different components of the endocrine axis (testosterone production vs. its effects on behavior through receptors) can evolve independently and influence a behavioral phenotype independently.

A third way to test these hypotheses is to use a combination of artificial selection studies combined with quantitative genetics, which has been used successfully for more than 20 years in studies regarding the endocrine basis and quantitative genetics of wing polymorphisms and dispersal phenotypes in crickets by Daphne Fairbairn, Derek Roff, Anthony Zera, and their colleagues (e.g., Fairbairn and Yadlowski, 1997; Roff et al., 1997; Zera, 2004). These studies show how hormone titers (juvenile hormone esterase) can respond to artificial selection acting directly on the hormone titers themselves (Zera and Zhang, 1998; Zera et al., 1996, 1998). In addition, they demonstrate that different components of an endocrine axis (e.g., juvenile hormone esterase and juvenile hormone binding activity) can be phenotypically and genetically correlated with one another (Gu and Zera, 1996), and that artificial selection acting only on hormone titers can produce an indirect response in other components of the endocrine axis (juvenile hormone esterase, the rate of juvenile hormone degradation, and juvenile hormone esterase binding activity: Zera and Zhang, 1995; Zera et al., 1996, 1998). Together, these studies

emphasize that the different components of the endocrine axis (production and synthesis, binding proteins, degradation enzymes) may not evolve independently of one another, which would support the evolutionary constraint or phenotypic integration hypothesis because selection acting on one component of the endocrine axis produces a response in other components.

Finally, a comparative approach may be used to test these two hypotheses. If the different components of an endocrine system can evolve independently, we would predict that the relationship between a hormone and phenotype would likely be inconsistent across species such that trade-offs or co-variation between two traits would not be associated with the level of circulating hormone across species but would rather be explained in species-specific manner. For example, species A exhibits increased sprint speed because of higher circulating testosterone levels but species B exhibits increased sprint speed because of increased androgen receptors at specific muscles. In a comparative study, we found that the association between circulating levels of insulin-like growth factor 1 and a major life history trade-off (growth and reproduction vs. lifespan) was conserved across species though there was substantial variation in this relationship (Swanson and Dantzer, 2014). This suggests that signal intensity (circulating hormone levels) is a good proxy for understanding what causes variation in the phenotypes that are of interest to organismal biologists but also that the circulating levels of the hormone may constrain the independent evolution of traits. This comparative study would support the evolutionary constraint or phenotypic integration hypothesis.

**Hormonal pleiotropy and phenotypic responses to selection**

The four approaches described above focus on identifying whether hormonal pleiotropy causes persistent patterns of co-variation between two or more phenotypes because it constrains

their independent evolution. We now shift our attention towards the other possible consequence of hormonal pleiotropy, how it may constrain or facilitate phenotypic responses to selection. When phenotypes are correlated due to a shared underlying mechanism, whether it be a gene or hormone, selection acting upon one trait may produce an indirect response in the other. For example, suppose individuals with increased sprint speed and parental behavior have higher reproductive success (i.e., positive selection on sprint speed and parental behavior) but the magnitude of selection acting upon sprint speed is higher than on parental behavior. Increased circulating testosterone levels may be associated with increased sprint speed but decreased parental behavior. Positive selection acting upon sprint speed may therefore produce an indirect response in parental behavior as individuals with lower parental behavior (and higher sprint speed) have higher reproductive success. In the absence of other mechanisms allowing the association between circulating testosterone and parental behavior to be attenuated, the optimal response to selection on parental behavior is therefore constrained due to the pleiotropic effects of testosterone on sprint speed. On the other hand, if increased testosterone levels were associated with increases in both sprint speed and parental behavior, the response to selection on either behavioral trait would be facilitated (greater than in the absence of hormonal pleiotropy).

To date, few empirical studies have addressed this other possible evolutionary consequence of hormonal pleiotropy (but see Ketterson et al. 2005; McGlothlin and Ketterson, 2008; Ketterson et al. 2009). This may be partly due to the lack of well-developed methodological approaches in addition to the difficulty associated with collecting the data necessary to examine it. To help spur future studies, we advocate one approach that uses classical methods in quantitative genetics and standard selection gradient analyses to uncover this possible consequence of hormonal pleiotropy (Fig. 1). We suggest this approach because

existing longitudinal individual-based studies of wild animals may be uniquely situated to test how hormonal pleiotropy may affect the phenotypic response to selection. Such field studies typically quantify behavioral, morphological, performance, or life history traits as well as their association with fitness metrics, thereby providing the opportunity to quantify standard selection gradients on those phenotypes (Lande and Arnold 1983; Morrissey et al., 2013). In addition, some longitudinal studies where there is a pedigree available afford the opportunity to quantify phenotypic and genetic correlations between physiological traits such as hormone levels and the phenotype of interest. Longitudinal individual-based studies can therefore 1) estimate the genetic covariance between a hormone measured in plasma/serum or another integrated measure of that hormone (feces, urine, saliva, hair, feathers, etc.) and two or more phenotypes (such as life history or performance traits) and 2) quantify selection gradients on the phenotypes of interest.

We developed a simple quantitative genetics model to illustrate how hormonal pleiotropy could constrain or facilitate adaptive phenotypic responses to selection and how data gathered from longitudinal individual-based studies could be used to test whether hormonal pleiotropy constrains or facilitates adaptive responses to selection. We use *constrain* to indicate that the phenotypic response to selection is not equal to the response that would be observed in absence of the hormonal pleiotropy whereas *facilitate* indicates that the response to selection is increased in magnitude compared to the absence of the hormonal pleiotropy. The components of this model are a single hormone that is genetically correlated with two phenotypes and linear selection gradients on the two phenotypes (Fig. 1), though the sign and magnitude of those genetic correlations and the selection gradients can vary from -1 to 1.

After developing this model, we gathered existing data from the literature regarding the strength of genetic correlations between endocrine traits and life history or performance traits

(Table S1) and extracted estimates of selection gradients on performance (Irshick et al. 2008) and life history (Kingsolver et al. 2012) traits from recent meta-analyses. The aim here was to examine how often hormonal pleiotropy might constrain or facilitate responses to selection on two traits given estimated values of model components from previous studies.

**Methods**

We implemented a simple quantitative genetic model in which two phenotypic traits and one hormone evolve in response to directional selection. The mechanistic effect of the hormone on each trait is modeled by a genetic correlation between the hormone and each trait. Note that we did not specify any actual mechanism underlying this genetic correlation. The two phenotypic traits are thus correlated to the extent of their mutual correlation with the hormone, simulating hormonal pleiotropy.

Each generation, directional selection occurs on the two phenotypic traits, not on the hormone. Any changes in the hormone result from the genetic correlation with the two traits. There is also a genetic correlation between the two traits resulting solely from each trait's genetic correlation with the hormone. In other words, the two phenotypic traits are genetically correlated due solely to each of their independent correlations with the hormone. The response to selection in each trait, as well as in the hormone, is modified by these genetic correlations. Evolution in this model simply followed the Breeder's equation (Eq. 1) using arbitrary initial trait values, and additive genetic variance values of 0.5. G here is the G matrix, and β is a vector of selection gradients.

$$\text{(Eq. 1)}\quad \Delta\bar{z} = G\beta$$

We ran the model out in this case over 100 generations, and with parameters informed by values from the literature. We obtained estimates of the genetic correlation between a hormone and life history or performance traits from previous studies (see Table S1: Davis and Simmen 1997; Roff et al. 1997; Nkrumah et al. 2007; Hayhurst et al., 2009; Hoque et al. 2009; Ruuskanen et al. 2016) and estimates of selection gradients on life history (95% credible intervals for selection gradients on size and fecundity from Table S1 in Kingsolver et al. 2012) and performance (Irschick et al. 2008) traits from recent meta-analyses. Parameters that we varied included the genetic correlation between the hormone and each trait, as well as the strength of selection on each trait. Results for a variety of parameters drawn from the literature (see Table S1) are given in Figure 3. Models can easily be made more complex in a wide variety of way. Examples include adding phenotypic covariances, using a more complex version of the Breeder's equation (Eq. 2). G and β are the same here as in Eq. 1, and P is the phenotypic covariance matrix. In the examples we drew from the literature, phenotypic and genetic covariance matrices were not available for the same cases, so we did not use this approach.

$$\text{(Eq. 2)}\ \Delta\bar{z} = GP^{-1}\beta$$

## Results

*General predictions about consequences of hormonal pleiotropy*

In our simple model to illustrate our predictions (Fig. 2), we set both the genetic correlation between the hormone and performance trait at 0.5 and the selection gradient on the performance trait at 1 and varied both the genetic correlation between the hormone and life history trait and the selection gradient on life history trait from -1 to 1. Here, a positive genetic

correlation indicates that increases in hormone concentrations enhances the expression of the trait whereas a negative genetic correlation reflects the opposite. When the genetic correlations are opposite in sign, it indicates that increases in the hormone enhances the expression of one trait and decreases the expression of the other (potentially causing apparent negative co-variation between the two phenotypes). Positive selection gradients indicate that individuals with enhanced expression of the traits have higher fitness whereas negative selection gradients indicate the opposite.

This simple model (Fig. 2) illustrates that when there is strong positive selection on a performance trait and a hormone is positively correlated with the expression of that performance trait, the response to selection on performance may be facilitated if the life history trait is also experiencing positive selection and there is a positive genetic correlation between the same hormone affecting the performance trait and the life history trait (upper right part of Fig. 2). For example, if individuals that are faster and larger have higher survival and those with higher concentrations of a hormone are faster and larger, the phenotypic response to selection on performance should be increased. Alternatively, under these fixed conditions for the performance trait, the response to selection on performance may be facilitated if there is negative selection on the life history trait and if there is a negative genetic correlation between the hormone and life history trait (lower left panel in Fig. 2).

The response to selection on performance may be constrained if a hormone enhances the expression of both the performance and life history traits but when there is positive selection on the performance trait but negative selection on the life history trait (lower right panel in Fig. 2). For example, if increases in hormone concentrations enhance both sprint speed and growth but selection favors faster individuals that grow more slowly (or are smaller), the phenotypic

response to selection on sprint speed may be reduced compared to the absence of the hormonal pleiotropy. Alternatively, hormonal pleiotropy may constrain the phenotypic response to selection on performance when selection favors individuals with increased expression of both the performance and life history traits but increases in hormone concentrations enhances expression of the performance trait but decreases the expression of the life history trait. For example, if selection favors individuals that exhibit higher sprint speeds and grow faster but increases in the concentrations of a pleiotropic hormone increases sprint speed but decreases the expression of the life history trait, the phenotypic response to selection on performance may be reduced.

*Model predictions using real estimates of genetic correlations and selection gradients*

We located estimates of the genetic correlation between steroid and peptide hormones and life history traits such as fecundity, inter-litter interval, growth, and egg mass (range = 0.88 to 0.65) in addition to a few estimates for the genetic correlation with performance traits such as the presence or absence of wings and food intake, (range = -0.24 to 0.9, Table S1). We used these values in addition to estimates of selection on performance and life history traits in our basic model (Fig. 2) to identify if the combinations of these four parameters (Fig.1) estimated from studies in captive animals would overlap with areas in which the model predicted that hormonal pleiotropy would constrain or facilitate phenotypic responses to selection.

Model behavior was similar to our general model (Fig. 2) where there were zones of facilitation and constraint (Fig. 3). However, in this model, we fixed the genetic correlation between a hormone and performance trait at -0.24 (Fig. 1A to 1C), 0.27 (Fig. 1D to 1F), or 0.9 (Fig. 1G to 1I), which represented the lowest, median, and highest values (Table S1). We also fixed selection on the performance trait at -0.4, 0.1, or 0.4 (corresponding to strongly negative,

weakly positive, or strongly positive selection). We again allowed the genetic correlation between the hormone and the life history trait and the sign and magnitude of selection on the life history trait to vary from -1 to 1. The dashed boxes in each panel of Fig. 3 show the range of values from the literature that estimated the genetic correlation between a life history trait and a hormone (-0.88 to 0.65, Table S1) and the 95% credible intervals for estimates of selection gradients on life history traits (size and fecundity, ranging from 0.051 to 0.218: Kingsolver et al. 2012).

The dashed boxes in each panel of Fig. 3 show the range of values from the literature that estimated the genetic correlation between a life history trait and a hormone (-0.88 to 0.65, Table S1) and the 95% credible intervals for estimates of selection gradients on life history traits (size and fecundity, ranging from 0.051 to 0.218: Kingsolver et al. 2012). When viewing the area inside of each of these boxes, it is notable that the only situation when there was some evidence that hormonal pleiotropy would constrain the phenotypic response to selection on the life history trait was when there was very weak positive selection on the performance trait ($\beta = 0.01$) and a very strong genetic correlation between the hormone and the performance trait ($r_g = 0.9$, Fig. 3H). Here, selection favors higher expression of the performance trait (e.g., faster individuals) and increases in the hormone concentration can strongly increase the expression of the performance trait (Fig. 3H). When there is a strong positive genetic correlation between the same hormone and the life history trait (far right of inset dashed box) and strong positive selection on the life history trait (top portion of inset dashed box), the phenotypic response to selection on the life history trait could be facilitated due to hormonal pleiotropy (upper right portion of the dashed box inset in Fig. 3H).

When selection on the performance trait was set at -0.4 or 0.4 and the genetic correlation between the hormone and the performance trait was fixed at -0.24 or 0.27 (Figs. 1A to 1F), there was little evidence that the phenotypic response to selection on the life history trait would be altered in light of the estimates of selection on life history traits and genetic correlations between a hormone and a life history trait from the literature (i.e., little evidence of color change inside each dashed box in Figs. 1A to 1F). In other words, under actual estimates of the genetic correlation between a hormone and life history trait and estimates of selection gradients on life history traits, these results suggest that the ability of hormonal pleiotropy to constrain the phenotypic response to selection is restricted to when there is a very strong genetic correlation between the same hormone and the performance trait.

## Discussion

Our results make the following general predictions. First, if the genetic correlations between the single hormone and the two traits has the same sign, the response to selection on one trait will be *facilitated* due to hormonal pleiotropy when the direction of the selection on the two traits is the same (e.g., area in top right of Figs. 1E, 1F, 1H, and 1I), though the magnitude of the facilitation varies depending upon the strength of selection on both traits. Second, even if there is positive selection on both traits, hormonal pleiotropy can *constrain* the response to selection on one trait if the genetic correlation between the hormone and the two traits is opposite in sign (e.g., bottom right and top left of Figs. 1G through 1I). Third, if the sign of the genetic correlation between the single hormone and the two traits is the same but the sign of the selection gradients on the two traits is the opposite, the phenotypic response to selection on one trait will be *constrained* by selection on the other. Fourth, if the sign of the genetic correlation between the

single hormone and the two traits is opposite but the sign of the selection gradients on the two traits is the same, the phenotypic response to selection on one trait will be *constrained* by selection on the other.

We do not claim that any of these predictions are anything other than intuitive and stem from basic quantitative genetic theory (Cheverud, 1984; Falconer and Mackay, 1996; Lynch and Walsh, 1998). We also interpret them through a skeptical lens given the simplicity of the model and the need to considerably extend it (e.g., using Eq. 2). However, we think that our proposed conceptual model (Fig. 1) and the associated predictions from a simple quantitative genetics model (Fig. 2) at least provide an explicit framework for new studies to address whether hormonal pleiotropy (or other physiological mechanisms causing such pleiotropy) does affect the phenotypic response to selection.

Despite the theoretical possibility of hormonal pleiotropy constraining or facilitating the phenotypic response to selection due to its effects on other traits influenced by the same hormone that are also under selection, estimates of the four parameters composing the model (Fig. 1) from the literature (Table S1) suggest that these conditions are rarely met. Given that there is almost always positive selection on performance (Irshick et al., 2008) and life history (e.g., size, fecundity: Kingsolver et al. 2012), measuring the sign and magnitude of the genetic correlation between hormones and these traits would be particularly useful to test predictions about how hormonal pleiotropy constrains or facilitates phenotypic responses to selection on performance. For example, selection may most frequently favor individuals with elevated sprint speeds and fecundity and so knowing whether there is a positive or negative genetic correlation between a single hormone and those two traits or if that correlation is very strong or very weak can help to predict whether the phenotypic response to selection on either the performance or life history

trait is constrained by selection on the other. Of course, the effects of such hormonal pleiotropy on constraining or retarding the phenotypic response to selection will also always be heavily influenced by the strength of selection on the two traits involved.

Admittedly, our literature search may have missed some estimates of the genetic correlations between hormones and life history or performance traits, though notably the range for these estimates was wide for both performance and life history traits (Table S1). Despite several studies estimating the heritabilities of hormone levels in wild species (Pavitt et al., Cox et al., 2016), all our estimates of genetic correlations between hormones and the traits were also conducted in captive populations except one study in wild nestling birds (Ruuskanen et al. 2016). Notably, this latter study was estimating the genetic correlations between hormones in egg yolks and egg mass (Ruuskanen et al., 2016), which are both likely to be heavily influenced by maternal investment. Thus, a crucial objective to test some of the predictions about the role of hormonal pleiotropy in affecting phenotypic responses to selection on any trait is to generate more estimates of genetic correlations between endocrine traits and life history, performance, and other phenotypes in juveniles or adults, as can be done in pedigreed populations (Wilson et al. 2009; Taylor et al. 2012). This is particularly needed in studies that estimate the genetic correlation between a single endocrine trait (such as hormone concentrations) and both a performance and life history trait in the same individuals (we found no such studies). An increased number of studies estimating these genetic correlations from natural populations would help to refine the predictions from our simple model by increasing the precision of our parameter estimates but they may also indicate whether the genetic correlations are attenuated in natural populations, which is likely given the greater degree of environment variability experienced by wild animals.

Ignoring any deficits in our estimates of genetic correlations between hormones and performance and life history traits, our results suggest that hormonal pleiotropy is only likely to constrain or facilitate responses to selection on performance traits when there is a very strong genetic correlation between a hormone and the performance trait (Fig. 3). For example, if selection favors larger individuals with elevated bite force (i.e., positive selection on both the life history and performance traits) and increased testosterone levels enhance size and bite force, the phenotypic response to selection on bite force may be increased but only substantially when the genetic correlation between bite force and testosterone is very high (such as 0.9 in Fig 3). It is possible that this upper estimate of the genetic correlation between a hormone and a performance trait (0.9) is quite rare given that this magnitude of genetic correlation would suggest that variation in a trait was almost entirely due to the concentration of a single hormone (a seemingly unlikely scenario). If increased estimates of the latter in wild populations do suggest that the genetic correlation between hormones and life history or performance traits is typically much weaker, this would further emphasize the rarity in which hormonal pleiotropy would affect the phenotypic responses to selection.

Despite our results suggesting that hormonal pleiotropy can only facilitate or retard phenotypic responses to selection under restrictive conditions, it is still possible. However, if the pleiotropic effects of a single hormone caused strong negative co-variation between two traits, selection should favor the evolution of mechanisms that enable the dissolution of such co-variation if selection favors increases in both traits. For example, exposure to stressors during key developmental periods could decouple any genetic correlations between physiological characteristics such as hormone levels and performance and/or life history traits (Careau et al., 2014). We note that our results suggest that weak genetic correlations between a hormone and

life history or performance trait does not appear to constrain the phenotypic response to selection. As such, it would not be surprising to find that weak genetic correlations between hormones and life history or performance traits are ubiquitous in studies of both captive and wild animals.

Although much research is still needed to understand whether hormonal pleiotropy can constrain the independent evolution of performance and life history traits (Hau, 2007; Ketterson et al., 2009; Swanson and Dantzer, 2014), there is a great need to identify if hormonal pleiotropy can have other evolutionary consequences. Our aim here was to provide a simple framework to spur future research about how hormonal pleiotropy could affect phenotypic responses to selection (see also Ketterson et al. 2005; McGlothlin and Ketterson, 2008; Ketterson et al. 2009). We propose that acquiring four parameters (Fig. 1) using classical quantitative genetics and phenotypic selection approaches can help to increase our understanding of the latter potential consequence of hormonal pleiotropy. Longitudinal studies that measure performance and life history traits in addition to fitness metrics from uniquely-marked individuals could be of great utility here if they also measured some endocrine trait from the same individuals (Fig. 1). Although we recognize the considerable effort to collect the data needed for this approach as well as the substantial statistical power required to obtain reliable estimates of genetic correlations and selection gradients, some well-established study systems may already possess these data. Such studies will be particularly useful to identify whether the predictions stemming from our simple model are supported and could have much broader implications in terms of identifying the evolutionary consequences of pleiotropy caused by physiological mechanisms beyond just endocrine traits (Finch and Rose, 1995).

**Acknowledgements**

We thank Simon Lailvaux and Jerry Husak for inviting us to participate in this symposium and anonymous reviewers for comments on a previous version.

**Supplementary Data**

Supplementary data available at *ICB* online.

**Funding**

Our participation in this symposium was funded by the Society for Integrative and Comparative Biology (Divisions of…), the US National Science Foundation IOS-XXXXXX to S. Lailvaux and J. Husak, and funds from the University of Michigan (B.D).

## References


Adkins-Regan, E. 2008. Do hormonal control systems produce evolutionary inertia? Phil Trans Roy Soc B 363:1599-1609.

Agrawal AF, Stinchcombe JR. 2009. How much do geneti;;c covariances alter the rate of adaptation? Proc Roy Soc B 276:1183-1191.

Careau V, Buttemer WA, Buchanan KL. 2014. Developmental stress can uncouple relationships between physiology and behaviour. Biol Lett 10:20140834.

Cheverud JM. 1984. Quantitative genetics and developmental constraints on evolution by selection. J Theor Biol 110:155-171.

Conner JK, Karoly K, Stewart C, Koelling VA, Sahli HF, Shaw FH. 2011. Rapid independent trait evolution despite a strong pleiotropic genetic correlation. Am Nat 178:429-441.

Cox RM, McGlothlin JM, Bonier F. 2016. Hormones as mediators of phenotypic and genetic integration: an evolutionary genetics approach. Integ Comp Biol 56:126-137.

Dantzer B, Swanson EM. 2012. Mediation of vertebrate life histories via insulin-like growth factor-1. Biol Rev 87:414-429.

Davis ME, Simmen RCM. 1997. Genetic parameter estimates for serum insulin-like growth factor I concentration and performance traits in Angus beef cattle. J Anim Sci 75:317-324.

Emlen DJ, Warren IA, Johns A, Dworkin I, Lavine LC. 2012. A mechanism of extreme growth and reliable signaling in sexually selected ornaments and weapons. Science 337:860-864.

Falconer DS, Mackay FC. 1996. *Introduction to Quantitative Genetics*. Longman, Harlow, UK.

Fairbairn DJ, Yadlowski DE. 1997. Coevolution of traits determining migratory tendency: correlated response of a critical enzyme, juvenile hormone esterase, to selection on wing morphology. J Evol Biol 10:495-513.

Finch CE, Rose MR. 1995. Hormones and the physiological architecture of life-history evolution. Q Rev Biol 70:1-52.

Gu X, Zera AJ. 1996. Quantitative genetics of juvenile hormone esterase, juvenile hormone binding and general esterase activity in the cricket *Gryllus assimilis*. Heredity 76:136-142.

Hau M. 2007. Regulation of male traits by testosterone: implications for the evolution of vertebrate life histories. BioEssays 29:133-144.

Hayhurst C, Flint APF, Løvendahl P, Woolliams JA, Royal MD. 2009. Genetic variation of metabolite and hormone concentration in UK Holstein-Friesian calves and the genetic relationship with economically important traits. J Dairy Sci 92:4001-4007.

Hoque MA, Katoh K, Suzuki K. 2009. Genetic associations of residual feed intake with serum insulin-like growth factor-I and leptin concentrations, meat quality, and carcass cross-sectional fat area ratios in Duroc pigs. J Anim Sci 87:3069-3075.

Irschick DJ, Meyers JJ, Husak JF, Le Gailliard J-F. 2008. How does selection operate on whole-organism functional performance capacities? A review and synthesis. Evol Ecol Res 10:177-196.

Ketterson ED, Nolan V, Jr. 1992. Hormones and life histories: an integrative approach. Am Nat 140: S33-S62.

Ketterson ED, Nolan V, Jr., Sandell M. 2005. Testosterone in females: Mediator of adaptive traits, constraint on sexual dimorphism, or both? Am Nat 166: S85-S98.

Ketterson ED, Atwell JW, McGlothlin JW. 2009. Phenotypic integration and independence: Hormones, performance, and response to environmental change. Integrative and Comparative Biology 49:365-379.

Kingsolver JG, Diamond SE, Siepielski AM, Carlson SM. 2012. Synthetic analyses of phenotypic selection in natural populations: lessons, limitations and future directions. Evol Ecol 26:1101-1118.

Lande R, Arnold SJ. 1983. The measurement of selection on correlated characters. Evolution 37: 1210-1226.

Lynch M, Walsh B. 1998. *Genetics and Analysis of Quantitative Traits*. Sinaeur and Associates, Inc. Sunderland, MA

McGlothlin JW, Ketterson ED. 2008. Hormone-mediated suites as adaptations and evolutionary constraints. Phil Trans Roy Soc B 363: 1611-1620.

McGlothlin JW, Jawor JM, Ketterson ED. 2007. Natural variation in a testosterone-mediated trade-off between mating effort and parental effort. Am Nat 170:864-875.

Morrissey MB, Walling CA, Wilson AJ, Pemberton JM, Clutton-Brock TH, Kruuk LEB. 2012. Genetic analysis of life-history constraint and evolution in a wild ungulate population. Am Nat 179:E97-E114.

Morrissey MB, Sakrejda K. 2013. Unification of regression-based methods for the analysis of natural selection. Evolution 67:2094-2100.

Nkrumah JD, Keisler DH, Crews DH, Jr., Basarab JA, Wang Z, Li C, Price MA, Okine EK,

Moore SS. 2007. Genetic and phenotypic relationships of serum leptin concentration with performance, efficiency of gain, and carcass merit of feedlot cattle. J Anim Sci 85:2147-2155.

Pavitt AT, Walling CA, Pemberton JM, Kruuk LEB. 2014. Heritability and cross-sex genetic correlations of early-life circulating testosterone levels in a wild mammal. Biol Lett 10: 20140685.

Roff DA, Stirling G, Fairbairn DJ. 1997. The evolution of threshold traits: a quantitative genetic analysis of the physiological and life-history correlates of wing dimorphism in the sand cricket. Evolution 51:1910-1919.

Rosvall KA, Bergeron Burns CM, Barske J, Goodson JL, Schlinger BA, Sengelaub DR, Ketterson ED. 2012. Neural sensitivity ot sex steroids predicts individual differences in aggression: implications for behavioural evolution. Proc Roy Soc B 279:3547-3555.

Ruuskanen S, Gienapp P, Groothuis TGG, Schaper SV, Darras VM, Pereira C, de Vries B, Visser ME. 2016. Heritable variation in maternally derived yolk androgens, thyroid hormones and immune factors. Heredity 117:184-190.

Sinervo B, Svensson E. 1998. Mechanistic and selective causes of life history trade-offs and plasticity. Oikos 83:432-442.

Stearns SC. 1989. Trade-offs in life-history evolution. Func Ecol 3:259-268.

Swanson EM, Dantzer B. 2014. Insulin-like growth factor-1 is associated with life-history variation across Mammalia. Proc R Soc B 281:20132458.

Taylor RW, Boon AK, Dantzer B, Réale D, Humphries MM, Boutin S, Gorrell JC, Coltman DW, McAdam AG. 2012. Low heritabilities, but genetic and maternal correlations between red squirrel behaviours. J Evol Biol 25:614-624.

Warren IA, Gotoh H, Dworkin IM, Emlen DJ, Lavine LC. 2013. A general mechanism for conditional expression of exaggerated sexually-selected traits BioEssays 35:889-899.

Wilson AJ, Réale D, Clements M, Morrissey M, Postma E, Walling C, et al. 2009. An ecologist's guide to the animal model. J Anim Ecol 79:13-26.

Zera AJ. 2004. The endocrine regulation of wing polymorphism: state of the art, recent surprises, and future directions. Integr Comp Biol 43:607-616.

Zera AJ, Zhang C. 1995. Direct and correlated responses to selection on hemolymph juvenile hormone esterase activity in *Gryllus assimilis*. Genetics 141:1125-1134.

Zera AJ, Zhang C. 1998. Evolutionary endocrinology of juvenile hormone esterase in *Gryllus assimilis*: direct and correlated responses to selection. Genetics 141:1125-1134.

Zera AJ, Sall J, Schwartz R. 1996. Artificial selection on JHE activity in *Gryllus assimilis*: nature of activity differences between lines and effect on JH binding and metabolism. Archives of Insect Biochemistry and Physiology 32:421-428.

Zera AJ, Sanger T, Cisper GL. 1998. Direct and correlated responses to selection on JHE activity in adult and juvenile *Gryllus assimilis*: implications for stage-specific evolution of insect endocrine traits. Heredity 80:300-309.

**Figure 1.** Overview of model components to identify if hormonal pleiotropy constrains or facilitates phenotypic responses to selection. The environment imposes selection upon performance and life history traits where the relationship between a phenotype (performance or life history trait, etc.) and some fitness metric can be quantified to estimate selection gradients (β). Quantitative genetics can be used to estimate the genetic correlations ($r_g$) between a single hormone and the two phenotypes. These four components make up our simple quantitative genetics model and are obtainable from longitudinal individual-based studies of wild animals.

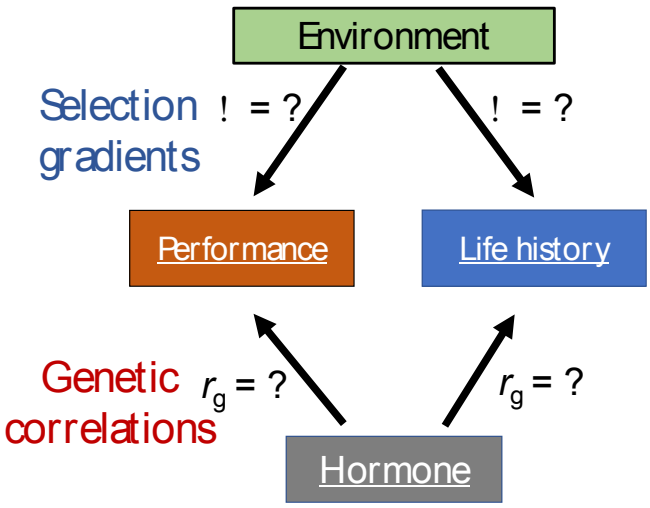


**Figure 2.** Hormonal pleiotropy can constrain or facilitate the response to selection depending upon the strength and sign of the genetic correlation between the hormone and the life history and performance traits and selection acting on each trait. Here, the model assumes that the performance trait experiences positive selection (Irshick et al. 2008) and there is a positive genetic correlation between the hormone and that performance trait. For example, individuals with faster sprint speeds are more likely to survive and a hormone such as testosterone enhances the expression of sprint speed (i.e., positive genetic correlation between testosterone and spring speed). If the same hormone influences a life history trait, selection on performance may be facilitated or constrained depending upon the sign and magnitude of both i) the genetic correlation between the hormone and the life history trait and ii) the selection gradient acting on the life history trait. For instance, if the same hormone enhances the expression of the life history trait (positive genetic correlation between the hormone and life history trait) and there is positive selection on the life history trait (upper right area in panel), the response to selection on performance would be facilitated. In contrast, if increases in the hormone (testosterone) enhance the expression of the life history trait (positive genetic correlation between the hormone and life history trait) but there is negative selection on the life history trait (bottom right area of figure), the response to selection on performance may be constrained. In this model, we varied both the

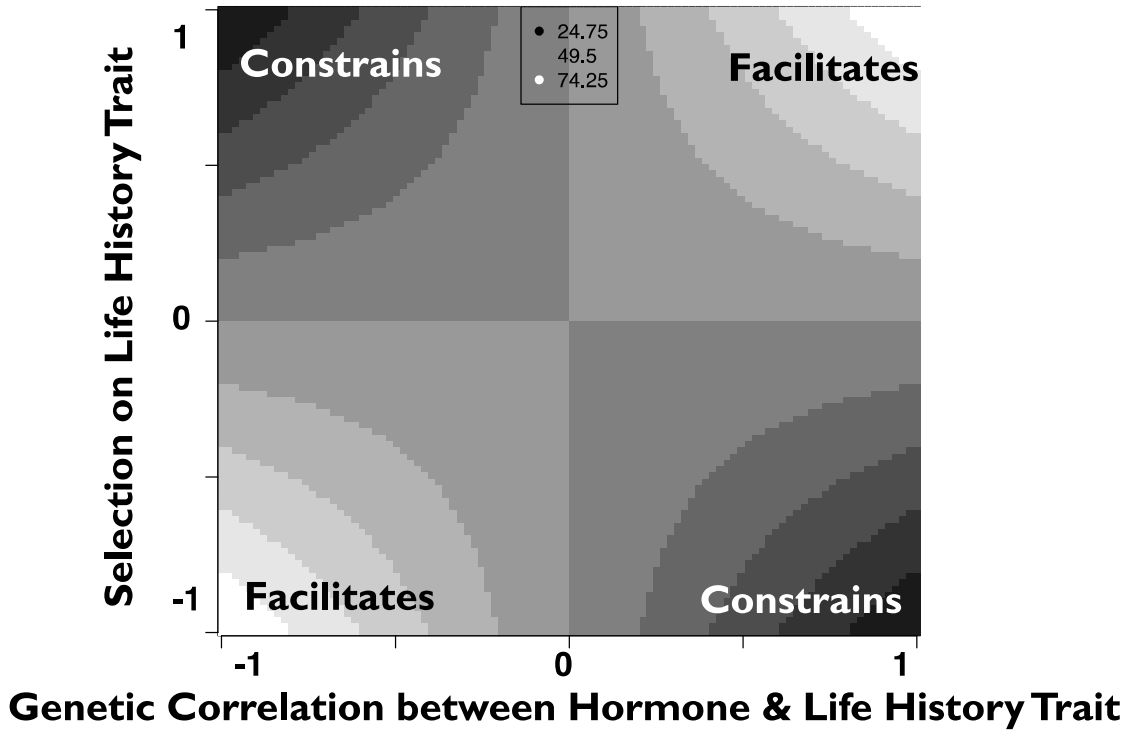
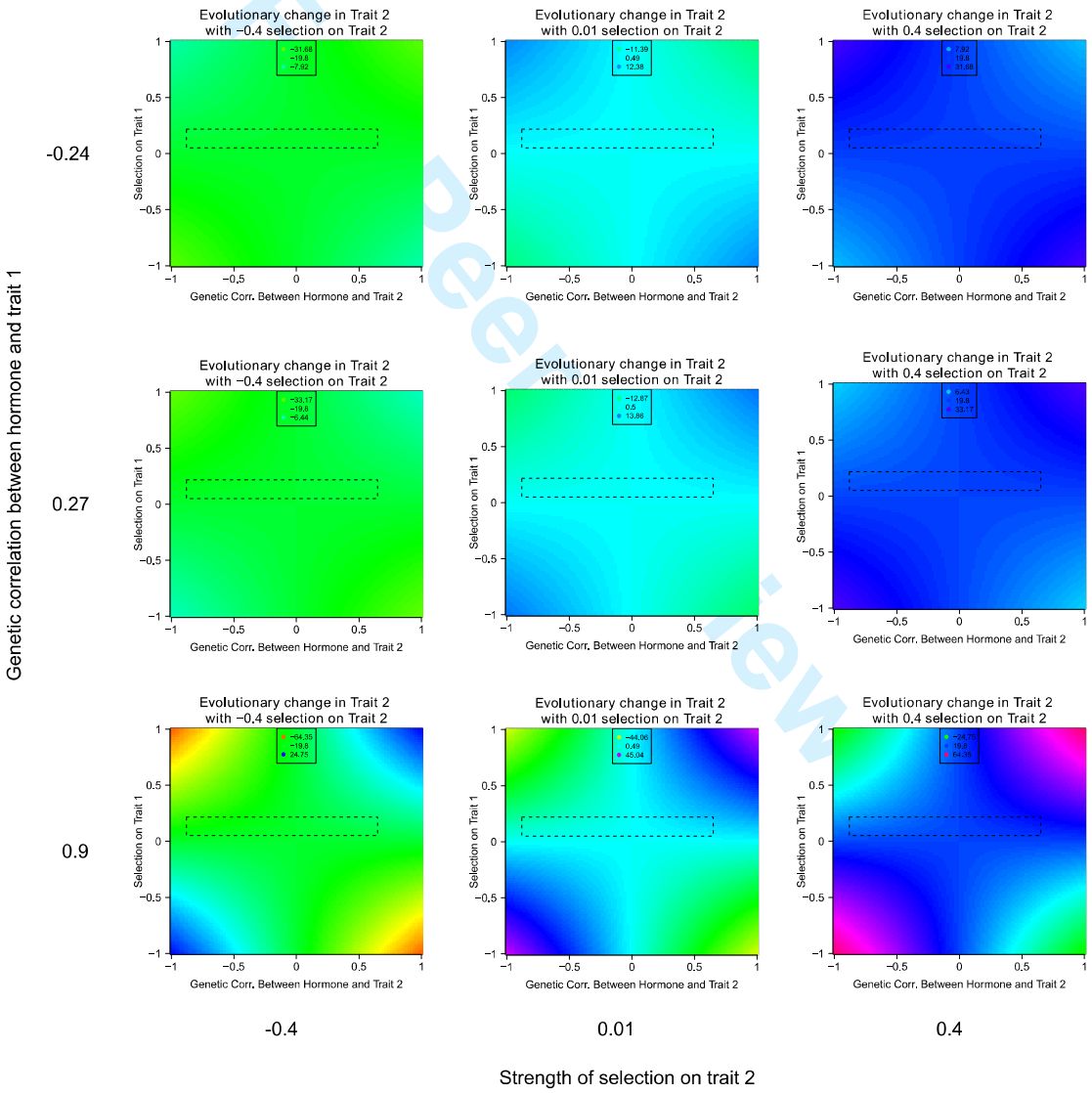


**Figure 2.** Color maps showing the magnitude of change in a performance trait after 100 generations of evolution. Each sub-plot has an independent x-axis that represents the genetic correlation between the hormone and the life history trait, and an independent y-axis that represents variation in strength of selection on the life history trait. Panels **A-C** were run with a genetic correlation between the hormone and the performance trait of -0.24, d-f of 0.27, and **G-I** 0.9. Panels **A**, **D**, and **G** exhibit a strength of selection on the performance trait of -0.4, **B**, **E**, and **H** of 0.01, and **C**, **F**, and **I** of 0.4. Each sub-plot has a legend showing the color for the minimum, mean, and maximum value for that sub-plot, but the colors in each plot have the same meaning. The dashed lines making up boxes on each plot are in the same place, and represent values for these parameters from existing literature (Table S1).



679

680

**Table S1.** List of studies that have estimated the genetic correlation between a hormone and life history or performance traits. We gathered a non-exhaustive list of those studies that have estimated the genetic correlation between a hormone or hormone derivative (Juvenile Hormone esterase) and performance and life history traits. Given the extreme rarity of studies investigating genetic correlations between hormones and performance traits, performance traits were broadly defined including the presence or absence of wings (wing polymorphism in crickets) and daily feed intake in pigs. We recognize that growth could be categorized as either a life history trait or performance trait but here we adhered to the former. Note that in some cases there are multiple estimates from the same study because the estimates were made either from the dam or sire. To generate this list, we searched Web of Science (December 2016) using a combination of keywords including "genetic correlation", "phenotypic correlation", "hormone", "endocrine", "heritability", "quantitative genetics", "performance", and "life history". We also conducted forward and backward searches using those sources we located using this initial search. The mean and SE of the genetic correlation (SE not shown if not available).

| Taxa | Species | Hormone | Life History Trait | Performance Trait | Sex | Genetic Correlation | Reference |
|---|---|---|---|---|---|---|---|
| Insect | *Gryllus firmus* | Juvenile hormone esterase | Fecundity | - | F | -0.88 ± 0.36¶ | Roff et al. (1997) |
| | *Gryllus firmus* | Juvenile hormone esterase | Fecundity | - | F | -0.5 ± 0.23* | Roff et al. (1997) |
| | *Gryllus firmus* | Juvenile hormone esterase | - | Wing polymorphism | F | 0.9 ± 0.20* | Roff et al. (1997) |
| | *Gryllus firmus* | Juvenile hormone esterase | - | Wing polymorphism | F | 0.28 ± 0.44¶ | Roff et al. (1997) |
| Bird | *Parus major* | Androstenedione | Egg mass | - | F | 0.65 ± 0.35 | Ruuskanen et al. (2016) |
| | *Parus major* | Testosterone | Egg mass | - | F | 0.33 ± 0.34 | Ruuskanen et al. (2016) |
| | *Parus major* | Triiodothyronine | Egg mass | - | F | 0.34 ± 0.43 | Ruuskanen et al. (2016) |
| Mammal | *Sus scrofa domesticus* | Insulin-like growth factor 1 (IGF-1) | - | Daily feed intake | M+F | 0.17 ± 0.07# | Hoque et al. (2009) |
| | *Sus scrofa domesticus* | Insulin-like growth factor 1 (IGF-1) | - | Daily feed intake | M+F | -0.24 ± 0.08§ | Hoque et al. (2009) |
| | *Sus scrofa domesticus* | Leptin | - | Daily feed intake | M+F | 0.26 ± 0.06 | Hoque et al. (2009) |
| | *Bos taurus* | Growth hormone | Calving interval | - | F | 0.64 ± 0.3 | Hayhurst et al. (2009) |
| | *Bos taurus* | Leptin | Growth | - | M | 0.05 ± 0.28 | Nkrumah et al. (2007) |
| | *Bos taurus* | Insulin-like growth factor 1 (IGF-1) | Growth | - | M+F | -0.4 | Davis and Simmen (1997) |

¶Estimate from sire
*Estimate from dam
#IGF-1 measured at 8 weeks
§IGF-1 measured when 105 kg