INTEGR. COMP. BIOL., 43:419–430 (2003)

Physiological Epistasis, Ontogenetic Conflict and Natural Selection on Physiology and Life History[1]

BARRY SINERVO[2,*] AND RYAN CALSBEEK†

*Department of Ecology and Evolutionary Biology, University of California, Santa Cruz, California 95064
†Center for Tropical Research, Institute of the Environment, 1609 Hershey Hall, University of California, Los Angeles, California 90095

SYNOPSIS. Ontogenetic conflict arises when optima for alleles governing fitness variation differ between juveniles and adults or between adult sexes. Loci that govern development of alternative phenotypes in the sexes, hereafter termed morph-determining loci, mediate development through the endocrine system. Morphotypic selection is defined to be multivariate selection favoring discrete alternative morphotypes (*e.g.*, optima). When the optimal combinations of alleles for alternative morphs differ between the sexes, it generates conflicting selection pressure and thus ontogenetic conflict. Selection on morph alleles promotes ontogenetic conflict because it perturbs physiological epistasis that governs the expression of male *versus* female traits. Expression of physiological traits arises from homeostasis that maintains trait expression within a normal range. The genetic basis of homeostasis is likely to arise from interactions among several genes (*e.g.*, genetic epistasis) or protein products (*e.g.*, physiological epistasis). For example, endocrine regulation arises from interactions between gondatropins, which are protein hormones produced by the hypothalamic-pituitary glands, and steroid hormones, which are produced by the gonads (*e.g.*, HPG axis). The side-blotched lizard system is discussed with respect to physiological bases of ontogenetic conflict. We also describe a novel molecular marker strategy for uncovering genome-wide physiological epistasis in nature. Finally, ontogenetic conflict exerts selection on females to evolve mate selection or cryptic choice that is reflected in different sires being chosen for son *versus* daughter production. We describe how side-blotched lizard females ameliorate ontogenetic conflict by cryptic choice of male genotypes to produce sons *versus* daughters.

INTRODUCTION

Life history trade-offs within versus *between the sexes*

Life history theory focuses on trade-offs between traits and optimal combinations of traits within the constraints imposed by such trade-offs. Life history ecologists focus on the study of female trade-offs to test natural selection theory. Behavioral ecologists focus on the study of male trade-offs to test sexual selection theory. However, adaptation of physiology is not only subject to the genetic constraints imposed on reproduction of a single sex, but also the genetic constraints expressed between the sexes (Sinervo and Svensson, 1998; Svensson and Sheldon, 1998). Recently, a paradigm for dealing with such between-sex trade-offs has emerged that has been termed ontogenetic conflict (Chippindale *et al.*, 2001; Rice and Chippindale, 2001).

Ontogenetic conflict refers to life history trade-offs that span juvenile and adult phases or trade-offs between adult males and females. Ontogenetic conflict arises when fitness optima for alleles governing male traits differ from those of females, or when fitness optima of adults differ from juveniles (Chippindale *et al.*, 2001; Rice and Chippindale, 2001). Such differences in optima between the sexes arise from genetic interactions between sex-determining loci (often located on sex chromosomes) and loci involved in the expression of male and female traits (Gibson *et al.*, 2002). Ontogenetic conflict is a special case of physiological epistasis, which arises from interactions between the gene products of two or more loci (Sinervo and Svensson, 2003). For example, gonadotropins that are produced by the hypothalamic-pituitary gland stimulate secretion of gonadal steroids (Licht *et al.*, 1974; Padmanabhan *et al.*, 2002). Gonadotropins are in turn regulated by gonadal sex steroids (Fig. 1). This feedback loop results in negative regulation that generates endocrine homeostasis. Any genes that are regulated by steroids will not be over-expressed given that production of these steroids declines when plasma levels of the steroids climb to high levels. This negative feedback loop is a 'thermostat' that regulates steroid levels during reproduction. Levels of sex steroids are also regulated by interactions with other endocrine axes, most notably steroid hormones like the adrenal glucocorticoids (Mazzocchi *et al.*, 1998) (Fig. 1), which regulate environmental stressors (Denver, 2000). Selection dictates the degree of trait expression in each sex and thus the evolution of steroid homeostasis.

While gonadotropins are common to both sexes, they differentially secrete the steroids testosterone [T] and estrogen [E] allowing different traits to be expressed at sexual maturity. These two steroids affect the development of sexual traits via sex-limited gene expression (Freedman and Luisi, 1993; Zajac and Chilco, 1995; Sanchez *et al.*, 2002). This cascade of endocrine regulation reflects the physiological epistasis of sex determining loci, genes controlling gonadotro-

[1] From the Symposium *Selection and Evolution of Performance in Nature* presented at the Annual Meeting of the Society for Integrative and Comparative Biology, 4–8 January 2003, at Toronto, Canada.

[2] E-mail: sinervo@biology.ucsc.edu

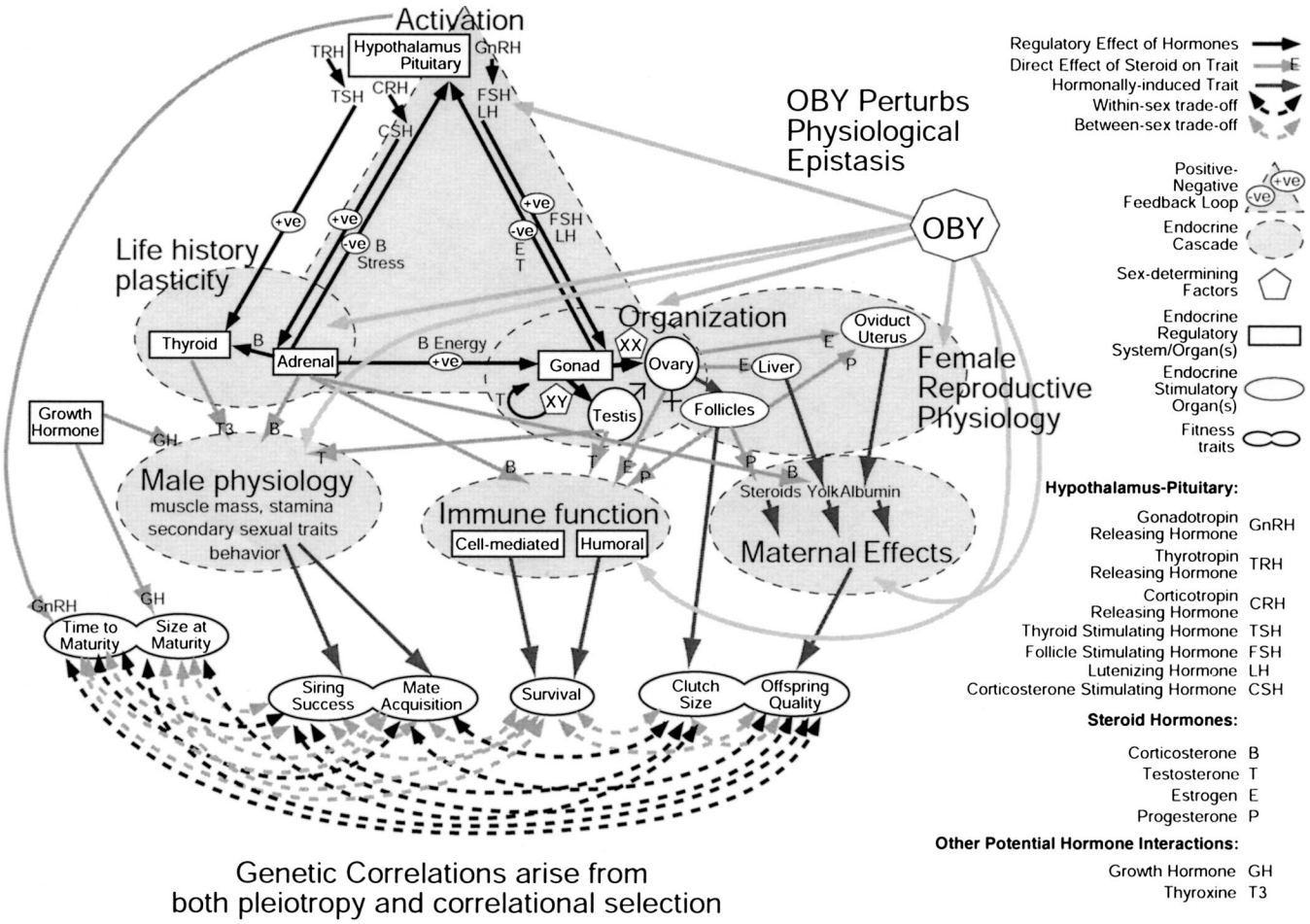

FIG. 1. Graphical depiction of the physiological epistasis arising from the vertebrate endocrine system and hypothesized effect of the OBY locus on endocrine regulation, based on the traits it is known to affect in *Uta* (*e.g.,* clutch size, egg mass, immune function, behavior, plasma hormones). The top triangle depicts the Hypothalamic-pituitary-gonadal (HPG) axis and Hypothalamic-pituitary-adrenal-gonadal (HPAG) axis. See text for a description of the hormone cascade. The endocrine system has control over loci that govern physiological and life history traits specific to male physiology and female reproductive physiology, which contribute to fitness (bottom of the figure). These mechanisms of endocrine regulation are also responsible for genetic correlations observed within each sex (*e.g.,* life history tradeoffs) and between the sexes (*e.g.,* ontogenetic conflict). Note steroid hormone interactions between the gonads and adrenal system can be viewed as life history plasticity generating machinery (Sinervo and Svensson, 2003; Denver, 2000). In principle, epistasis can also extend to the traits governed by other endocrine interactions such as the thyroxine system or growth hormones, but such genetic links have not yet been shown for side-blotched lizards.

pins, and sex steroid-induced gene expression of male and female traits.

Consider sex differences in yolk production by females but lack of yolk production by males (Fig. 1). In females, E produced by ovarian follicles induces RNA transcription and translation of vitelloproteins in the liver (Ho *et al.*, 1982). Males normally lack high levels of plasma E and hence the capacity to produce vitelloprotein, but they can be induced to do so by experimentally increasing levels of E (Ho *et al.*, 1982). This potential ontogenetic conflict sexes is alleviated by female-limited steroidal regulation of vitelloproteins (*i.e.,* E). Consider the converse situation of more muscle mass in males *versus* females. T produced in the testis travels to target cells in the body and alters gene expression (Fig. 1). In the musculoskeletal system, T has two sets of target tissues: motor muscle development and muscle development of secondary sexual traits such as male vocal structures (Arnold, 1994; Whaling *et al.*, 1995; Van Duyse *et al.*, 2002). The tissue-specific effects of sex steroids act in association with enzymes that metabolize one steroid hormone into another. For example in birds, the localized activity of aromatase in the male brain converts E to T and results in development of song centers (Arnold, 1994). Females lack high levels of aromatase in the brain and hence the capacity for development of male traits such as the song center. However, these structures can be induced in females with exogenous T (Arnold, 1994) as can dimorphic male plumage (Lank *et al.*, 1999).

Potential ontogenetic conflict of the sexes is alleviated by sex-limited gene expression via steroid ''switches'' that control the development of diverse

physiological, morphological and neuroanotomical traits. Sex-specific steroid effects reflect the physiological epistasis considered by Wright (1968): while important to fitness, the epistasis is genetically fixed in most species. Males and females express sex-specific traits owing to these endocrine regulatory networks.

The origin of such physiological homeostasis is a more general evolutionary problem that was treated by Sewall Wright, J. B. S. Haldane, and Ronald Fisher (Provine, 1971). Each of these pioneers of the Neo-Darwinian synthesis had a different explanation for the evolution of genetic dominance. The evolution of dominance deals with the problem of physiological homeostasis in a situation where recessive alleles are deleterious, wild type alleles are normal, but heterozygous individuals with only one functional copy of an allele are also normal (*e.g.*, same phenotype as the wild type). This implies regulation of gene expression in circumstances with one *versus* two functional copies of the allele, a form of genetic homeostasis. Physiological epistasis is the multilocus analog of homeostasis associated with dominance. In the case of physiological epistasis heterozygous allele combinations at many loci interact to produce non-linear effects on traits relative to homozygous combinations at these loci. Indeed, Wright's explanation for the evolution of dominance involved physiological epistasis or interactions between regulatory loci and those traits exhibiting dominance variation (Provine, 1971).

During steroidal regulation of male *versus* female development, physiological epistasis appears to be largely fixed. Males do not usually express female traits. Interestingly, females often express some degree of secondary sexual traits of males suggesting that there might be genetic correlations between the sexes in endocrine regulation of these sex-limited traits. One hypothesis to explain some expression of male secondary traits in females is that during the process of sexual selection, assortative mating can transiently fuel a build-up of the epistasis in the endocrine networks that contribute to the expression of secondary sexual traits.

Epistasis is a minor component of genetic variation in most populations at evolutionary equilibrium (Whitlock *et al.*, 1995; Goodnight, 1995). In most populations, dominance and additive variation comprise the major portions of genetic variation that is shaped by selection. Additive variation is that portion of the genetic variance that contributes to narrow sense heritability or the genetic resemblance between parents and offpring (Lynch and Walsh, 1998). Other situations besides sexual selection can fuel a build-up of physiological epistasis, which also generates fitness epistasis. Fitness epistasis is an interaction between two or more loci that has non-linear effects on fitness (*e.g.*, non-additive). Fitness epistasis can result from the process of correlational selection in which multivariate trait combinations are simultaneously selected at several loci (Sinervo and Svensson, 2002) (Fig. 2). Discrete morphs present a situation in which correlational selection is strong, resulting in fitness epistasis. Fitness epistasis also occurs at contact zones between species where low-fitness hybrid progeny with heterozygous combinations of each species genomes are disfavored by selection. In such situations, assortative mating within species is favored, which reinforces and intensifies the strength of fitness epistasis.

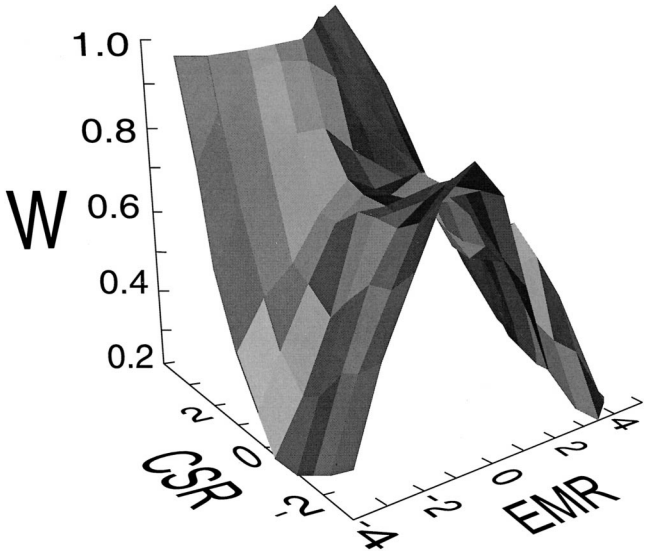

FIG. 2. Correlational selection favors optimal combinations of clutch size and egg mass in *Uta* that are in opposite corners of the fitness landscape (residuals computed about the trade-off between clutch size and egg mass; from Sinervo, 2000).

Uncovering the physiological bases of epistasis in morphs

Aside from these exceptions, physiological homeostatic networks within most species are—fixed genetically and are thus, difficult to study. However, intraspecific morphs provide an avenue for studying epistasis and physiological networks governing evolution of homeostasis. The physiological epistasis of endocrine regulation in polymorphic taxa is perturbed relative to monomorphic taxa, which generates fitness epistasis (Fig. 1). Fitness epsitasis arises because morphs with heterozygous multilocus allele combinations have low fitness while those with homozygous combinations have high fitness (Sinervo and Clobert, 2003), a process similar to speciation at hybrid zones (Sinervo and Svensson, 2002). A classic morph fitness surface has optima in opposing corners, but low fitness elsewhere on the fitness landscape (Fig. 2).

Ontogenetic conflict between the sexes arises in situations with alternative sexual strategies because sexual selection chronically favors a build-up of genetic covariation that enhances male function even if it negatively affects female function. However, average fitness from male and female function will be equal in a population because all offspring have a mother and a father. Thus, alternative morphs that enhance male fitness, but reduce female fitness, must be balanced by

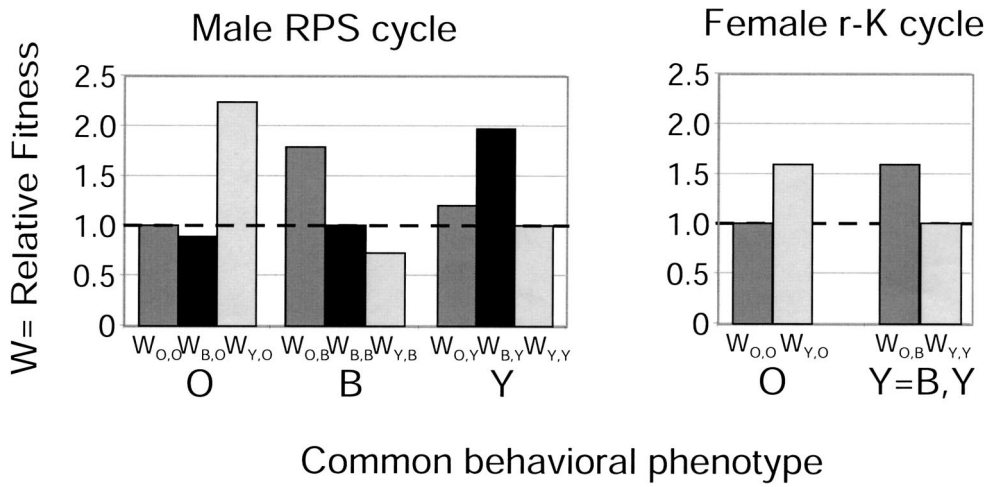

FIG. 3. A) Payoffs to rare **Y**, **B**, and **O** male strategies playing against common strategies. Male payoffs were calculated from siring success (Zamudio and Sinervo, 2000; Sinervo 2001*a*). B) Payoffs for rare **Y**/**B**, and **O** female strategies playing against each common strategy (*e.g.*, in boom versus crash years) (from Sinervo *et al.*, 2000*b*). Three different optima (high-payoff strategies) are present for males in the RPS mating system (*e.g.*, when O, B, Y), but only two optima are present for females in the r-K cycle. The difference in number of optima between the sexes is a form of ontogenetic conflict.

other strategies that enhance female fitness, but decrement male fitness.

The side-blotched lizard, *Uta stansburiana*, exhibits conspicuous female and male morphs (Sinervo, 2001*a*). Furthermore, fitness optima of the morph genotypes differ between the sexes (Fig. 3). Here we argue that a study of the complex mating system of *Uta*, reveals general processes of ontogenetic conflict faced by all organisms, which only express the simple set of morphs, namely juveniles, males, and females. While we restrict discussion of how selection on morphs perturbs the physiological epistasis of endocrine regulation of animals, the same effects will be true in plants because alternative pollination morphs have long been recognized as alternative sexual strategies (Darwin, 1871). In principle, within-species morphs could be used to study homeostasis in other physiological networks such as behavioral thermoregulation or metabolism if suitable model species with alternative morphs for these physiological processes are found. This could form a new direction for studies on natural selection of physiological traits.

Genetic consequences of alternative morph optima and ontogenetic conflict

As noted above, endocrine regulation is well coordinated when the number of morphs in a life history is restricted to the set consisting of male and female phases. However, in situations where there are alternative reproductive strategies within one sex, there is likely to be chronic misalignment of allelic fitness optima between the sexes (Fig. 3). In addition, multiple fitness peaks associated with male and female morphs maintain genetic variation of the sexes in a chronic state of selection (Fig. 2). This is because genetic variation of morph-determining loci interacts epistatically with genes located on autosomes as well as with sex-determining loci on the sex chromosomes. Unfortunately, at meiosis, recombination and segregation mixes up these optimal combinations built up by correlational selection (Sinervo and Svensson, 2002) because the loci are distributed on many chromosomes. However, each generation, a new round of correlational selection on the morphs rebuilds multivariate trait combinations eroded by meiosis.

For more detail on these genetic processes, we refer interested readers to companion review papers including: Sinervo (2001*a*, *b*) that describe how alternative strategies generate frequency dependent selection, Sinervo and Svensson (2002) that describes how frequency-dependent selection generates correlation selection, and Sinervo and Svensson (2003) that describes how correlational selection on endocrine regulation generates epistatic selection. This paper extends these ideas by showing how correlational selection promotes intense ontogenetic conflict between the sexes that appears to act on the endocrine regulation of reproductive traits.

DETECTING SELECTION ON ONTOGENETIC CONFLICT IN NATURE

Trade-offs within the sexes

To understand trade-offs between the sexes it is first necessary to understand trade-offs within each sex. We refer the reader to our work on the side-blotched lizard in which many of the mechanisms underlying trade-offs have been verified with experimental manipulations of endocrine traits (Sinervo and Basolo, 1996). Life history trade-offs of females arise from selection on optimal allocation to offspring size versus quality and the additional life history trade-off that involves investment in current versus future reproduction (cost of reproduction) (Sinervo, 1999; Reznick *et al.*, 2000).

In males, sexually selected trade-offs arise from number of mates balanced against number of sired progeny in the context of sperm competition, which is related to male strategies of territory defense (Zamudio and Sinervo, 2000, 2002; Sinervo *et al.*, 2000*a*).

The costs-of-reproduction trade-off noted above for females applies to males. Investment in future reproduction over current reproduction implies a linkage with maintenance physiology. The immune system provides a physiological link for this trade-off (Sinervo and Svensson, 1998). To survive to future reproductive episodes individuals must keep infections in check. Reproduction in males is thought to be costly because T favors development of elaborate ornaments that draw resources away from immune function (Folstad and Karter, 1992). Likewise, elevated levels of corticosterone [B], which is related to stress maintenance and regulation of energy during reproduction, may depress immune function (Lochmiller and Dabbert, 1993). We have verified salient aspects of this theory for female *Uta*. The stress hormone B differentially affects the survival of two female morphs (Comendant *et al.*, 2003) through effects on immune function (Svensson *et al.*, 2002*a*, *b*, 2003) (Fig. 3). Effects of B on immune function arise from socially-induced stresses and crowding (Svensson *et al.*, 2002*a*, *b*, 2003: Comendant *et al.*, 2003).

Genetics of reproductive strategies in male and female morphs of Uta

Male side-blotched lizards exhibit a three-morph strategy set that we have analogized with the children's rock-paper-scissors (RPS) strategy set (Sinervo and Lively, 1996). Males with orange throats express an ultra-dominant territorial strategy (O), high plasma T, high stamina, and low inter-annual survival (Fig. 4) (Sinervo *et al.*, 2000*a* Sinervo and Lively, 1996). Blue males also express a territorial strategy (B) but with smaller average territory sizes, intermediate plasma T and intermediate stamina. Yellow-throated males (Y) are not territorial, but possess a large home range and exhibit low plasma T and low stamina. These morphs are arrayed along the trade-offs noted above for males regarding mate acquisition versus siring success (*e.g.*, success in sperm competition). Strategically, orange males usurp territory from blue males (Calsbeek *et al.*, 2002), but their wide-ranging strategy makes them susceptible to cuckoldry by the strategy of yellow males (Zamudio and Sinervo, 2000). Yellow males are morphologically similar to females (in back pattern and throat color), exhibit female mimicry behavior, and are very cryptic when moving through their home range.

O males are quite successful against the strategy of B males owing to the high resource usurping potential of O (Calsbeek and Sinervo, 2002*a*, *b*). B males mate-guard their females and are successful against Y males even though B males loose in contests with O. Furthermore, B males cooperate in territory defense to thwart Y sneakers (Sinervo and Clobert, 2003). However, the O male strategy with a huge territory is vulnerable to the sneaky strategy of Y males. Thus, O beats B, Y beats O, and B beats Y in a rock-paper-scissors cycle (RPS = OYB) (Sinervo, 2001*a*, *b*).

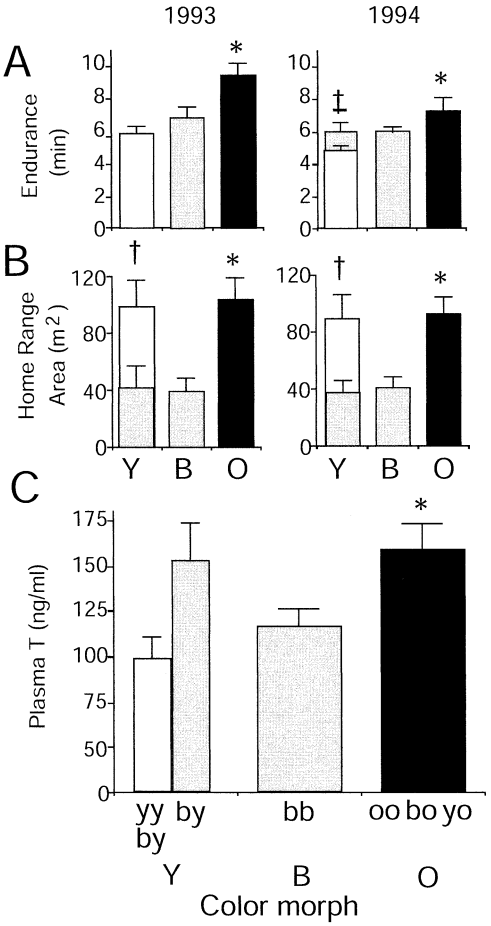

FIG. 4. Compared to yellow- (white and shaded bars) or blue-morphs (shaded bars) of male *Uta*, orange morphs (solid bars) of male *Uta* have significantly higher A) endurance performance as measured on a laboratory treadmill, larger B) home ranges (m^2) in the wild, and higher plasma T. Two histograms are shown for yellow males where tests indicated a significant difference ''before'' (open) *versus* ''during'' (shaded) transformation of *by* genotype males from the Y to B strategy [*e.g.*, endurance (‡), home range area (†), plasma T *]. The plasticity of *by* male genotypes is more thoroughly described in Sinervo, 2001*a*.

Laboratory breeding studies (Sinervo *et al.*, 2001) indicate that a single locus model readily explains the 6 color genotypes (Table 1): *oo*—bright orange throat and flanks, *bb*—dark blue throat, *yy*—solid yellow throat, *bo*—dark blue with orange stripes and light orange flanks, *by*—pale blue with yellow stripes, *yo*—pale yellow and pale blue throat with light orange flanks. Indeed the heritability of color axes from sire to son are nearly one (Sinervo *et al.*, 2001; Sinervo and Svensson, 2002) indicating purely additive effects of the three color components (o, b, y) in both field pedigrees (Sinervo and Zamudio, 2001; Sinervo, 2001*a*) and laboratory mating studies (Sinervo *et al.*, 2001) (Table 1). We refer to this locus as OBY. The O strategy consists of *oo*, *bo*, and *yo*, while the B

TABLE 1. *Heritability and genetic correlations for various life history and morphological traits that we have measured in free-ranging* Uta *and in controlled laboratory crosses*.*

Trait(s)	Familial relationship	Genetic parameter	Source
Clutch size	dam-daughter	$h^2 = 0.62$	Sinervo, 2000
Egg mass	dam-daughter	$h^2 = 0.58$	Sinervo, 2000
Antibody responsiveness	dam-daughter	$h^2 = 0.88$	Svensson *et al*., 2001*b*
Clutch size and egg mass	dam-daughter	$G = -0.92$	Sinervo, 2000
O color	dam-daughter	$h^2 = 0.48$	Sinervo *et al*., 2000*b*
O color and clutch size	dam-daughter	$G = 1.09$	Sinervo *et al*., 2000*b*
O color and egg mass	dam-daughter	$G = -0.84$	Sinervo *et al*., 2000*b*
O color and antibody response	dam-daughter	$G = -1.36$	Svensson *et al*., 2001*b*
Orange color in field pedigrees	sire-son	$h^2 = 1.24$	Sinervo and Zamudio, 2001
	sire-daughter	$h^2 = 0.88$	
O color in crosses	sire-progeny	$h^2 = 1.06$	Sinervo *et al*., 2001
	dam-progeny	$h^2 = 0.86$	
B color crosses	sire-progeny	$h^2 = 1.40$	Sinervo *et al*., 2001
	sire-son	$h^2 = 1.00$	
	sire-daughter	$h^2 = 1.80$	
O and B color in crosses	sire-progeny	$G = -1.01$	Sinervo *et al*., 2001

* See Sinervo *et al*. (2001) for further details on additive regression models of color expression (*e.g.*, O versus B versus Y color scales).

strategy consists of *bb*, and the Y strategy consists of *yy* and *by* genotypes.

Color on the sire's throat is likewise genetically correlated with daughter's throat color (Sinervo and Zamudio, 2001; Sinervo *et al.*, 2001) (Table 1). Dam-son pedigrees indicate that the converse genetic correlations are large (Sinervo *et al.*, 2001; Sinervo and Svensson, 2002; Sinervo, 2001*a*). Thus, the OBY locus gives rise to morphs in both sexes. Females exhibit the same 6 color genotypes seen in males. However, while males have 3 phenotypic strategies (*e.g.*, RPS), females only have 2 strategies (Sinervo *et al.*, 2000*b*). Females can be categorized as either r-strategists if they possess at least 1 *o* allele (Sinervo *et al.*, 2000*b*), and K-strategists if they possess *b* or *y* alleles (Sinervo *et al.*, 2000*b*). The O female strategy consists of *oo*, *bo*, and *yo* genotypes, while the Y strategy consists of *bb*, *by*, and *yy* genotypes. O females lay large clutches of small eggs. The small progeny of O females survive well at low density, but poorly at high density (Sinervo *et al.*, 2000*b*). Y females lay small clutches of large eggs. The large progeny of Y females survive well at high density. Female morphs cycle with a 2-year phase, which is autocorrelated with a density cycle. Frequency of O females crashes when the population transitions from high density to low density, but immediately rebounds the next year. During this rebound, the carrying capacity of adults on the outcrop is exceeded the following year, which triggers a new population crash (Sinervo *et al.*, 2000*b*; Sinervo, 2001*a*).

A simple way to envision ontogenetic conflict due to the OBY locus is to note that in the long-run (averaged across the male cycle) there are 3 fitness optima in the male strategy set (OBY) (Sinervo, 2001*a*), but only 2 fitness optima in the female strategy set (Sinervo *et al.*, 2000*b*) (Figs. 2, 3). The distinct strategy of *bb* genotypes (*e.g.*, B) of males is lumped in with *by* and *yy* genotypes in the female strategies (*e.g.*, Y). Presence of 3 optima in males and only 2 optima in females generates ontogenetic conflict between the sexes. This mismatch in male and female optima generates intense ontogenetic conflict between the sexes (Alonzo and Sinervo, 2001). Females cycle through 2 strategies in a rapid 2-year cycle. Males cycle through 3 strategies in a slower 4 to 5-year male cycle. Genetic models of 1 locus with 3 alleles for the 3 male strategies (*oo*, *bo*, *yo* = O, *bb* = B, *by*, *yy* = Y) and 2 female strategies (*oo*, *bo*, *yo* = O, *bb*, *by*, *yy* = Y) are capable of producing 4-year RPS cycle of males and 2-year r-K cycle of females (Sinervo, 2001*a*). The genetic cycles arise from ontogenetic conflict. The more rapid 2-year cycles of the female game destabilizes male genotype frequencies from the stable frequency for the RPS game (attractor), thereby generating perpetual cycles in both sexes (Alonzo and Sinervo, 2001). Modeling has also shown that other genetic systems (e.g., where OBY is sex-linked; or due to 2 loci) are incompatible with rapid 2- and 4-year cycles of the sexes (Sinervo, 2001*a*). Only one-locus models are capable of reproducing the 2- and 4-year cycles of female and male morphs.

Direct genetic evidence of this conflict can be seen in the extremely low survival of female versus male progeny from *bb* male genotypes, which greatly distorts heritability estimates of the sexes on the B color scale (Table 1 and Appendix, Sinervo *et al.*, 2001). Moreover, *bb* male genotypes that cooperate in territory defense can have three times higher fitness compared to *bb* male genotypes that do not find a genetically suitable territorial partner (Sinervo and Clobert, 2003). No such advantage has been identified for *bb* females (Sinervo *et al.*, 2001). Thus, *bb* genotypes have high fitness in males but low fitness in females, a form of ontogenetic conflict.

Alternative morph alleles perturb endocrine regulation of the sexes

How is the endocrine system involved in the male and female strategies and how does it promote onto-

TABLE 2. *Examples of correlational selection gradients (γ's) acting on pairs of traits that have been estimated in natural populations of* Uta.

Traits	γ	Source
Color and immunocompetence	−0.365	Svensson *et al*., 2001*b*
Color and clutch size	0.397	Sinervo *et al*., 2000*b*
Color and egg mass	−0.487	Sinervo *et al*., 2000*b*
Clutch size and egg mass:		
Progeny survival	−0.306	Sinervo *et al*., 2000*b*
Adult survival	−0.261	Sinervo, 2000
Color and male dispersal and settlement behavior	0.56	Sinervo and Clobert, 2003

genetic conflict? We hypothesize that intense correlational selection on morph loci perturbs physiological epistasis of endocrine regulation. As noted above, endocrine regulation arises from loci distributed on many chromosomes. Thus, fitness epsistasis is generated from recombination and segregation, which erodes optimal combinations built up by correlational selection. The variation in physiological traits among the morphs, which are under correlational selection, are controlled by different levels of steroids. Steroids generate sex-specific effects, but males and females also share aspects of endocrine regulation in common (*e.g.*, GnRH, FSH, LH).

What evidence is available that morph loci interact with loci governing reproduction of the sexes? Clutch and egg size strategies of female morphs are subject to the offspring size and number trade-off. Clutch and egg size variation are under correlational selection with female morphs (Table 2). Any loci that contribute to genetic variation in clutch and egg size (Table 1) will be under chronic correlational selection with the OBY locus, thereby intensifying genetic correlations between OBY, clutch size and egg mass. Manipulative experiments indicate that follicle-stimulating hormone (FSH) simultaneously governs clutch size and egg mass (Sinervo and Licht, 1991; Sinervo and DeNardo, 1996; Sinervo, 1999, 2000) (Fig. 1). Thus, regulatory mechanisms of FSH should also be under correlational selection with OBY.

FSH also triggers gonadal growth in males and LH is responsible for steroidogenesis and spermatogenesis (Licht, 1970, 1972) (Fig. 1). In lizards, the precise role of lutenizing hormone (LH) remains to be elucidated, because until very recently (Desantis *et al.*, 1998, 2000) it was thought that lizards lacked LH (Licht *et al.*, 1977). FSH and LH are regulated by GnRH (Phillips *et al.*, 1987; Padmanabhan *et al.*, 2002) (Fig. 1). Regardless of the precise mechanisms regulating gonadotropins among morphs of *Uta*, plasma T varies among the male morphs of side-blotched lizards (Fig. 4). This implies some differences in the regulation of T among the morphs such as in sensitivity of LH or FSH stimulation, or perhaps GnRH production as has been observed in the alternative strategies of fish (Grober *et al.*, 1994).

In *Uta*, orange males are selected for usurping behavior. Any loci with modifiers that elevate T will be favored because T enhances male stamina, which enhances the usurper strategy of O males (Sinervo *et al.*, 2000*a*). Conversely, intermediate levels of T will be favored in blue males and even lower levels of T should be favored in yellow males. We are currently assessing the fitness consequences of steroid and gonadotropin interaction (FSH and LH) on male morphs, to complement mechanistic studies on female life history strategies. The role of T in altering expression of physiological and morphological traits of morphs is quite general for vertebrates and has been implicated in morphotypic differences in a variety of lizard species (Hews *et al.*, 1994; Hews and Moore, 1995; Rand, 1992) and fish species (Brantley *et al.*, 1993).

The physiological epsitasis of endocrine regulation noted above implies that there are many potential loci regulated by the basic hypothalamic-pituitary-gonadal (HPG) axis (Fig. 1) (Mazzochi *et al.*, 1998). Each hormone in this chain can potentially affect a suite of traits and thus the hormones are involved in epistasis with many loci (e.g., FSH controls clutch size and egg mass, LH, T controls behavior and morphology of males, and E controls vitellogenesis, etc.). The physiological epistasis of the HPG axis also extends to the Hypothalamic-Pituitary-Gonadal-Adrenal axes (Tanriverdi *et al.*, 2003) that involves the hormone corticosterone [B] (Denver, 2000), the primary glucocorticoid of reptiles (DeNardo and Sinervo, 1994; Comendant *et al.*, 2003) (Fig. 1). The HPGA axes are already known to be in fitness epistasis with female morphs (Comendant *et al.*, 2003; Svensson *et al.*, 2002). Furthermore, immune function of side-blotched lizard females is in physiological epistasis with both the adrenocortical response and the HPG axis (Svensson *et al.*, 2001*b*, 2002). Epistasis of the HPGA axis and male morphs (Fig. 4) is also likely, given steroid interactions between B and T on territory behavior (DeNardo and Sinervo, 1994; DeNardo and Licht, 1993). Thus, the OBY locus is also in epistasis with key endocrine regulatory networks like corticosterone hormones (e.*g.*, HPGA axes) that mediate cost-of-reproduction trade-offs (Sinervo and DeNardo, 1996). Effects of corticosterone are likely to be general: B differentially modulates stress associated with male-male contest in morphs of *Urosaurus* (Knapp and Moore, 1995, 1996), a sister genus to *Uta*.

A strategy for constructing genomic maps of physiological epistasis

The physiological epistasis of endocrine regulatory networks can generate physiological and fitness epis-

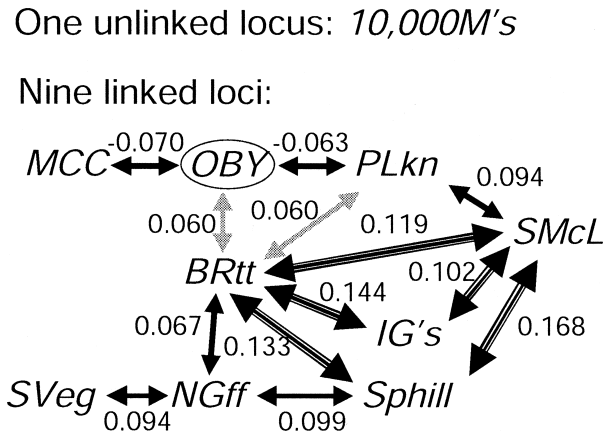

FIG. 5. Linkage disequilibrium among the 9 microsatellite loci and the **OBY** locus (N = 129 males, 1992). Linkage disequilibrium was significant among 8 of the 9 loci, which are connected by an epistatic network (heavy lines—$P < 0.01$, black—$0.05 > P > 0.01$, gray—$0.06 > P > 0.09$). Only the 10,000 M's microsatellite locus was not linked to the network. Linkage disequilibrium is indicative of genome-wide fitness epistasis that is consistent with the hypothesis of physiological epistasis depicted in Figure 1, and strong genetic correlations we have measured on free-ranging *Uta* (Table 1) (from Sinervo and Clobert, 2003).

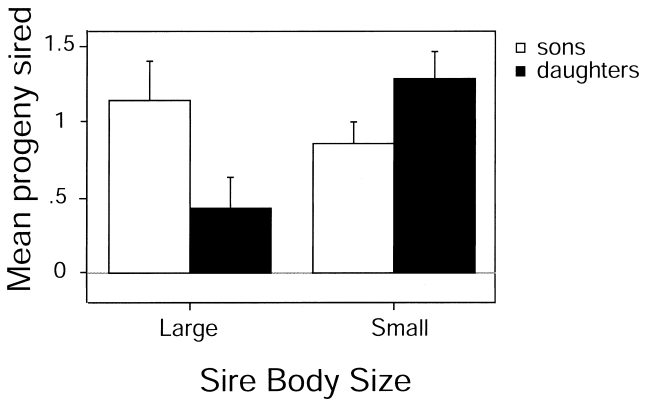

FIG. 6. Ontogenetic conflict as resolved by cryptic female choice. The mean number of sons versus daughters (±1 SE) sired by large and small sires within a female's clutch during 1999. Females produced significantly more sons with the sperm from relatively larger sires and females also produced significantly more daughters with the sperm from relatively smaller sires (from Calsbeek and Sinervo, 2002).

tasis that results in correlational selection on many traits related to reproduction and immune function (Table 2). This correlational selection should build-up very strong genetic correlations (Lynch and Walsh, 1998; Whitlock *et al.*, 1995), and significant genetic correlations have been measured for every trait that we have tested in the field pedigrees (Table 1). Most genetic correlations are calculated for dam-progeny traits, thus maternal effects may inflate or deflate these estimates. However, sire-progeny correlations in controlled crosses are near unity for color traits (Table 1). Furthermore, genetic correlations among sire morphotype, life history traits of daughters, and sexually selected traits of sons are also near unity (unpublished data, B.S. and R.G.C.). Thus, the OBY locus exerts a high degree of control over a suite of traits.

Another way to assess physiological epistasis is to measure fitness epistasis between the OBY locus and other loci in the genome. The genetic signature of fitness epistasis, linkage disequilibrium, can be assessed with microsatellite markers developed for paternity analysis. In principle, microsatellite markers are neutral in the context of OBY, but sit next to strategic loci that interact epistatically with OBY. Strategic loci refer to loci (other than OBY) with alleles each of which is beneficial for one morph genotype but detrimental to other genoytpes.

We have already used this approach (Sinervo and Clobert, 2003) to test for the genome-wide linkage disequilibrium that is predicted to form between such strategic loci and OBY (Fig. 5) under the action of strong correlational selection on life history, physiological, and behavioral traits (Table 2). Sinervo and Clobert (2003) specifically demonstrated a genetic link between color genotypes, cooperative behavior, dispersal and settlement patterns of males that were associated with strong correlational selection on this same set of traits. If by chance strategic loci (such as those that govern male dispersal and settlement) are located next to any microsatellite markers, linkage disequilibrium will form by chronic correlational selection, coupling OBY to strategic loci and any tightly-linked microsatellite loci markers. This analysis is conceptually analogous to analysis of coadapted gene complexes of speciation (Rieseberg *et al.*, 1996) except in *Uta* we test for ''coadapted morph complexes'' within a single species.

In *Uta*, we detected pervasive linkage among 9 of 10 loci (*e.g.*, OBY + 9 microsatellites) (Sinervo and Clobert, 2003). A poisson model of 10 loci (randomly distributed on the 17 chromosomes of *Uta*, Pennock *et al.*, 1969) predicts that only 2 loci should reside on a common linkage group; 8 should be unlinked (Sinervo and Clobert, 2003). The converse was observed (9 linked loci; 1 unlinked) (Fig. 6). Thus, epistasis appears to be genome-wide given that 8 of 9 microsatellite loci were coupled to OBY (e.g., 8/10 loci ~80%) by linkage forming highly integrated coadapted morph complexes. Determining the molecular identity of the loci that are involved in this molecular signature of epistasis is the subject of ongoing study in our laboratory.

Resolution of ontogenetic conflict: Cryptic female choice for sperm genotypes

The intense ontogenetic conflict imposes tremendous selection on females to mitigate its effects on her progeny. Mate choice would allow females to select male genotypes that minimize ontogenetic conflict as a function of her genotype. Past models of sexual selection and mate choice have focused on choice for traits that signal male genetic quality and confer benefits to sexy sons (Iwasa and Pomiankowski, 1991 or mate choice for fixed genetic preference of male traits,

which promote runaway processes (Lande, 1981). We have developed a theory of context-dependent mate choice that is different from Fisherian runaway or good genes models, which assumes fixed genetic preferences (Alonzo and Sinervo, 2001). In context-dependent mate choice plastic preferences evolve to mitigate impacts of mate quality on progeny quality. These models specifically address the ontogenetic conflict between loci that govern male and female strategies. Given recent evidence that female choice depends on social environment, experience, and condition (reviewed in Alonzo and Sinervo, 2001), the focus of past models of sexual selection on choice for specific traits of the male or genetically-based preference is an oversimplification of the process. Females should be selected to choose mates with genetic qualities that maximize fitness of each progeny sex in the context of social environments faced in the next generation.

In the side-blotched lizard, females should choose sire morphs to maximize progeny fitness, given changing social environments of progeny (*e.g.*, male and female cycles). Theory predicts that females will choose rare morphs, enhancing the rare male advantage, and thereby driving more rapid RPS cycles. However, a female should also maximize fitness of both sons and daughters. Thus, every other generation of the density cycle a female should choose orange sires to produce orange daughters that do best when the population is at low density (Alonzo and Sinervo, 2001). These results have two implications for the evolution of mate choice in the context of ontogenetic conflict. First, female choice for good genes often results in a tradeoff between high quality female and high quality male offspring. Female mate choice will depend on the resolution of this tradeoff (Alonzo and Sinervo, 2001). Second, choice for good genes may not be static, but instead vary as a function of social or ecological conditions faced by progeny.

To test this theory, we have focused on the role of cryptic choice in mitigating effects of ontogenetic conflict in the wild as a function of body size. Cryptic female choice is a post-copulatory strategy of the female that is out of the male's control (Eberhard, 1996). Female *Uta* copulate with as many as 5 males with the modal number being 2 mates (Zamudio and Sinervo, 2000, 2002). The polyandry of female *Uta* may be a strategy to obtain genes to produce both high quality sons and daughters (Calsbeek and Sinervo, 2002*b*). For example consider male body size, a trait under strong sexual selection in size-dimorphic species. *Uta* is highly dimorphic in size: males are 1.8 times larger than females. Sexual selection may favor alleles for large size in males but antagonistic natural selection on female life history traits pulls body size alleles in the other direction. This divergent selection places females in the grip of chronic ontogenetic conflict.

One way for females to mitigate this conflict is by sorting male benefit/female detriment genes into sons and female benefit/male detriment genes into daughters. In nature, female side-blotched lizards that mate with two males are capable of such extreme cryptic sperm choice. Females produce sons with the sperm from large-bodied sires and daughters with the sperm from small-bodied sires (Calsbeek and Sinervo, 2002*b*) (Fig. 6). Controlled mating demonstrates that these results are not due to biased sperm production by males or by meiotic distortion of progeny sex (unpublished data, R.G.C. and B.S.). Rather, the data are consistent with our interpretation of female bias in the allocation of progeny sex based on the phenotype (*i.e.*, body size) of sires.

DISCUSSION

The role of organizational and activational events in ameliorating ontogenetic conflict

Two endocrine regulatory processes control the ontogeny of sexual differentiation and have evolved to specifically mitigate impacts of ontogenetic conflict between juveniles and adults, and between adult males and females. Organizational effects of hormones act during embryogenesis and establish a blueprint for each of the sexes (Caro and Bateson, 1984; Moore, 1991; Sinervo and Svensson, 2003) (Fig. 1). During organizational events, presence of T differentiates male morphology and neurophysiology, while its absence differentiates female morphology and neurophysiology (Moore, 1991; Bass, 1993, 1996; Brantley *et al.*, 1993) (Fig. 1). However, the organizational effects of hormones on differentiation of the sexes are only realized when the activational effects of hormones take control of gene expression at maturity. Organizational events set-up basic blueprints of female and male traits during embryogenesis, however juveniles remain sexually undifferentiated. This lack of conspicuous differentiation of juveniles buffers them from any potential ontogenetic conflict arising from sexual adult phases of the life history.

During maturation, activational events are triggered by a hormonal cascade involving (Moore, 1991; Licht *et al.*, 1974; Padmanabhan *et al.*, 2002) (Fig. 1): 1) gonadatropin releasing hormone (GnRH) and gonadotropins (follicle stimulating hormone—FSH; lutenizing hormone—LH), and 2) gonadal cells that produce either T or E. In turn, gonadal steroid hormones E and T bind to DNA via carrier proteins to directly alter patterns of gene expression in both sexes. These interactions reflect physiological epistasis among sex determining loci and sex-limited patterns of gene expression due to steroids (Sinervo and Svensson, 2003). The activational effects of sex-limited steroids buffer male and female phenotypes from ontogenetic conflict.

Mutation-selection balance versus *selection on the sexes as the source of ontogenetic conflict*

One way to envision selection on physiological epistasis in the context of ontogenetic conflict is to consider the sexes as two alternative strategies. The sex-limited expression of physiological traits allows each sex to be fine-tuned for their respective strategies.

T governs male-specific traits while E governs female-specific traits. Consider mutations with male-benefits that enhance male function, but which also have female-detriment effects (deleterious for female fitness). Such pleiotropic mutations will be selected against in the next generation: successful males should produce both quality male and quality female progeny. The converse situation holds for female-benefit mutations. Thus, mutations with both male benefit and female benefit will rapidly fix. However, at evolutionary equilibrium mutation-selection balance will generate a large standing crop of male-benefit but female-detriment alleles or female-benefit but male-detriment alleles (*e.g.,* pleiotropy). Genetic variation in endocrine regulation will be largely comprised of these pleiotropic male-benefit and female-detriment alleles and female-benefit and male-detriment alleles. This argument for the origin of ontogenetic conflict between the sexes is similar to Falconer's (1981) argument concerning prevalence of negative pleiotropy among life history traits within a single sex, the source of genetically-based trade-offs (Reznick *et al.,* 2000).

Laboratory studies of the genetics of ontogenetic conflict in *Drosophila* have tested for the standing crop of male and female benefit-detriment alleles that arises from mutation-selection balance (*e.g.,* Chippindale *et al.,* 2001; Gibson *et al.,* 2002; Rice and Chippindale, 2001). In nature, however, male and female strategies also have a genetic component that arises from selection on the sexes. Thus, ontogenetic conflict in such situations will be more intense than the portion of genetic variance due to mutation-selection balance. Studies of ontogenetic conflict in nature (*e.g., Uta*) complement laboratory studies (*e.g., Drosophila*). The former reveals the selective source of ontogenetic conflict while the latter reveals the mutational source. Given that this ontogenetic conflict has a physiological basis in endocrine regulation, studies of ontogenetic conflict in nature address selection on the physiological regulation of male *versus* female traits.

Selective environments that generate strong linkage disequilibrium and ontogenetic conflict must be intense (Lynch and Walsh, 1998). Otherwise, recombination will break apart genetic associations that are formed by selection (Lande, 1984). One aspect of the side-blotched lizard system that is seminal to the maintenance of linkage groups is the OBY locus. The three male optima (RPS) *versus* two female optima (r-K) promote chronic correlational selection for successful combinations of traits in each morph and in each sex (Table 2). Correlational selection varies significantly with throat color frequency and maintains linkage disequilibrium even in the face of recombination and segregation (Sinervo and Svensson, 2002).

The OBY locus creates a nucleus around which ontogenetic conflict forms owing to the ways in which the OBY locus perturbs the epistatic networks of endocrine regulation (Fig. 1). Although natural selection may operate in similar ways in other taxa, resolving the adaptive landscape in these taxa will be difficult unless there exists discrete phenotypic variation that is correlated with fitness-related traits. As noted above, physiological and fitness epistasis will be fixed in most organisms. However, ontogenetic conflict will still arise from mutation-selection balance, even though it will be difficult to measure such effects in nature. Measuring the selective consequences of ontogenetic conflict is the most promising avenue of study in nature.

The genetic signatures of selection on ontogenetic conflict

To measure ontogenetic conflict there is no substitute for detailed data on fitness (Figs. 2, 3), and how fitness traits map onto male and female traits (Figs. 2, 4). Mapping the linkage disequilibrium that arises from ontogenetic conflict onto specific traits (Fig. 5) is the next step that will allow for analysis of the genomic architecture of physiological epistasis (Sinervo and Clobert, 2003). Such efforts are currently underway (unpublished data, B.S.). The analysis of Fig. 5 illustrates the power of the approach of mapping a phenotypic attribute (*e.g.,* color: o, b, y) onto fitness epistasis, which is indicated by linkage disequilibrium among many genetic markers. Traditional approaches for analyzing such quantitative trait loci (QTL) require pedigrees (Lynch and Walsh, 1998). Chronic correlational selection and high heritability for traits of *Uta* allow us to resolve genomic maps of physiological and fitness epistasis without the need of pedigrees. Nevertheless, maternal and paternal pedigrees available for side-blotched lizards (Sinervo and Clobert, 2003 will allow us to corroborate this new approach to studying physiological epistasis.

Cryptic sperm choice on the part of female side-blotched lizards indicates the potential for highly refined adaptive solutions to adaptational problems imposed by ontogenetic conflict. In side-blotched lizards, females sort sperm into sons and daughters as a function of male traits (Fig. 6), and they also change the size of eggs that produce sons and daughters via corticosterone (Sinervo and DeNardo, 1996). This kind of cryptic choice and sex-biased maternal investment provides another signature of the action of ontogenetic conflict. We argue that such a response to selection may be very general. Just as females of most taxa have been shown to choose males based on various phenotypic traits (active choice), we suspect that females also make allocation decisions based on male genetic quality. Identifying phenotypic markers used by females to mitigate the effects of ontogenetic conflict is a challenge for future studies. The OBY locus reflects a highly refined sexual signal that allows females to make these adaptive choices.

In this regard, the OBY locus is an extremely useful tool for studying the adaptation of physiological networks like endocrine regulation. The fact that we can pick up a side-blotched lizard and understand so much about its genetic architecture by simply glancing at its throat color is a tool that could be applied to the evo-

lution of regulatory mechanisms in other physiological systems besides hormones. Perhaps similar species await discovery by intrepid physiological ecologists interested in studying the evolution of other kinds of physiological homeostasis.

ACKNOWLEDGMENTS

Work on *Uta* has been supported by NSF grants to B.S. (from 1989–2003). Preparation of this manuscript was supported by a grant from the Integrative Behavior and Neurobiology Panel to B.S., Lisa Hazard, D. B. Miles and Dan Costa. We thank an anonymous reviewer for constructive comments on earlier versions of this manuscript. We also wish to thank Adam Chippindale, Bill Rice, John Gibson, and Suzanne Alonzo for conversations on ontogenetic conflict over the years.

REFERENCES

Alonzo, S. and B. Sinervo. 2001. Mate choice games, good genes, and genetic cycles. Behav. Ecol. and Sociobiol. 49:176–186.

Arnold, A. P. 1994. Critical events in the development of bird song: What can neurobiology contribute to the study of the evolution of behavior. *In* L. Real (ed.), *Behavioral mechanisms in evolutionary ecology*, pp. 219–237. University of Chicago Press, Chicago.

Bass, A. H. 1993. From brains to behavior: Hormonal cascades and alternative mating tactics in teleost fishes. Rev. Fish Biol. 3: 181–186.

Bass, A. H. 1996. Shaping brain sexuality. Am. Sci. 84:352–363.

Brantley, R. K., J. C. Wingfield, and A. H. Bass. 1993. Sex steroid levels in *Porichthys notatus*, a fish with alternative reproductive tactics, and a review of the hormonal bases for male dimorphism among teleost fishes. Horm. Behav. 27:332–347.

Calsbeek, R. and B. Sinervo. 2002*a*. The ontogeny of territoriality during maturation. Oeologia 132:468–477.

Calsbeek, R. and B. Sinervo. 2002*b*. Uncoupling direct and indirect components of female choice in the wild. Proc. Natl. Acad. Sci., U.S.A. 99:14897–14902.

Calsbeek, R., S. H. Alonzo, K. Zamudio, and B. Sinervo. 2002. Sexual selection and alternative mating behaviours generate demographic stochasticity in small populations. Proc. Roy. Soc. London Series B. 269:157–164.

Caro, G. M. and P. Bateson. 1986. Organization and ontogeny of alternative tactics. Anim. Behav. 34:1483–1499.

Chippindale, A. K., J. R. Gibson, and W. R. Rice. 2001. Negative genetic correlation between the sexes reveals ontogenetic conflict. Proc. Natl. Acad. Sci. U.S.A. 98:1671–1675.

Comendant, T., B. Sinervo, E. I. Svensson, and J. Wingfield. 2003. Social competition, corticosterone and natural selection on female lizard morphs. J. Evol. Biol. (In press)

Darwin. C. 1871. *The descent of man and selection in relation to sex.* Murray, London, UK.

DeNardo, D. F. and P. Licht. 1993. Effects of corticosterone on social behavior of male lizards. Horm. Behav. 27:184–199.

DeNardo, D. F. and B. Sinervo. 1994. Effects of steroid hormone interaction on territorial behavior of male lizards. Horm. Behav. 28:273–287.

Denver, R. J. 2000. Evolution of the corticotropin-releasing hormone signaling and its role in stress-induced developmental plasticity. Amer. Zool. 40:995–996.

Desantis, S., M. Labate, and A. Corriero. 1998. Immunohistochemical localization of FSH and LH in pituitary of male ruin lizards, *Podarcis sicula campestris* De Betta. Europ. J. Histochem. 42: 77–84.

Desantis, S., M. Labate, G. M. Labate, and G. De Metrio. 2000. Immunohistochemical evidence seasonal changes of gonadtrops in male ruin lizards, *Podarcis sicula campestris* De Betta. Europ. J. Histochem. 44:385–395.

Eberhard, W. G. 1996. *Monographs in behavior and ecology: Female control: Sexual selection by cryptic female choice.* Princeton University Press, Princeton, New Jersey.

Falconer, D. 1981. *Introduction to quantitative genetics.* Longman Publishing, New York.

Folstad, I. and A. J. Karter. 1992. Parasites, bright males and the immunocompetence handicap. Am. Nat. 139:603–622.

Freedman, L. P. and B. F. Luisi. 1993. On the mechanism of DNA-binding by nuclear hormone receptors: A structural and functional perspective. J. Cell. Biochem. 51:140–150.

Gibson, J. R., A. K. Chippindale, and W. R. Rice. 2002. The X chromosome is a hot spot for sexually antagonistic fitness variation. Proc. Natl. Acad. Sci. U.S.A. 269:499–505.

Goodnight, C. J. 1995. Epistasis and the increase in additive genetic variance: Implications for phase 1 of Wright's shifting-balance process. Evolution 49:502–511.

Grober, M. S., S. H. Fox, C. Laughlin, and A. H. Bass. 1994. GnRH cell size and number in a teleost with two male reproductive morphs: Sexual maturation, final sexual status and body size allometry. Brain Behav. Evol. 43:61–78.

Hews, D. K., R. Knapp, and M. C. Moore. 1994. Early exposure to androgens affects adult expression of alternative male types in tree lizards. Horm. Behav. 28:96–115.

Hews, D. K. and M. C. Moore. 1995. Influence of androgens on differentiation of secondary sex characters in tree lizards, *Urosaurus ornatus*. Gen. Comp. Endocrinol. 97:86–102.

Ho, S.-M. S. Kleis, R. McPherson, G. J. Heisermann, and I. P. Callard. 1982. Regulation of vitellogenesis in reptiles. Herpetologica 38:40–50.

Iwasa, Y. and A. Pomiankowski. 1991. Good parent and good genes models of handicap evolution. J. Theor. Biol. 200:97–109.

Knapp, R. and M. C. Moore. 1995. Hormonal responses to aggression vary in different types of agonistic encounters in male tree lizards. Horm. Behav. 29:85–105.

Knapp, R. and M. C. Moore. 1996. Male morphs in tree lizards, *Urosaurus ornatus*, have different delayed hormonal responses to aggressive encounters. Anim. Behav. 52:1045–1055.

Lande, R. 1981. Models of speciation by sexual selection on polygenic traits. Proc. Natl. Acad. Sci. U.S.A. 78:3721–3725.

Lande, R. 1984. The genetic correlation between characters maintained by selection, linkage, and inbreeding. Genet. Res. Camb. 44:309–320.

Lank, D. B., M. Coupe, and K. E. Wynne-Edwards. 1999. Testosterone-induced male traits in female ruffs (*Philomachus pugnax*): Autosomal inheritance and gender differentiation. Proc. Roy Soc. London Ser. B 266:2323–2330.

Licht, P. 1970. Effects of mammalian gonadotropins (ovine FSH and LH) in female lizards. Gen. Comp. Endocrinol. 22:463–469.

Licht, P. 1972. Actions of mammalian gonadotropins (FSH and LH) in reptiles. I. Male snakes. Gen. Comp. Endocrinol. 19:273–281.

Licht, P., H. Papkoff, S. W. Farmer, C. H. Muller, H. W. Tsui, and D. Crews. 1977. Evolution of gonadotropin structure and function. Recent Prog. Horm. Res. 33:169–248.

Lochmiller, R. L. and C. B. Dabbert. 1993. Immunocompetence, environmental stress, and the regulation of animal populations. Trends Comp. Biochem. Physiol. 1:823–855.

Lynch, M. and B. Walsh. 1998. *Genetics and analysis of quantitative traits.* Sinauer, Sunderland, Massachusetts.

Mazzocchi, G., G. Gottardo, and G. G. Nussdorfer. 1998. A local immuno-endocrine interaction may mediate rat adrenal glucocorticoid response to bacterial endotoxins. Life Sci. 62:1783–1787.

Moore, M. C. 1991. Application of organization-activation theory to alternative male strategies: A review. Horm. Behav. 25:154–179.

Padmanabhan, V., F. J. Karsch, and J. S. Lee. 2002. Hypothalamic, pituitary and gonadal regulation of FSH. Reproduction Suppl. 59:67–82.

Pennock, L. A., D. W. Tinkle, and M. W. Shaw. 1969. Minute Y chromosome in the lizard genus *Uta* (family Iguanidae). Cytogenetics 8:9–19.

Phillips, J. A., F. Frye, A. Berkovitz, P. Calle, R. Millar, J. Rívíer,

and B. E. Lasley. 1987. Exogenous GnRH overrides the endogenous annual reproductive rhythm in green iguanas, *Iguana iguana*. J. Exp. Zool. 241:227–236.
Provine, W. 1971. *The origins of theoretical population genetics.* University of Chicago Press, Chicago.
Rand, M. S. 1992. Hormonal control of polymorphic and sexually dimorphic coloration in the lizard *Sceloporus undulatus erythrocheiluz*. Gen. Comp. Endocrinol. 88:461–468.
Reznick, D., L. Nunney, and A. Tessier. 2000. Big houses, big cars, superfleas and the costs of reproduction. Trends Ecol. Evol. 15: 421–425.
Rieseberg, L. H., B. Sinervo, C. R. Linder, M. C. Ungerer, and D. M. Arias. 1996. Role of gene interactions in hybrid speciation: Evidence from ancient and experimental hybrids. Science 272: 741–745.
Rice, W. R and A. K. Chippindale. 2001. Intersexual ontogenetic conflict. J. Evol. Biol. 14:685–693.
Sanchez, R., D. Nguyen and W. Rocha. 2002. Diversity in the mechanisms of gene regulation by estrogen receptors. Bioessays 24: 244–254.
Sinervo, B. 1999. Mechanistic analysis of natural selection and a refinement of Lack's and Williams's principles. Amer. Natur. 154:S26–S42.
Sinervo, B. 2000. Adaptation, natural selection, and optimal life history allocation in the face of genetically-based trade-offs. *In* T. Mousseau, B. Sinervo, and J. A. Endler (eds.), *Adaptive genetic variation in the wild.* Oxford Univ. Press, Oxford, UK.
Sinervo, B. 200l*a*. Runaway social games, genetic cycles driven by alternative male and female strategies, and the origin of morphs. Genetica 112:417–434.
Sinervo, B. 2001*b*. Selection in local neighborhoods, graininess of social environments, and the ecology of alternative strategies. *In* L. Dugatkin (ed)., *Model systems in behavioral ecology*. Princeton University Press, Princeton, New Jersey.
Sinervo, B. and A. L. Basolo. 1996. Testing adaptation using phenotypic manipulations. *In* M. R. Rose and G. Lauder (eds.), *Adaptation*, pp. 148–185.Academic Press, New York.
Sinervo, B., C. Bleay, and C. Adamopoulou. 2001. Social causes of correlational selection and the resolution of a heritable throat color polymorphism in a lizard. Evolution 55:2040–2052.
Sinervo, B. and J. Clobert. 2003. A lizard color polymorphism drives settlement behavior owing to selective benefits of cooperation. Science 300:1949–1951.
Sinervo, B. and D. F. DeNardo. 1996. Costs of reproduction in the wild: Path analysis of natural selection and experimental tests of causation. Evolution 50:1299–1313.
Sinervo, B. and P. Licht. 1991. The physiological and hormonal control of clutch size, egg size, and egg shape in *Uta stansburiana*: Constraints on the evolution of lizard life histories. J. Exp. Zool. 257:252–264.
Sinervo, B. and C. M. Lively. 1996. The rock-paper-scissors game and the evolution of alternative male reproductive strategies. Nature 380:240–243.
Sinervo, B., D. B. Miles, W. A. Frankino, M. Klukowski, and D. F. DeNardo. 2000*a*. Testosterone, endurance, and Darwinian fitness: Natural and sexual selection on the physiological bases of alternative male behaviors in side-blotched lizards. Horm. Behav. 38:222–233.
Sinervo, B. and E. Svensson. 1998. Mechanistic and selective causes of life history trade-offs and plasticity. Oikos 83:432–442.
Sinervo, B. and E. Svensson. 2002. Correlational selection and the evolution of genomic architecture. Heredity 89:329–338.
Sinervo, B. and E. Svensson, E. 2003. The origin of novel phenotypes: Correlational selection, epistasis and speciation. *In* B. K. Hall (ed.), *Fins into limbs.* The University of Chicago Press, Chicago. (In press).
Sinervo, B., E. Svensson, and T. Comendant. 2000*b*. Density cycles and an offspring quantity and quality game driven by natural selection. Nature 406:985–988.
Sinervo, B. and K. Zamudio. 2001. The mechanistic source of genetic correlations and the evolution of alternative reproductive strategies in lizards. J. Heredity. (In press)
Svensson, E. and B. C. Sheldon. 1998. The social context of life history evolution. Oikos 83:466–477.
Svensson, E., B. Sinervo, and T. Comendant. 2001*a*. Condition, genotype-by-environment interaction, and correlational selection in lizard life-history morphs. Evolution 55:2053–2069.
Svensson, E., B. Sinervo, and T. Comendant. 2001*b*. Density-dependent competition and selection on immune function in genetic lizard morphs. Proc. Natl. Acad. Sci. U.S.A. 98:12561–12565.
Svensson, E., B. Sinervo, and T. Comendant. 2002. Mechanistic and experimental analysis of condition and reproduction in a polymorphic lizard. J. Evol. Biol. 15:1034–1047.
Tanriverdi, F., L. F. G. Silveira, and G. S. MacColl. 2003. The hypothalamic-pituitary-gonadal axis: Immune function and autoimmunity. J. Endocrinol. 176:293–304.
Van Duyse, E., R. Pinxten, and M. Eens. 2002. Effects of testosterone on song, aggression, and nestling feeding behavior in male great tits, *Parus major*. Horm. Behav. 41:178–186.
Whaling, C. S., D. A. Nelson, and P. Marler. 1995. Testosterone-induced shortening of the storage phase of song development in Birds interferes with vocal learning. Dev. Psychobiol. 28: 367–376.
Whitlock, M. C., P. C. Phillips, F. B. G. Moore, and S. J. Tonsor. 1995. Multiple fitness peaks and epistasis. Ann. Rev. Ecol. Syst. 26:601–629.
Wright, S. 1968. *Evolution and the genetics of populations.* University of Chicago Press, Chicago, Illinois.
Zajac, J. D. and P. J. Chilco, 1995. Transcriptional control and the regulation of endocrine genes. Clin. Exp. Pharmacol. P. 22:935–943.
Zamudio, K. and B. Sinervo. 2000. Polygyny, mate-guarding, and posthumous fertilizations as alternative male strategies. Proc. Natl. Acad. Sci. U.S.A. 97:14427–14432.
Zamudio, K. and B. Sinervo. 2002. Ecological and social contexts for the evolution of alternative mating strategies. *In* S. Fox, J. K. McCoy, and T. A. Baird (eds.), *Territoriality, dominance, and sexual selection: Adaptive variation in social behavior among individuals, populations, and species of lizards.* John Hopkins University Press, Baltimore, Maryland.