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SYMPOSIUM

Social Regulation of Male Reproductive Plasticity in an African Cichlid Fish

Karen P. Maruska[1,*,†] and Russell D. Fernald*

*Department of Biology, Stanford University, Stanford, CA 94305, USA; †Department of Biological Sciences, Louisiana State University, Baton Rouge, LA 70803, USA

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[1]E-mail: kmaruska@lsu.edu

Synopsis Social interactions with the outcome of a position in a dominance hierarchy can have profound effects on reproductive behavior and physiology, requiring animals to integrate environmental information with their internal physiological state; but how is salient information from the animal's dynamic social environment transformed into adaptive behavioral, physiological, and molecular-level changes? The African cichlid fish, *Astatotilapia burtoni,* is ideally suited to understand socially controlled reproductive plasticity because activity of the male reproductive (brain–pituitary–gonad) axis is tightly linked to social status. Males form hierarchies in which a small percentage of brightly colored dominant individuals have an active reproductive axis, defend territories, and spawn with females, while the remaining males are subordinate, drably colored, do not hold a territory, and have a suppressed reproductive system with minimal opportunities for spawning. These social phenotypes are plastic and quickly reversible, meaning that individual males may switch between dominant and subordinate status multiple times within a lifetime. Here, we review the rapid and remarkable plasticity that occurs along the entire reproductive axis when males rise in social rank, a transition that has important implications for the operational sex ratio of the population. When males rise in rank, transformations occur in the brain, pituitary, circulation, and testes over short time-scales (minutes to days). Changes are evident in overt behavior, as well as modifications at the physiological, cellular, and molecular levels that regulate reproductive capacity. Widespread changes triggered by a switch in rank highlight the significance of external social information in shaping internal physiology and reproductive competence.

Introduction

Plasticity in the reproductive system triggered by external stimuli is widespread among vertebrate taxa (Bass and Grober 2001; Dufty et al. 2002; Lemaitre et al. 2011; Oliveira 2012; Stevenson et al. 2012). From fishes to mammals, there are numerous examples of how environmental cues such as photoperiod and temperature, and social interactions such as aggression and exposure to the opposite sex, can alter reproductive physiology in adult sexually mature animals (Whittier et al. 1987; Wingfield et al. 1990; Demas and Nelson 1998; Taranger et al. 2003; Sapolsky 2005; Stevenson et al. 2008; Maruska and Fernald 2011b). By necessity, this plasticity occurs at multiple levels of biological organization (i.e., behavioral, cellular, and molecular) on different temporal scales (i.e., short-term interaction or long-term seasonal changes). Thus, in addition to the plasticity that can occur during vertebrates' sex determination, and that produces specific ratios of males and females (Gamble and Zarkower 2012; Munger and Capel 2012), many species living in dynamic social groups show a form of socially-mediated reproductive plasticity that occurs within a single sex (Altmann et al. 1995; Koyama and Kamimura 2000; Fernald 2009; Ramm and Stockley 2009). In these cases, there are two or more different phenotypes within a sex that have drastically different and typically unequal reproductive potential. For example, it is usually the high-ranking dominant individuals that have active reproductive systems, greater access to mates and other resources, and

higher reproductive success compared with their socially suppressed subordinate counterparts. However, since long-term maintenance of this dominant phenotype can be costly (Sapolsky 2005; Bell et al. 2012), social and environmental instability offers opportunities for lower-ranking individuals to challenge or replace higher-ranking ones and move into a position of superior status. Although it is well known that this type of transition is associated with adaptive changes in behavior and reproductive physiology, many of the mechanisms involved remain enigmatic.

Since social interactions have consequences for reproduction in all vertebrates, including humans (Hopcroft 2006), many of the neural and hormonal processes regulating these behaviors are likely to be well conserved (Insel and Fernald 2004); but how do animals recognize and then adjust their reproductive behavior and physiology in response to social cues? In this review, we use a representative example from fishes, the largest and most diverse group of vertebrates, to illustrate how an animal's external social environment can rapidly and dramatically change his reproductive behavior, physiology, and resource-holding potential. We begin by introducing the African cichlid fish model system, and how our ability to manipulate this species' social environment allows us to examine the precise timing of plasticity in its reproductive system. Although hormones influence sex ratios in many vertebrates (Krackow 2008; Paul-Prasanth et al. 2011), our example in the cichlid fish represents a case in which social interactions dictate which individual males comprise the sexually active population available to receptive females. These social interactions help determine male dominance status, which then sets the activity of his brain–pituitary–gonad (BPG) axis and hormonal levels, thereby maintaining his sexually active role and influencing the operational sex ratio of the population. Our focus here, however, is solely on males' reproductive plasticity, while discussions of female plasticity in this species are presented elsewhere (White and Fernald 1993; Fernald 1995, 2009; Renn et al. 2012; Maruska and Fernald 2013). Next, we focus on each level of the male reproductive axis, from behavior to the brain to the testis, and highlight the rapid changes that occur as a male makes the transition from a low-ranking subordinate to a high-ranking dominant phenotype. Collectively, these studies represent one of the most complete examples we have to date of how social salience can impact reproductive function at multiple biological levels and time-scales within a single sex of a single species. We conclude by emphasizing what remains undiscovered, present several future directions to advance the field, and highlight the potential of cichlid fishes as models for studying socially-mediated reproductive plasticity. Because many of the physiological and hormonal processes mediating social behaviors are conserved, these studies in a model fish have broad implications for all vertebrates.

The African cichlid fish *Astatotilapia burtoni* as a model for studying adult social reproductive plasticity

Over the past several decades, the African cichlid fish, *A. burtoni*, has become a valuable vertebrate model system for studying how the social environment influences behavior, the brain, and the reproductive system (Fernald and Hirata 1977; Hofmann and Fernald 2001; Fernald 2012; Fernald and Maruska 2012; Maruska and Fernald 2013). *Astatotilapia burtoni* is a maternal mouth-brooding cichlid fish endemic to Lake Tanganyika in the rift valley system in Eastern Africa where it lives in shallow shorepools and riverine estuaries (Fernald and Hirata 1977). The males of this species exist in two distinct, rapidly reversible, phenotypes (Fig. 1). Furthermore, the reproductive capacity of these two male phenotypes is tightly coupled to their social status (Fernald 2009). Dominant, or territorial, males represent a small percentage of the population (10–30%), are brightly colored (blue or yellow color morphs) with a black stripe through the eye (eye-bar), an opercular black spot at the caudal edge of the gill cover, prominent egg-spots on the anal fin, and a red humeral patch on the side of the body (Fig. 1). Yellow and blue dominant males both exist in nature and in laboratory environments, and they differ in behavioral and hormonal profiles (Korzan and Fernald 2007; Korzan et al. 2008). These dominant males, however, can and do reversibly change between yellow and blue coloration, suggesting they may use color change as a flexible behavioral strategy (Korzan et al. 2008). Dominant males of both colors hold territories that they defend vigorously and spend substantial time attempting to court and spawn with females (Fernald 1977; Fernald and Hirata 1977; Maruska and Fernald 2010a). In contrast, subordinate, or non-territorial, males make up the majority of the male population (70–90%); show more faded coloration (lacking eye-bar and humeral patch); do not hold territories or typically reproduce, school with females and other subordinates; and flee from aggressive dominant males (Fig. 1). *Astatotilapia burtoni* live in a lek-like social system in which dominant males defend clustered territories that provide food, shelter, and

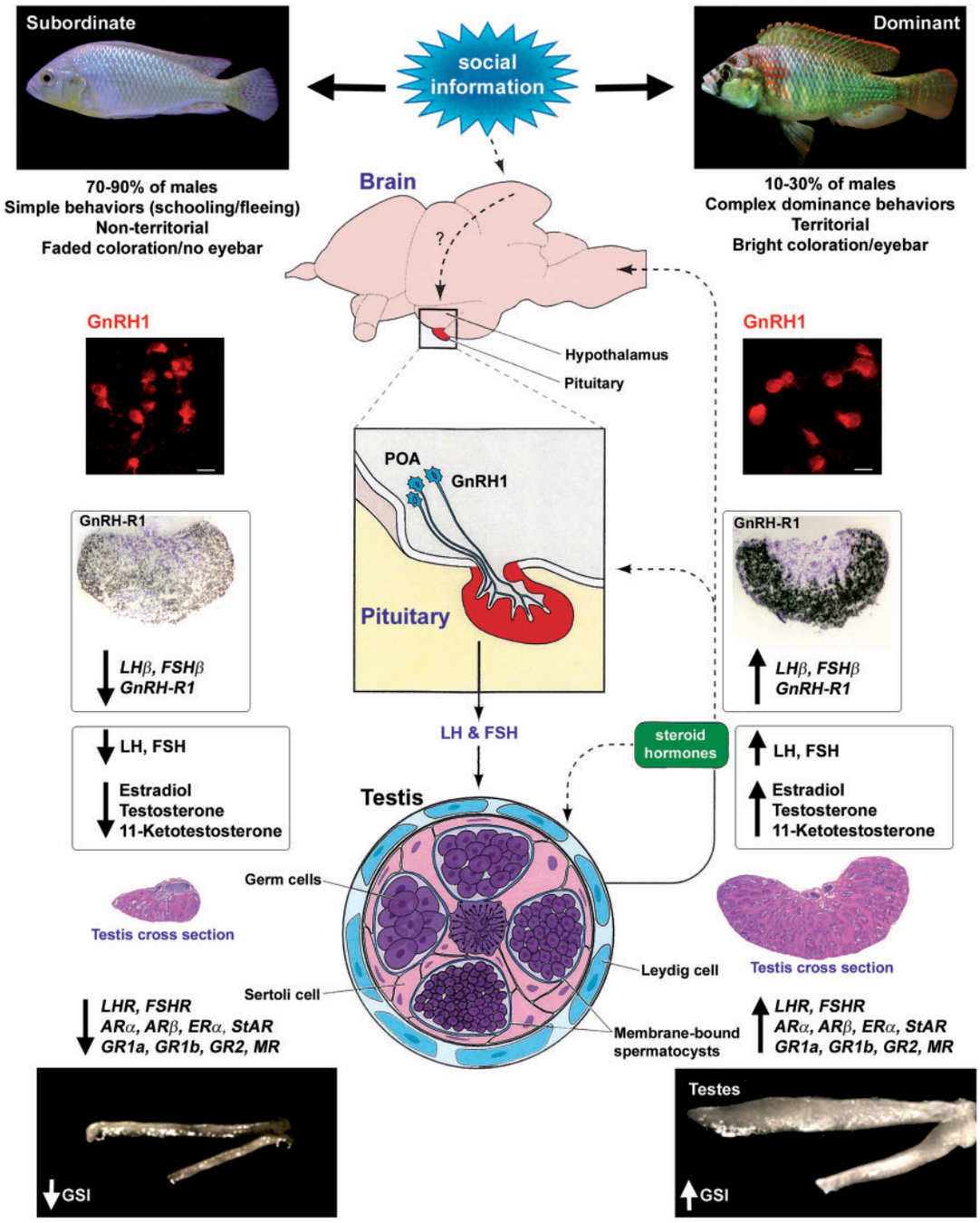

Fig. 1 Summary of socially-mediated differences in the BPG axis between stable subordinate and stable dominant male phenotypes of *Astatotilapia burtoni*. Dominant males (right) have an up-regulated BPG axis, defend territories, and regularly court and spawn with females, whereas subordinate males (left) have a suppressed BPG axis, do not hold territories, and typically do not reproduce. All of these features are influenced by the social environment and can rapidly change (minutes to days) when males are given a social opportunity to ascend, or rise, to a higher-ranking status. Only those measures directly relevant to the BPG axis are shown. Red GnRH1 neurons represent immunohistochemical staining in the preoptic area of the brain, and GnRH-R1 staining (black label; with purple cresyl violet counterstain) in the pituitary gland is from an *in situ* hybridization experiment. Italicized genes indicate mRNA levels measured via qPCR. Cross sections of testes were stained with hemotoxylin and eosin. Modified in part from Maruska and Fernald (2011b) and Maruska et al. (2013), and information was compiled from a number of studies (Davis and Fernald 1990; Chen and Fernald 2006; Maruska and Fernald 2010a, 2011a; Maruska et al. 2011; Huffman et al. 2012). ↑, higher relative levels; ↓, lower relative levels. ARα, ARβ, androgen receptor subtypes α and β; ERα, estrogen receptor subtype α; FSHβ, β-subunit of follicle stimulating hormone; FSHR, FSH receptor; GnRH1, gonadotropin releasing hormone 1; GnRH-R1, GnRH receptor subtype 1; GR1a, GR1b, GR2, glucocorticoid receptor subtypes 1a, 1b, 2; GSI, gonadosomatic index; LHβ, β-subunit of luteinizing hormone; LHR, LH receptor; MR, mineralocorticoid receptor; StAR, steroidogenic acute regulatory protein.

substrate for spawning. Since suitable space for these defendable territories is often limited, and females are less likely to mate outside the protection of a shelter, there is intense competition for this resource, and as a result, only a minority of males at any one time will defend territories and court females. This fierce pressure among males helps set the evolutionary stage for their reproductive plasticity.

The two male phenotypes described above also differ in reproductive physiology such that dominant males have an active and up-regulated BPG axis compared with subordinate males (see sections below). Importantly, these behavioral and physiological features of each male phenotype are reversible and under social control, such that when a territory is vacated, a subordinate male will quickly rise in social rank (or ascend in status) and take it over. In nature, the social and physical environment fluctuates often, providing frequent opportunities for this phenotypic switching (Fernald and Hirata 1977). This transition between subordinate and dominant states also can be experimentally controlled in the laboratory (Burmeister et al. 2005; Maruska and Fernald 2010a), and it is this natural phenotypic plasticity that provides an excellent opportunity to understand the physiological consequences induced by changes in dominance status.

To provide an opportunity for males to rise in rank, or socially ascend, we use an experimental paradigm that begins by placing a socially suppressed subject male into the center compartment of an experimental tank with a larger dominant resident male and several females, a situation that keeps him in a subordinate position (Burmeister et al. 2005; Maruska and Fernald 2010a). This central experimental compartment is separated from groups of fish (dominant males, subordinate males, and females) on either side with transparent acrylic barriers so that fish can interact visually, but not physically, across the dividers. On the day we create the social opportunity, the larger resident dominant male is removed with a net 1 h prior to light onset using infrared night-vision goggles, a procedure that minimizes disturbance and ensures that visual absence of the resident occurs consistently at light onset for all subject individuals. Suppressed fish presented with a social opportunity in this paradigm intensify their body coloration, turn on their eye-bar, and begin performing dominance behaviors (territorial and reproductive) toward males and females within just a few minutes. By then sampling these subject males at different times after triggering social ascent, we can discover "what" changes occur, "where" along the reproductive axis they occur, and "how quickly" they occur during the social transition. Stable dominant males and stable subordinate males (males that maintained their respective social status for 4–5 weeks prior to experiments) are used as control comparisons to the males rising (ascending) in rank.

Social regulation of behavior

Subordinate males that do not hold territories must continuously monitor their surroundings both to protect themselves from the attacks of dominant males, and to watch for newly vacated territories that improve their chances of spawning. Since territory real estate is often limited in nature, when space does become available, it is in a males' best interest to occupy it quickly, signal his new ownership, and advertise his spawning readiness to females. In fact, within minutes (mean latency = 12 min) of being presented with a social opportunity (e.g., vacant territory), subordinate males begin performing both aggressive and reproductive behaviors (Burmeister et al. 2005; Maruska and Fernald 2010a). Levels of overt aggressive behaviors such as frontal displays, lateral displays, and border fights that are directed at neighboring dominant males across the transparent barriers are highest during the first 30 min after social opportunity. Over the course of the next few hours, however, these territorial behaviors decrease concomitantly with an increase in reproductive behaviors such as courtship quivers, leading, entering the shelter used for spawning, and chasing females (Maruska and Fernald 2010a). This rapid switch in behavioral priority is likely an adaptation that allows these previously suppressed males to first quickly establish dominance and then begin spawning in their competitive breeding environment. While the salient sensory cues that subordinate males use to detect the absence of the resident dominant male, and evaluate whether they should take over the territory and begin to display dominance, are not completely understood, it likely involves a cognitive appraisal of multisensory information including vision, chemoreception, mechanoreception, audition, and tactile signals (Fernald 2002; Maruska and Fernald 2010b, 2012; Chen and Fernald 2011; Maruska et al. 2012b).

Social regulation of the brain and gonadotropin-releasing hormone 1 neurons

To initiate a change in reproductive physiology, a male must first evaluate and perceive an opportunity in his social environment, integrate this information with other relevant internal signals, and then

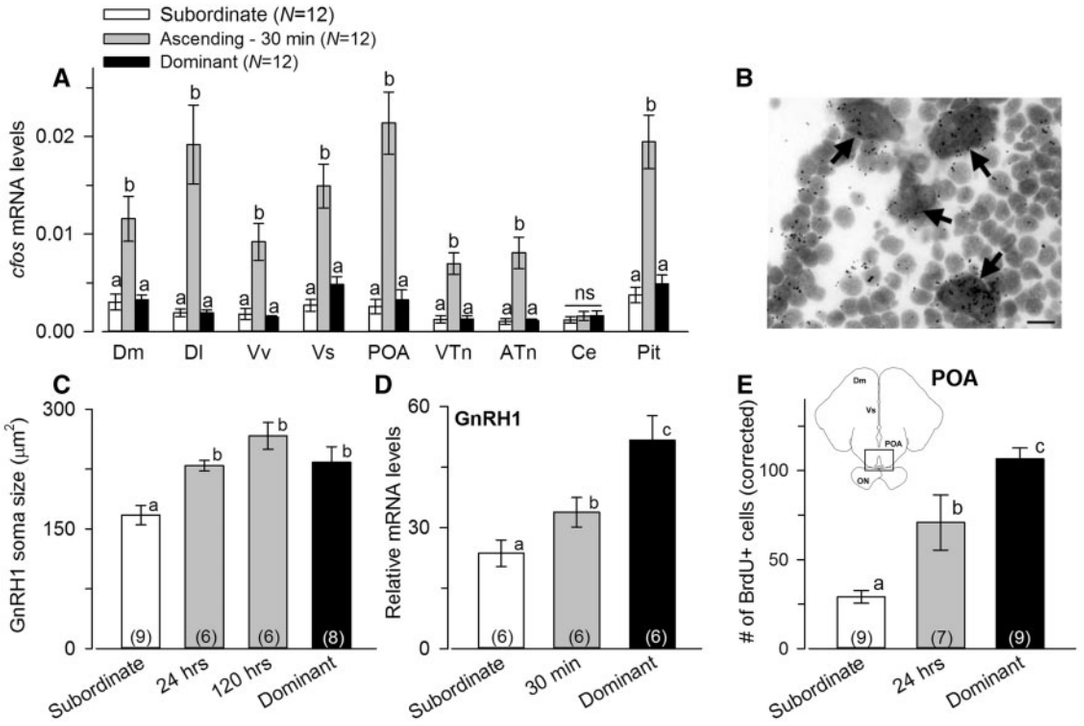

Fig. 2 Social opportunity rapidly activates the brain in male *A. burtoni* rising in status. (**A**) Social opportunity rapidly increases mRNA levels of the IEG *cfos* in brain nuclei involved in processing social information. Relative mRNA levels (normalized to the reference genes *18s* and *g3pdh*) measured via qPCR in microdissected regions of the brain were higher in males that ascended in social status 30 min prior compared with either stable subordinate or stable dominant control males (Maruska et al. 2013). ATn, anterior tuberal nucleus; Ce, cerebellum; Dm, medial part of the dorsal telencephalon; Dl, lateral part of the dorsal telencephalon; Pit, pituitary; POA, preoptic area; Vs, supracommissural nucleus of the ventral telencephalon; VTn, ventral tuberal nucleus; Vv, ventral nucleus of the ventral telencephalon. (**B**) The IEG *egr-1* (small black dots detected via *in situ* hybridization) is rapidly up-regulated in GnRH1 neurons (arrows) of the preoptic area within 20 min of a male rising in social rank (Burmeister et al. 2005). (**C**) Stable dominant males have larger GnRH1 neurons compared with stable subordinate males, but an increase in soma size is detected just 24 h after males ascended in social status. (**D**) GnRH1 mRNA levels measured in whole brains via qPCR are higher in newly ascended males at 30 min after social opportunity compared with stable subordinate males, but still lower than that of stable dominant males. (**E**) Cell proliferation, quantified by BrdU labeling, in the preoptic area (POA) is relatively low in stable subordinate males, but has increased in males at 24 h after they rise in social rank (Maruska et al. 2012a). Sample sizes represent the number of animals used for each experiment and are indicated in parentheses. Bars with different letters indicate significant differences at $P < 0.05$.

translate this "decision" into behavioral and physiological adjustments. Although the mechanisms are not completely understood, this complex task is essentially mediated by the brain (Fernald 2012; Fernald and Maruska 2012). How then, does the brain respond to a change in social position, and how does it notify the reproductive axis of this impending transition? When a suppressed subordinate male is provided with an opportunity to acquire a vacant territory and rise in rank, within just 30 min, there are increases in mRNA levels of the transcription factor immediate early genes (IEGs) *egr-1* (also called *zenk*, *zif-268*, and *ngfi-a*) and *cfos* throughout socially-relevant regions of the brain, including the preoptic area (Maruska et al. 2013) (Fig. 2A and B). These IEGs reflect rapid changes in relative neuronal activity that lead to downstream transcriptional changes in the cell and commonly are used to provide information about which brain regions or cell types are involved in activation of context-dependent neural circuits (Clayton 2000; Kovacs 2008; Robinson et al. 2008). Thus, activation of IEGs from a social opportunity likely represents a neuromolecular switch that helps transduce social information into changes in brain function and behavior, and ultimately reproductive output. Future studies using "module" or "network" types of approaches could help identify suites of genes that are co-regulated with IEGs during transitions in status (Renn et al. 2008; O'Connell and Hofmann 2012a, 2012b). These types of studies will advance our understanding of how changes in gene transcription are related to behavioral and other physiological measures of social reproductive plasticity.

In addition to activation of socially-relevant regions of the brain, there are also several rapid changes in gonadotropin-releasing hormone 1 (GnRH1) neurons, which sit at the apex of the conserved reproductive axis and in fishes, directly project to the pituitary gland (Fig. 1). First, the social opportunity causes a rapid (20–30 min) induction of *egr-1* in the preoptic area and specifically in GnRH1 neurons (Fig. 2B) (Burmeister et al. 2005; Maruska et al. 2013). This response is likely due to the recognition of the social opportunity because it is not evident in males who are already dominant and performing similar behaviors. This type of molecular response to an opportunity may be conserved across vertebrates because socially-relevant reproductive stimuli also induce IEG expression within GnRH1 neurons in fishes (Burmeister et al. 2005), birds (Stevenson et al. 2012), and mammals (Pfaus et al. 1994; Meredith and Fewell 2001; Gelez and Fabre-Nys 2006). Second, an increase in GnRH1 soma size is detected as soon as 1 day after males rise in rank (McCurdy 2011), and these neurons reach or exceed sizes characteristic of stable dominant males within 5–7 days (White et al. 2002) (Fig. 2C). The significance of this structural change in soma size is not known, but it may function in accommodating changes in the cellular and molecular demands of the cell. Although not yet examined during the transition period, the larger GnRH1 neurons in stable dominant males also have distinct membrane properties, e.g., higher membrane capacitance, lower input resistance, shorter duration of action potentials (Greenwood and Fernald 2004), and greater dendritic complexity (Scanlon et al. 2003) compared with stable subordinate males. The male's social transition does not, however, alter the total number of GnRH1 cells (Davis and Fernald 1990; Fernald 2009). Third, there is an increase in GnRH1 mRNA levels in the brain at 30 min after ascent (Fig. 2D), suggesting that the transcriptional machinery in these cells is quickly stimulated, and possibly mediated via induction of *egr-1* from the novel social opportunity. Thus, very quickly after rising in social rank, many regions of the brain, along with the GnRH1 neurons that directly control the reproductive axis, have been stimulated.

Male *A. burtoni* that recently ascended in social status also show higher cell proliferation throughout the brain, including in the preoptic area where the GnRH1 neurons and other regulatory neuropeptides are located, compared with stable subordinate males (Maruska et al. 2012a) (Fig. 2E). Remarkably, this increased cell proliferation was estimated to occur quickly (within 2–4 h) after males were given an opportunity to rise in social rank, based on the metabolic activity of the BrdU marker. Although the cellular fate of these new brain cells is unknown, their increased proliferation may serve to accommodate the new neural and cognitive demands associated with transition to dominance, including those involved with social learning and regulation of the reproductive axis. Subordinate and dominant males also have different brain transcriptome profiles, suggesting that social status regulates gene expression within large gene networks, leading to many structural and physiological changes that characterize each social phenotype (Renn et al. 2008). Future use of high-throughput technologies that allow simultaneous measures of many mRNAs, proteins, or microRNAs will certainly provide valuable information on the cellular and molecular mechanisms underlying complex social behaviors and changes in dominance in *A. burtoni,* as well as identify common themes among all social animals.

Social regulation of the pituitary gland and gonadotropin hormones

In fishes, GnRH1 neurons in the preoptic area of the brain project directly to the gonadotropin-producing cells in the anterior pituitary gland (Fig. 1). GnRH1 peptide is released in the pituitary and then binds to G-protein-coupled receptors that stimulate the release and synthesis of the gonadotropin hormones, luteinizing hormone (LH), and follicle stimulating hormone (FSH). In males, LH and FSH then target the testes to stimulate steroid production and spermatogenesis. Multiple forms of GnRH receptors (i.e., types I, II, and III) are found in mammals (Millar 2005), amphibians (Wang et al. 2001), and fishes (Robison et al. 2001; Lethimonier et al. 2004; Moncaut et al. 2005; Flanagan et al. 2007). These multiple receptor types are common even within a single species and often show different spatial and temporal patterns of expression (e.g., among different types of tissues and cells; across season, reproductive stage, development, or social status), which suggests functional specializations (Crowley et al. 1998; Levavi-Sivan et al. 2004; Au et al. 2006; Chen and Fernald 2006; Lin et al. 2010). In male *A. burtoni*, pituitary mRNA levels of *GnRH-R1*, but not *GnRH-R2*, are socially regulated such that stable dominant males have higher levels compared with stable subordinate males (Au et al. 2006; Maruska et al. 2011). The increase in *GnRH-R1* during the social transition occurs over several days following social ascent, even though the effects of the GnRH1-receptor-binding interaction are evident by

higher levels of LH and FSH (mRNA and circulating mature hormone) within minutes (Maruska et al. 2011). Pituitary mRNA levels of the IEGs *egr-1* and *cfos* are also increased at 30 min after males rise in rank (Maruska et al. 2013) (Fig. 2A), although the cellular identities of this IEG induction are not known. In mammals, GnRH1 stimulates transcription of *LHβ* and *FSHβ* via *egr-1* and *cfos* induction, respectively, and recently was shown to extend the half-life of cFos via posttranslational modifications that allows increased FSH production during periods of low GnRH1 (Reddy et al. 2012). Similar mechanisms may exist in the fish that rapidly modify pituitary output in different social contexts, but this remains to be tested.

Pituitary mRNA levels of *LHβ* and *FSHβ* are rapidly increased at just 30 min after males rise in social rank, to levels similar to those seen in stable, dominant males (Maruska et al. 2011). Furthermore, because circulating levels of LH and FSH protein are also higher at 30 min after ascent, again to levels that do not differ from those of stable dominant males, it suggests that GnRH1 activation of the pituitary stimulates both the release "and" the synthesis of gonadotropins (Maruska et al. 2011). Thus, within minutes of a social opportunity, the pituitary portion of the axis has been stimulated by GnRH1 and potentially by other neuromodulators as well. The increased levels of circulating LH and FSH indicate that the testes are also stimulated within this short time-frame. Moreover, there are also rapid increases in mRNA levels of some estrogen receptor subtypes (ERα and ERβa) and of aromatase in the pituitary gland at 30 min after males rise in rank (Maruska et al. 2013). This suggests that steroid sensitivity of the pituitary, in addition to that of the brain, may be an important regulatory mechanism during socially-mediated reproductive plasticity, thereby fine-tuning the activity of the BPG axis.

Social regulation of the testes

In addition to small GnRH1 neurons and low activity of the BPG axis, subordinate males also have small testes. However, despite their reduced size, the testes continue to produce sperm during the suppression period and also likely retain viable sperm from the time they were last dominant (Maruska and Fernald 2011a; Kustan et al. 2012). This is significant, and adaptive, because it allows reproductively suppressed males to immediately spawn with females when they rise in rank, without having to wait several days for the testes to grow and produce new sperm (Maruska and Fernald 2011a; Kustan et al. 2012). It also suggests that lower-ranking males that do not hold territories can still reproduce by engaging in sneak attempts at fertilization, a behavior observed frequently in laboratory settings (Kustan et al. 2012). There are also rapid changes in sperm quality (percent motility) in ascending males when compared with stable subordinate males (Kustan et al. 2012), which could result from direct steroid action on the testes or be mediated via effects on the central nervous system. These mechanisms would allow for quick adjustments in a competitive dynamic breeding environment, similar to that recently described for changes in ejaculate volume and sperm density in goldfish (Mangiamele and Thompson 2012). Behavioral experiments also showed that suppressed *A. burtoni* males can successfully spawn and fertilize eggs within minutes-hours after rising in social rank, a latency that does not differ from that of stable dominant males with much larger testes that were tested in the same experimental setup (Kustan et al. 2012). Thus, despite their lack of a territory and their suppressed reproductive system, subordinate males maintain sufficient testicular activity to quickly take advantage of any opportunities for mating; the type of opportunity, however, depends on their social status and relative position in the dominance hierarchy.

During males' transition from subordinate to dominant status, the morphological and structural changes in composition of testicular cells and in relative testicular size takes several days, while many molecular changes in the testes are detected more quickly (Maruska and Fernald 2011a; Huffman et al. 2012). For example, there are increases in the early stages of spermatogenesis (type B spermatogonia and spermatocytes) by 3 days after ascent, which is before any increases in size of the testes, or in gonadosomatic index, are detected at 5–7 days (White et al. 2002; Maruska and Fernald 2011a). Social opportunity also triggers rapid (minutes to hours) changes in mRNA levels of some receptor types (*FSHR*; androgen receptors), as well as slower (days) changes in other receptor types (*LHR*; estrogen receptors; and *aromatase*, the enzyme that converts testosterone to estradiol) (Maruska and Fernald 2011a). Glucocorticoid and mineralocorticoid receptors are also quickly elevated by 30 min after social opportunity, suggesting that testicular sensitivity to stress hormones may also contribute to the social regulation of spermatogenesis, sperm quality, and production of sex-steroids (Milla et al. 2009). Collectively, the rapid transcriptional responses observed in the testes, the most downstream component of the BPG axis, highlight the importance of

social information as a regulator of reproductive function at every level of the axis.

In *A. burtoni* males, therefore, there are measureable morphological, cellular, and transcriptional changes from the brain to the testes, all within minutes of a social opportunity, which is much more rapid than previously realized. The exact mechanisms that transduce the social information into molecular changes, particularly in the testes, remain unknown. Further, the swift molecular changes in the testes raise the alternate possibility that there might be other signaling pathways that perhaps bypass the inferred linear cascade from release of brain GnRH1 to release of pituitary gonadotropins to activation of the testicular gonadotropin receptors. For example, the recent discovery of multiple types of vasotocin receptors in the gonads of fishes (Lema 2010; Lema et al. 2012) suggests that there may be alternate neuroendocrine pathways, such as release of vasotocin or isotocin from the posterior pituitary gland, acting directly on the testes that in turn stimulate release of steroids, thereby controlling the production and quality of sperm. The hypothesized involvement of alternate signaling pathways, however, requires further study.

Social regulation of circulating steroid hormones and of steroid receptor expression

The outcome of the up-regulated BPG axis in dominant males is large, mature testes, which in addition to producing sperm also synthesize and release sex-steroid hormones that can modulate behaviors. Circulating sex-steroids (e.g., androgens, estrogens, and progestins) play vital roles in translating social and physiological cues into behavioral responses by both acting via membrane-bound receptors and via nuclear receptors that function as transcription factors that modulate gene expression (Sakamoto et al. 2012). Steroids can therefore directly influence behavioral circuits through rapid non-genomic mechanisms, or via modulating the expression levels of downstream genes (genomic mechanism). Nuclear receptors for sex-steroids and corticosteroids are widespread throughout the brain of *A. burtoni*, show social-status differences in expression levels within specific brain nuclei, and therefore have the potential to help integrate the internal hormonal state with external social information (Greenwood et al. 2003; Harbott et al. 2007; Munchrath and Hofmann 2010; Maruska et al. 2013). Feedback of sex steroids on the GnRH1 system, for example, is important for regulation of the BPG axis in male *A. burtoni*. Androgen receptors in *A. burtoni* are expressed in GnRH1 neurons (Harbott et al. 2007), and androgens, but not estrogens, were shown to regulate GnRH1 cell size (Soma et al. 1996). Castrated males have hypertrophied GnRH1 neurons (Francis et al. 1992, 1993; Soma et al. 1996), and therefore, the set-point for GnRH1 cell size appears to be determined by social cues and then maintained by negative feedback from androgens (Soma et al. 1996). Additional studies are needed to test this "social-set-point hypothesis" and to examine how different sex-steroid-receptor subtypes might regulate socially-controlled plasticity of GnRH1 neurons.

In many vertebrates, levels of circulating sex-steroids can increase rapidly following social interactions as part of a physiological response to challenges (i.e., "Challenge Hypothesis") (Wingfield et al. 1990; Oliveira et al. 2002; Hirschenhauser and Oliveira 2006; Dijkstra et al. 2012). When subordinate male *A. burtoni* are given an opportunity to rise in rank, there is a robust increase in circulating levels of androgens (testosterone, 11-ketotestosterone), 17β-estradiol, and cortisol at just 30 min after ascent (the earliest time-point measured) (Maruska and Fernald 2010a; Maruska et al. 2013). It is not known, however, whether this endocrine response is necessary for, or is a consequence of, the observed rapid behavioral changes. However, there appears to be little correlation between circulating androgen levels and aggressive behaviors, particularly in males ascending in status, either in *A. burtoni* or in other fish species with dominance hierarchies (Maruska and Fernald 2010a; Alonso et al. 2012). This suggests that circulating steroids may play little to no role in regulating quick behavioral changes during social transition, or at least that their levels are not predictive of an individual's behaviors. There are, however, rapid changes in mRNA levels of sex-steroid receptors within distinct brain regions on this same timescale, suggesting that localized changes in steroid sensitivity of brain nuclei may be more important for behavioral adjustments (Maruska et al. 2013). The hypothesis that behavioral variation in aggression may be less related to circulating steroids and more related to neural sensitivity to steroids was also recently supported in birds (Ball and Balthazart 2008; Rosvall et al. 2012). Importantly, the conserved social-processing regions of the brain express abundant steroid receptors (e.g., social decision-making network), and hormonal action can change the relative inputs from different nuclei within a network and allow integration of social inputs with internal animal physiological state to coordinate context-appropriate behaviors (Newman 1999; Goodson 2005;

O'Connell and Hofmann 2011, 2012a). Although unexplored in *A. burtoni*, localized changes in steroid production in specific circuits or nuclei in the brain (i.e., neurosteroids) also may play an important role in regulating perception of social information and the output of adaptive behaviors (Do-Rego et al. 2006; Remage-Healey and Bass 2006; Remage-Healey et al. 2010; Remage-Healey and Joshi 2012).

There are also many differences in mRNA levels of sex-steroid receptor subtypes between dominant and subordinate *A. burtoni* males that vary among different regions of the brain, suggesting a complex regulatory system within each stable phenotype (Burmeister et al. 2007; O'Connell and Hofmann 2012b; Maruska et al. 2013). For example, androgens and progestins were found to modulate courtship behavior solely in dominant *A. burtoni* males, whereas estrogens influenced aggressive behaviors independent of social status (O'Connell and Hofmann 2012b). Further, there was a greater proportion of changes in gene expression in the preoptic area of dominant (8.25%) compared with subordinate (0.56%) males between individuals that were treated with vehicle versus an estrogen receptor antagonist (O'Connell and Hofmann 2012b). That study suggests that social status may act as a permissive factor for sex-steroid regulation of gene expression and complex behaviors, but that socially induced changes at one level of biological organization (e.g., behavioral, hormonal, and gene expression) do not simply predict changes at other levels. Rather, there may be status-specific network modules that integrate behavior, gene expression, and hormone profiles to regulate male sociality (O'Connell and Hofmann 2012b). However, the steroid regulation of behaviors and gene expression in socially transitioning animals may differ substantially from these stable subordinate and dominant phenotypes and require further investigation.

Conclusions and future directions

In social species that form dominance hierarchies, position or rank in the society comes with consequences that impact survival and reproductive fitness (Altmann et al. 1995; Gage et al. 1995; Sapolsky 2005; Maruska and Fernald 2013). In many cases, however, an individual's rank is not fixed and can be changed rapidly depending on the outcome of interactions within an animal's "social niche" (Fernald 2009; Ryan 2011). As our example in male *A. burtoni* illustrates, this social information can impact every level of the conserved reproductive axis (e.g., brain, pituitary, bloodstream, and testes), as well as influence multiple levels of biological organization (e.g., behavioral, morphological, hormonal, cellular, and molecular). Interestingly, socially suppressed subordinate *A. burtoni* males maintain some activity at every level of their reproductive axis, which then serves as a substrate for quick physiological change. This is consistent with the notion that the ascent of a male is associated with increased activity of the already functional BPG axis that has important parallels to puberty in mammals (Ebling 2005; Choi and Yoo 2013). These subordinate males are therefore physiologically competent to reproduce, but remarkably, the aggressive social interactions from territory-holding males are effective at preventing them from spawning. The number of dominant versus subordinate males can therefore affect the population's operational sex ratio by regulating the availability of territory-holding, sexually active males. The inherent plasticity in this system also allows males constantly to evaluate their relative reproductive potential in relation to social status, territory ownership, and internal physiology, thereby tipping the scale toward investing in either growth or reproduction depending on the circumstances (Hofmann et al. 1999). The natural Lake Tanganyikan habitat of *A. burtoni* is relatively unstable, and avian predators, winds, and large animals such as hippopotami can quickly change the community structure, habitat complexity, and availability of territories (Fernald and Hirata 1977). As a result, ownership of a territory can be brief, and opportunities for reproduction for individual males may appear and vanish quickly and unpredictably. Thus, their immediate realization of any change in their social or physical environment allows them to quickly react behaviorally, and then to initiate cascades of cellular and molecular processes leading to adaptation to their new surroundings. Since social interactions are crucial for reproduction, the neural and hormonal processes sub-serving these social behaviors are probably well conserved (Insel and Fernald 2004). Thus, this type of adult socially-mediated plasticity of the reproductive axis is likely to exist in other species as well.

Clearly, social information and relative rank in a dominance hierarchy have profound effects on the activity of the BPG axis, and hence, reproductive potential and fitness. While the *A. burtoni* model system has provided many insights into understanding and appreciating the extent of this socially-mediated plasticity on multiple levels, and how quickly the axis can change, many important unanswered questions remain. For example, how do animals perceive social information and how does it reach the GnRH1 neurons at the apex of the reproductive axis?

In other words, what senses, neurons, and circuits lie upstream of GnRH1 neurons that modulate their activity? What role(s) do kisspeptin, gonadotropin inhibitory hormone, corticotropin releasing factor, vasotocin, isotocin, and other potential upstream modulators play in this transition? Moreover, how do perceived changes in an animal's social environment trigger modifications of gene expression within social neural networks, and then translate this neurogenomic response into adaptive changes in behavior and physiology? Since many animals that live in hierarchical societies, like *A. burtoni*, can also switch between low-ranking and high-ranking status, how do individuals process and store social information for subsequent retrieval during future cognitive social tasks such as recognition of individuals, territory defense and fighting, or courtship and spawning? The cichlid fish *A. burtoni*, now with genomic resources and a plethora of background knowledge on the BPG axis, will continue to be a valuable model for addressing these and related questions on how external social cues impact the function of the reproductive system. Further, comparative studies using the great diversity of reproductive and parental-care strategies within the cichlid family should be useful for identifying both common themes and unique attributes contributing to speciation. The emerging "omic" fields (e.g., transcriptomics, proteomics, and epigenomics) will also likely provide a wealth of new data that will advance our understanding of how social signals are translated into adaptive changes in behavior and reproductive fitness in dynamic environments.

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