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# A model for social control of sex change: interactions of behavior, neuropeptides, glucocorticoids, and sex steroids

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## Abstract

The optimal regulation of vertebrate sexual development and reproductive function involves integration of internal physiological signals, indicative of an individual's sexual status and capability for reproduction, with signals from the external environment. While these environmental cues are diverse, and oftentimes species-specific, the induction of sexual readiness is typically carried out through the same basic components of the hypothalamic–pituitary–gonadal axis conserved among vertebrates. Therefore, species exhibiting diverse patterns of reproduction can contribute to the understanding of the general mechanisms underlying the expression of adult sexual phenotypes. The bluehead wrasse, *Thalassoma bifasciatum*, is a tropical coral reef fish that displays social control of sex change, whereby dominant males inhibit sex change in other members of the social group using aggressive interactions. In many fish species and vertebrates in general, individuals that lose these interactions often experience increased serum glucocorticoids, which can have a subsequent impact on their physiology and behavior. We discuss glucocorticoid regulation of both neuropeptide gene transcription and the major steroid biosynthetic pathways as potential mechanisms involved in the regulation of sex change in the bluehead wrasse. We present a model describing behavioral regulation of sex change in the bluehead wrasse and then describe the potential mechanistic roles of glucocorticoids, gonadal steroids, and neuropeptides in generating the changes predicted by the model. Through the use of alternative model systems it is possible to observe novel interactions among the neuroendocrine axes that regulate major life history events, like reproduction. These insights may then shed light on similar functional mechanisms underlying behavioral regulation of reproduction in all vertebrates.

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## Impact of the social environment on reproduction

The social environment is an important regulator of reproduction in many vertebrate species. The presence of a conspecific can induce sexual receptivity in a dyadic encounter (Carter et al., 1989; Marchlewska-Koj et al., 2000), or suppress the reproduction of subordinates in a social group (Creel et al., 1997; Fox et al., 1997). While different environmental cues are used by different species, the impact on reproduction is generally mediated through the highly conserved hypothalamic–pituitary–gonadal (HPG) axis.

The HPG axis is in turn regulated at many levels by the hypothalamic–pituitary–adrenal (HPA) axis or its equivalent, therefore implicating a role for glucocorticoids (GCs) in the social control of reproduction. Prolonged exposure to GCs has been demonstrated to reduce the gonadotropin-releasing hormone (GnRH) content of the brain (Consten et al., 2001), decrease the responsiveness of the pituitary to GnRH (Rivier and Rivest, 1991), and directly lower the steroidogenic activity of the gonads independent of circulating levels of leutinizing hormone (Charpenet et al., 1981; Monder et al., 1994; Sapolsky, 1987).

Interactions between dominant and subordinate individuals in a social group can affect circulating levels of GCs (Eloffson et al., 2000; Sapolsky, 1987), and once estab-

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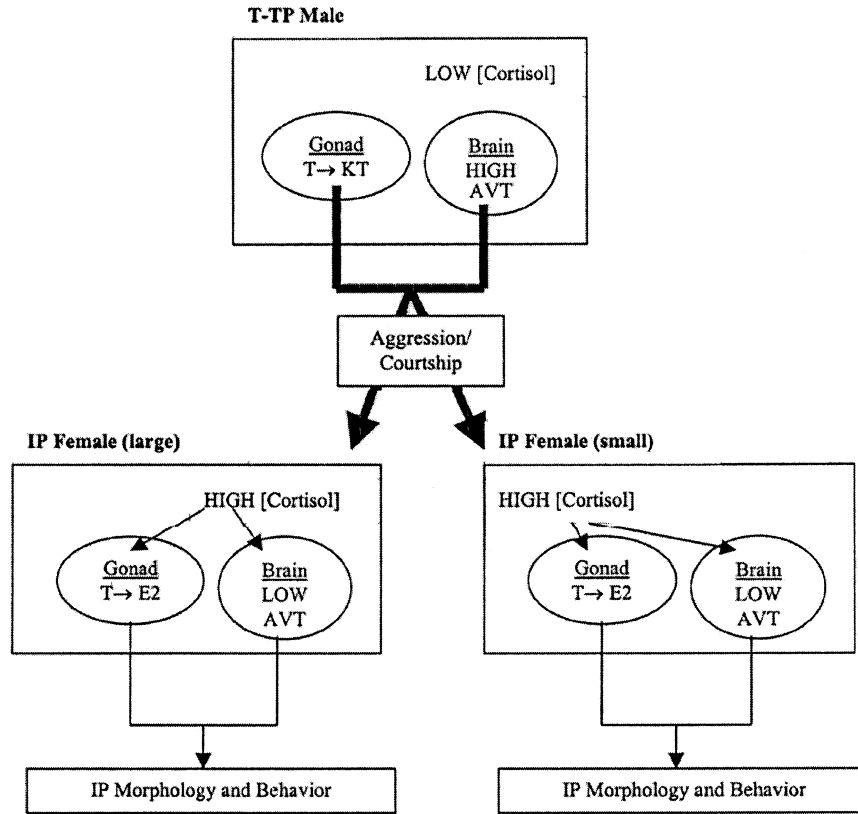


Fig. 1. Proposed model of glucocorticoid suppression of sex change in the bluehead wrasse. Aggression and courtship behavior from the T-TP male may suppress sex change in IP fish by maintaining elevated cortisol levels. Cortisol then promotes the pathway for estrogen production in the gonad and maintains low levels of AVT in the brain. Refer to text for details.

lished, an individual's GC levels are typically maintained within the context of a stable social group. Thus, the chronic effects of GCs are more likely to contribute to the social control of reproduction than are the responses invoked by acute stressful stimuli (Rivier and Rivest, 1991).

### Social control of sex change in the bluehead wrasse

The bluehead wrasse, *Thalassoma bifasciatum*, is a sequential hermaphrodite with multiple male morphs (diandry). Individuals can be categorized into initial and terminal phases based on their morphology and behavior (Warner, 1984). Initial phase (IP) fish are either male or female, whereas terminal phase (TP) fish are always male. TP males can be further subdivided into territorial TP (T-TP) males and nonterritorial TP (NT-TP) males (Semsar et al., 2001). T-TP males pair spawn with IP females and aggressively defend courting sites, excluding IP and NT-TP males (Warner, 1984). NT-TP males do not display the aggressive and courtship behavior typical of T-TP males and do not have access to females or spawning sites (Semsar et al., 2001). IP males spawn in large aggregations where the operational sex ratio can exceed 50 IP males per female or streak into T-TP/IP female pairs and release gametes (Warner, 1984).

Loss of TP males from the social group triggers the largest IP female to initiate the process of sex change (Warner and Swearer, 1991). Therefore, T-TP male-associated social cues (e.g., aggression and courtship behavior) normally serve to inhibit sex change in IP females (Fig. 1). During sex change there are rapid changes in behavior, including increased aggression and the initiation of T-TP male courtship behavior, as well as the adoption of TP coloration. Behavioral sex change can occur in gonadectomized females, demonstrating that conversion of the gonad is not required for the display of T-TP male behavior (Godwin et al., 1996). The existence of NT-TP males also shows that the expression of TP coloration and morphology can be independent of the neuroendocrine changes required to display T-TP male behavior.

NT-TP males are typically found on reefs that are too large to allow for complete domination by T-TP males, and most likely originate from IP fish that do not receive sufficient behavioral suppression from resident T-TP males (Fig. 2). NT-TP males appear to have overcome the inhibition of gonadal conversion, as evidenced by their display of TP coloration, a trait that requires androgens (McIntyre, 1998). NT-TP males fail to display aggression and courtship behavior, indicating that they are unable to complete the neuroendocrine changes required for the display of T-TP male behavior.

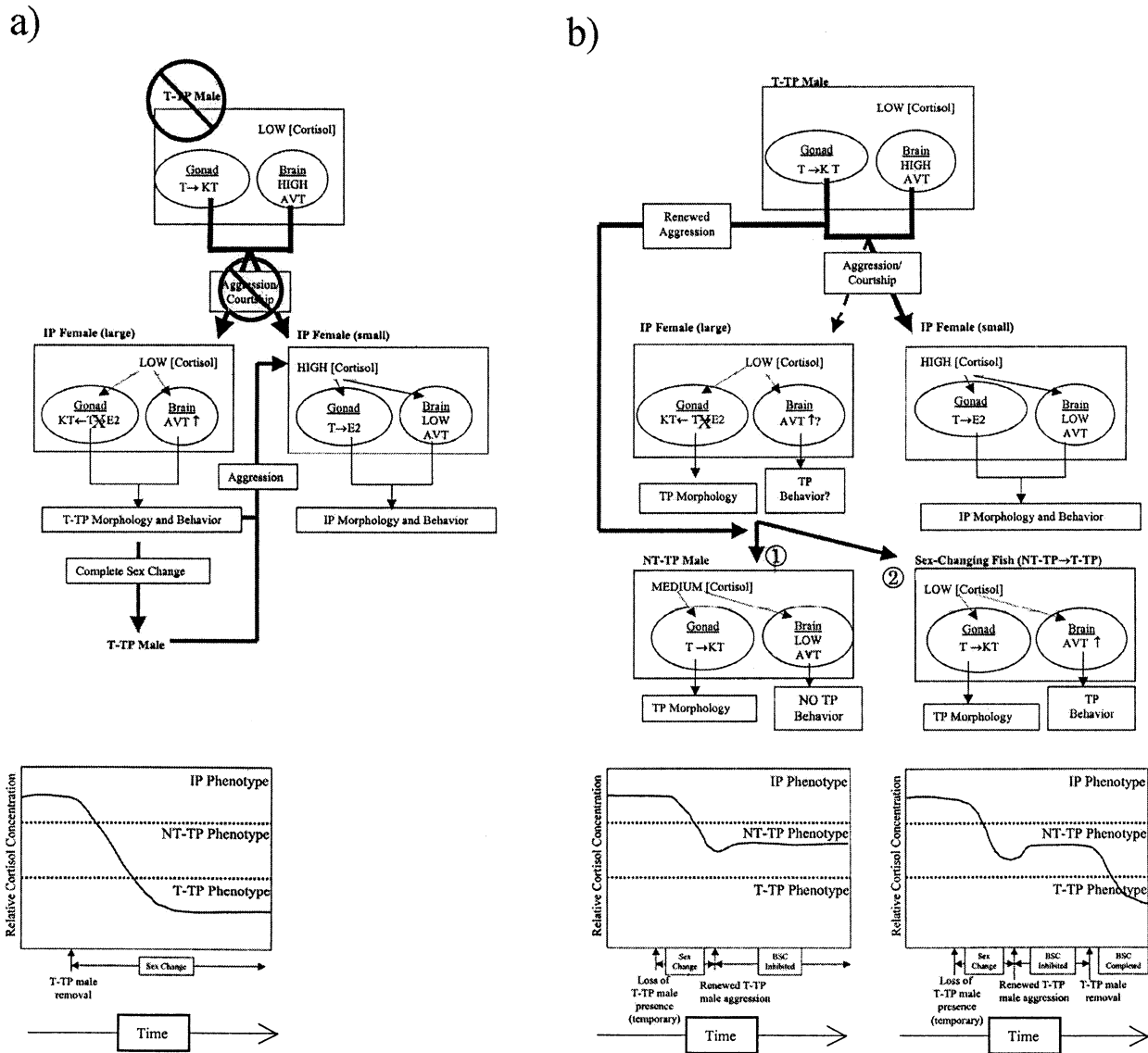


Fig. 2. (a) Following the removal of the T-TP male, the largest IP female initiates the behavioral, morphological, and steroidogenic changes resulting in complete sex reversal and the assumption of the T-TP male position. Inhibition of sex change in other IP fish is achieved by the immediate display of T-TP behavior by the sex-changing fish. (b) Temporary loss or reduction of T-TP male social signals may result in the largest IP female initiating sex change. Renewed aggression from the T-TP male reinstates inhibition of behavioral sex change (BSC), resulting in a NT-TP male ①. Only after the T-TP male is removed from the group can the NT-TP male complete the process of sex change ②. Beneath each model, the relative cortisol levels of the sex or role changing fish is depicted along with the time course of events. Refer to text for details.

The dissociation of behavioral sex change and gonadal conversion suggests that these processes are either regulated by separate mechanisms or that each has a different threshold of sensitivity to the same inhibitory mechanisms.

In this paper, we describe a model for the social control of sex change that targets GCs as key regulators of the changes in both the brain and the gonad during sex reversal. Support for this model is drawn from literature on teleosts and other vertebrates to highlight the conservation of mechanisms that regulate reproduction. While certain aspects of this model are only pertinent to sex-changing teleosts, the general concepts put forth can be applied to other vertebrate

systems in order to understand the general neuroendocrine mechanisms underlying the social control of reproduction.

### The neurochemical basis of behavioral sex change

Our model for behavioral sex change is based upon changes in arginine vasotocin (AVT) expression that are sensitive to changes in cortisol, which result from changes in the social environment. AVT and its mammalian homologue arginine vasopressin (AVP) have been implicated in the expression of sociosexual behavior in many vertebrates (Goodson and Bass, 2001; Grober et al., 2002; Moore,

1992). In the bluehead wrasse, behavioral sex change is associated with an increase in AVT mRNA in the preoptic area of the hypothalamus (Godwin et al., 2000). Additionally, AVT mRNA levels in magnocellular and parvocellular neurons in the preoptic area appear to be independently regulated during sex change (Perry, 2001).

Magnocellular and parvocellular neurons are functionally distinct and have been shown to respond preferentially to different stimuli. Confinement stress in rainbow trout (*Oncorhynchus mykiss*) increases AVT transcripts in parvocellular perikarya, but not in magnocellular perikarya (Gilchrist et al., 2000). This separation of function is also seen in rats, where magnocellular neurons of the paraventricular nucleus (PVN) are responsible for the peripheral release of AVP and fluid homeostasis, whereas parvocellular neurons are involved in stress responses (McCabe and Burrell, 2001). Magnocellular and parvocellular neurons in the PVN of rats are also differentially sensitive to GCs (Swanson, 1993).

The pattern of changes in hypothalamic AVT mRNA levels in sex-changing fish supports the differential sensitivity of magnocellular and parvocellular neurons to GCs. Changes in circulating cortisol levels, the predominant GC in teleosts, might therefore be a key regulator of behavioral sex change in the bluehead wrasse. Within the first day of TP male removal in the bluehead wrasse, magnocellular neurons display an increase in AVT mRNA levels. Parvocellular neurons have a delayed increase in AVT transcripts that peaks around 3 days after TP male removal (Perry, 2001). The delayed changes in parvocellular AVT mRNA levels may reflect continued GC-mediated suppression of AVT transcription in these neurons. Magnocellular neurons that are not sensitive to GC suppression might increase AVT production in response to the immediate changes in the social environment, until cortisol levels decline or parvocellular neurons are able to overcome GC suppression. Therefore, peripherally released AVT from magnocellular neurons would contribute to the rapid behavioral changes resulting from TP male removal (Perry, 2001). Intraperitoneal injections of AVT have been shown to increase aggressive and reproductive behavior in the bluehead wrasse (Semsar et al., 2001), supporting a role for peripheral AVT in the mediation of the early events of sex change. Further studies suggest that AVT is not sufficient to induce male behavior in an inhibitory social environment, but AVT is necessary for the production of male behavior in a permissive social environment (Semsar and Godwin, 2002).

Biochemical switching of neuronal phenotypes might also contribute to the behavioral changes observed during sex reversal. Parvocellular neurons have several potential neurotransmitter phenotypes and can produce corticotropin-releasing hormone (CRH), AVT, or both CRH and AVT. As parvocellular neurons are released from glucocorticoid suppression, AVT expression could increase and these neurons would release a different ratio of AVT and CRH. Target neurons with AVT receptors would therefore only be acti-

vated by AVT when GC levels were relatively low. As noted for rats, this biochemical switching of neuronal phenotypes could contribute to synaptic plasticity and allow the expression of new behavioral patterns without the formation of new synapses (Swanson, 1993).

11-ketotestosterone (11-KT) is the primary androgen in fishes (Borg, 1994). The production of 11-KT is a key component of gonadal sex change, a process that involves conversion of the ovary into a testis. Interestingly, 11-KT biosynthesis is also sensitive to regulation by cortisol (Consten, 2001). Keuning and colleagues administered cortisol to the common carp, *Cyprinus carpio*, and detected an accumulation of one of the precursors of 11-KT, 11-hydroxyandrostenedione, suggesting that cortisol temporarily inhibits 11-KT synthesis in vivo. Following the clearance of exogenous cortisol, 11-hydroxyandrostenedione levels decreased in conjunction with an increase in 11-KT levels, indicating that in the absence of substrate competition, 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD) was able to metabolize the accumulated precursors.

We predict that IP fish possess tonic and modest elevations in cortisol levels due to the regular aggressive intrusions by the socially dominant T-TP male. In the bluehead wrasse, IP males and females are more responsive to capture stress in terms of plasma cortisol elevations than are T-TP males (Semsar and Godwin, personal communication). In other teleost fishes, subordinates possess high cortisol levels resulting from aggressive interactions with dominant individuals (Eloffson et al., 2000; Sloman et al., 2001). In the bluehead wrasse, these elevated cortisol levels would presumably result in the sustained inhibition of 11-KT synthesis in IP fish. Consistent with this idea, IP females and males in other sex changing fish have undetectable levels of 11-KT (e.g., Cardwell and Liley, 1990; Hourigan et al., 1991). Aggression directed toward other fish, such as IP and NT-TP males, might also increase cortisol levels in IP females that do not directly receive aggressive intrusions. The observation of aggressive encounters between other individuals has also been shown to alter gonadal steroid production in cichlid “bystanders” (Oliveira et al., 2001).

The biosynthesis of 11-KT requires the oxygenation of testosterone by the enzymes 11 $\beta$ -hydroxylase (11 $\beta$ -H) and 11 $\beta$ -HSD. 11 $\beta$ -H is responsible for the conversion of testosterone into 11-hydroxytestosterone. 11 $\beta$ -HSD then converts 11-hydroxytestosterone into 11-KT. In addition to their roles in 11-KT synthesis, 11 $\beta$ -H and 11 $\beta$ -HSD are also involved in the synthesis and inactivation of GCs (Fig. 3). Therefore, the in vitro and in vivo suppression of 11-KT synthesis by cortisol and its metabolites may occur through the competitive inhibition of 11 $\beta$ -H and 11 $\beta$ -HSD. In the longear sunfish, cuckolder males have higher plasma cortisol levels than parental males, suggesting that cuckolder males have lower 11 $\beta$ -HSD activity in the interrenals and testes relative to parental males (Knapp et al., 2002).

Competitive inhibition of 11-KT synthesis by cortisol could explain why IP fish have undetectable levels of 11-

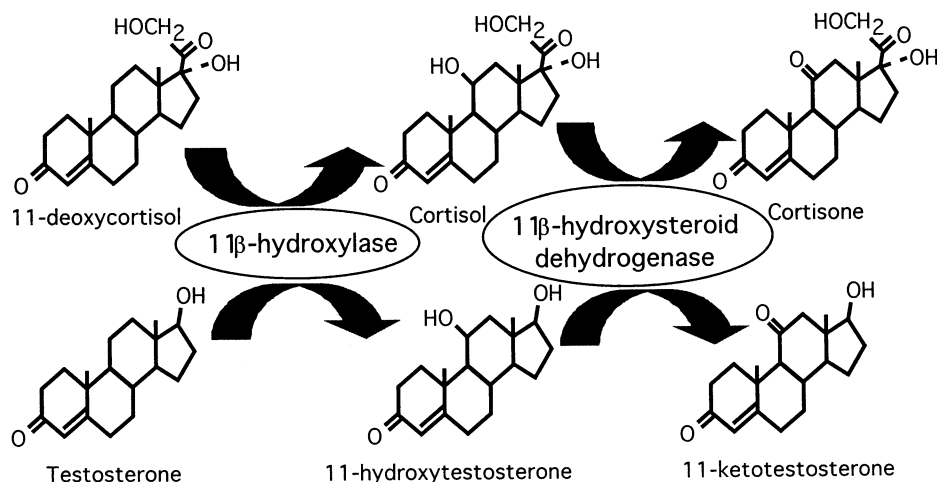


Fig. 3. The enzymes  $11\beta$ -hydroxylase and  $11\beta$ -hydroxysteroid dehydrogenase are responsible for glucocorticoid synthesis and inactivation, as well as 11-ketotestosterone synthesis. The common use of these enzymes creates the potential for competitive inhibition by the substrates and products of these two steroidogenic pathways.

KT. Moreover, since inhibition of 11-KT synthesis does not inhibit testosterone production, IP males would still be able to maintain reproductive function without displaying the 11-KT-mediated TP coloration. Additionally, inhibition of 11-KT synthesis would lead to the accumulation of its precursors, namely testosterone, and IP males are characterized by high levels of testosterone (Cardwell and Liley, 1991).

Removal of TP males may lead to the initiation of sex change in IP females through the reduction of aggressive social interactions and a resultant decrease in cortisol. This would diminish the competitive inhibition by cortisol and permit 11-KT synthesis. Increased levels of 11-KT in a variety of fishes result in morphological changes similar to those observed during sex reversal including restructuring of the genital papilla (Carlisle et al., 2001), changes in coloration (McIntyre, 1998), increased GnRH cell number (Grober et al., 1991), and further modification of the gonad and accessory reproductive structures (Marxer-Miller et al., in preparation). All of these changes occur during natural sex change in the bluehead wrasse, once again emphasizing the importance of 11-KT in the sex change process and the potential role for inhibition by cortisol.

### Multifunctional enzymes, steroid microdomains, and substrate competition

The relatively low substrate specificity and multiple functions of many steroidogenic enzymes suggest that additional regulation of steroid biosynthesis might be achieved through substrate competition and controlling the local availability of steroid precursors.

In addition to its role in the aromatization of androgens, there is evidence that aromatase might also function as an estrogen 2-hydroxylase (Osawa et al., 1993). Osawa et al.

(1993) found that testosterone and androstenedione competitively inhibited estradiol 2-hydroxylation, and estrone and estradiol competitively inhibited aromatization of both testosterone and androstenedione. Substrate competition can therefore direct enzyme function and alter the pattern of steroid production.

Substrate competition can also occur between steroids and nonsteroidal molecules. Catechol *O*-methyl transferase (COMT) is the enzyme responsible for the metabolism of both catecholamines and catechol-estrogens. Through competitive inhibition of COMT, catechol-estrogens can lead to the accumulation of catecholamines in the synaptic cleft and an enhancement of their activity (Balthazart and Ball, 1998). Thus, competitive inhibition may be a relatively widespread mechanism through which steroids exert their influence on physiology and behavior.

Through the metabolism of various substrates, steroidogenic enzymes establish steroid microdomains, in which local levels of steroids can be maintained independent of levels in general circulation. These enzymes can locally inactivate steroids and protect responsive cells from their influence. Conversely, steroid-metabolizing enzymes can reconstitute steroids from their inert forms to amplify the effects of steroids on local targets. The formation of microdomains by steroidogenic enzymes is exemplified by the two isoforms of  $11\beta$ -HSD.

$11\beta$ -HSD1 is expressed in the liver, brain, and pituitary where it functions primarily as an  $11\beta$ -reductase. The reduction of inert GCs, such as cortisone and 11-dehydrocorticosterone, results in the reconstitution of active GCs (Jamieson et al., 1995).  $11\beta$ -HSD1-deficient mice exhibited GC hypersecretion and increased levels of adrenocorticotropic hormone, supporting a role for the reconstitution of GCs in negative feedback (Harris et al., 2001).

$11\beta$ -HSD2 is found predominately in the kidney where it functions primarily as an  $11\beta$ -dehydrogenase, thereby con-

Table 1  
Putative neuroendocrine correlates of social status and sex change in the bluehead wrasse

Status	Presence of T-TP Male		Removal of T-TP Male (Cortisol ↓)		
	Cortisol	Sex steroid profile	Neuroendocrine changes	Sex steroid profile	New status
IP Female	Promotes E <sub>2</sub> synthesis Inhibits AVT expression	E <sub>2</sub> > T	↓ aromatase ↑ 11β-H ↑ 11β-HSD ↑ AVT	11-KT ≫ T, E <sub>2</sub>	T-TP Male
IP Male	Inhibits 11-KT synthesis Inhibits AVT expression	T > E <sub>2</sub>	↑ 11β-H ↑ 11β-HSD ↑ AVT	11-KT ≫ T, E <sub>2</sub>	T-TP Male
NT-TP Male	Inhibits AVT expression	11-KT ≫ T, E <sub>2</sub>	↑ AVT	11-KT ≫ T, E <sub>2</sub>	T-TP Male

verting active GCs into their inert 11-keto forms (Albiston et al., 1994). GC inactivation selectively limits corticosteroid access to the type I adrenal steroid receptor, which has a nearly equal affinity for mineralcorticoids (e.g., aldosterone) and GCs (Rupprecht et al., 1993; Veldhuis et al., 1982). In order for terrestrial vertebrates to properly regulate their plasma osmolarity, the type I adrenal steroid receptor must respond specifically to circulating levels of aldosterone. This specificity is achieved through the local inactivation of GCs to their inert 11-keto forms by 11β-HSD2. This enzyme is able to oxygenate GCs but not aldosterone, thereby preventing the activation of the nonselective adrenal steroid receptor by GCs (Baker, 2001).

Many tissues are unable to synthesize the precursors for their own steroidogenic pathways due to the lack of certain enzymes. Aromatase activity in osteoblasts and chondrocytes is constrained by the availability of androgenic substrates (Labrie et al., 1998). These cells lack the enzymes required for the conversion of cholesterol to androgens, and therefore rely on circulating androgens for local estrogen synthesis. Competitive inhibition could regulate numerous steroidogenic pathways by blocking the synthesis of precursors for other pathways in a given cell or tissue. For instance, the competitive inhibition of 11β-HSD by cortisol could lead to the local accumulation of testosterone and increase the amount of substrate available for aromatization.

As 11-KT is the primary androgen in fishes (Borg, 1994), a direct connection between the reproductive and stress axes is clearly defined in teleosts through the shared use of 11β-H and 11β-HSD for the metabolism of both androgens and GCs. Moreover, the gonad of a sex changing grouper is able to produce both gonadal steroids and GCs, and this capability is altered by sex inversion (Lee et al., 2000).

In many other vertebrates, 11-KT has limited biological activity; thus the enzymes 11β-H and 11β-HSD have received little attention in terms of the effects of GCs on reproductive function. Even though the biological activities of many steroid metabolites are negligible in terms of their affinity to endogenous receptors, they still have the potential to affect reproductive physiology and behavior through their capacity as precursors and competitive inhibitors of other biosynthetic pathways. Disorders resulting from congenital enzyme deficiencies, such as congenital adrenal hyperplasia

and 5α-reductase deficiencies, clearly demonstrate that the accumulation or shortage of certain precursors can shift metabolic processes and impact physiology and behavior (Berenbaum et al., 2000; Gell and Bradshaw, 1998). Therefore, the connections between steroidogenic pathways that share common enzymes should be considered an important source of developmental regulation.

### Two sides of a coin: inhibition of sex change/promotion of IP status

In addition to inhibiting 11-KT synthesis, GCs may also actively promote the synthesis of estrogens, thereby maintaining the endocrine profile of IP females and discouraging sex change. Cortisol derived from the fetal androgen glands in mammals has been implicated in the increase in estrogen concentrations leading to parturition and placental maturation (Throburn and Challis, 1979). Additionally in cows, the application of the synthetic GC dexamethasone increased the *in vitro* production of estrogen (Gross and Williams, 1988). If GCs exert this proestrogen effect in nonplacental steroidogenic tissues, such as the brain or gonad, then cortisol may inhibit sex change by promoting ovarian function in IP females (see also, Morrey et al., 2002).

### Sex on the brain: a role for nongonadal steroids

Regulation of the complex sociosexual behavior involved in reproduction is clearly not achieved through a single mechanism; however, it is likely that critical gating mechanisms exist that influence the other components of the regulatory system. GCs have been shown to reflect changes in the social environment and impact the development and behavior of many vertebrate species. In this current model, GCs are proposed to regulate both the changes in the brain and gonads that are required for complete sex reversal, namely the production of AVT and 11-KT (Table 1). This model is also predicated on the idea that behavioral sex change and gonadal conversion possess different sensitivities to GC suppression. We suggest that NT-TP males represent IP individuals that have overcome the GC suppres-

sion of 11-KT synthesis but are still sensitive to GC-mediated repression of AVT transcription in parvocellular neurons of the hypothalamus.

Changes in the production of aggression and courtship behavior (and ostensibly the central nervous system) in gonadectomized bluehead wrasse have been observed in field studies of sex change (Godwin et al., 1996, 2000). This demonstrates that changes in the gonad are not required for the initiation of behavioral sex change, a process that requires increased hypothalamic AVT expression. While it appears that AVT production and T-TP male behavior are not dependent upon gonadal steroids, these observations do not negate a role for steroids in sex change. AVT might increase an individual's responsiveness to steroids, or alter the synthesis of steroids in the brain or other steroidogenic tissues. Alternatively, if the rapid increase in magnocellular AVT expression increased the activity or number of steroid receptors in neurons controlling reproductive behavior, then these neurons would be able to respond to the relatively low levels of 11-KT produced by the IP gonad. Thus, 11-KT-mediated behavior could be observed in sex changing fish before the completion of gonadal conversion. Alternatively, AVT could affect neural steroidogenesis, and thereby rapidly alter steroid profiles and behavior before gonadal conversion. This suggests that steroidogenesis in the brain may be driving the changes in the gonads, and thus may be more critical in the regulation of sexual development (e.g., Schlinger, 1998; Tsai et al., 2001).

Studies of temperature-dependent sex determination and neural aromatase activity in the red-eared slider turtle also suggest that the brain is more important than the gonads in terms of initiating sexual differentiation in this species (Willingham et al., 2000). Thus, in the bluehead wrasse, changes in neural aromatase activity or neural steroid receptors might be the critical factor mediating behavior sex change by altering the influence of steroids before gonadal conversion has occurred (Grober, 1997), possibly by increasing the expression of other neuropeptides or the activity of their receptors (Frye, 2001; Lephart et al., 2001).

The notion of altered steroid sensitivity opens up other intriguing possibilities. For instance, if T-TP males have increased levels or activity of 11 $\beta$ -H and 11 $\beta$ -HSD for 11-KT synthesis, they might be more resistant to the effects of stress, as these enzymes would allow for a more rapid inactivation of GCs. As noted above, IP males and females are more responsive to capture stress in terms of plasma cortisol elevations than are T-TP males (Semsar and Godwin, personal communication). This resistance to GC accumulation could also allow T-TP males to maintain their dominant position in the social group. Substrate competition might also contribute to the sex differences seen in stress reactivity in other vertebrate species, as males and females will have different levels of these enzymes according to their sex-specific patterns of steroid production.

The social control of sex change is most likely mediated through the same basic components of the HPG and HPA

axes that are conserved among vertebrates. Our model of the neuroendocrine mechanisms underlying the social control of sex change in the bluehead wrasse suggests that GCs, functioning both as modulators of transcription and competitive inhibitors of steroid production, could serve as critical gating signals in the regulation of sexual function. These regulatory mechanisms can be applied to other vertebrate systems, in which their contribution might not be as readily apparent.

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