



Recent advances in behavioral neuroendocrinology: Insights from studies on birds

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Abstract

Ever since investigations in the field of behavioral endocrinology were hatched with experiments on roosters, birds have provided original insights into issues of fundamental importance for all vertebrate groups. Here we focus on more recent advances that continue this tradition, including (1) environmental regulation of neuroendocrine and behavioral systems, (2) steroidogenic enzyme functions that are related to intracrine processes and de novo production of neurosteroids, and (3) hormonal regulation of neuroplasticity. We also review recent findings on the anatomical and functional organization of steroid-sensitive circuits in the basal forebrain and midbrain. A burgeoning body of data now demonstrates that these circuits comprise an evolutionarily conserved network, thus numerous novel insights obtained from birds can be used (in a relatively straightforward manner) to generate predictions for other taxa as well. We close by using birdsong as an example that links these areas together, thereby highlighting the exceptional opportunities that birds offer for integrative studies of behavioral neuroendocrinology and behavioral biology in general.

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Birds offer excellent opportunities for behavioral and neuroendocrine experiments in both the field and the laboratory, and studies conducted at this interface have historically placed avian models on the cutting edge of research (Konishi et al., 1989; also see Wingfield, this issue). Indeed, wild birds offer a combination of accessibility (being diurnal and terrestrial) and diversity (social and ecological) that makes them invaluable models for studying mechanistic and evolutionary questions that are not as tractable in other vertebrate groups. This diversity can be studied within the context of neural and endocrine systems that share many features with those of other taxa (thereby increasing the general relevance of avian studies) (Goodson,

2005), although these features are often more pronounced in birds. Such examples include exceptionally robust and widespread neural aromatase activity, and adult neurogenesis in the forebrain, both of which are considered further below (also see Ball and Balthazart, 2004; Balthazart et al., 2004). Thus, in keeping with its rich history, avian behavioral neuroendocrinology continues to offer an unparalleled proving ground for new and broadly relevant ideas.

Steroid-sensitive circuits of the basal forebrain and midbrain: new ideas on an old system

The social behavior network

During the 1970s, the neural distribution of sex steroid receptors was described for a variety of vertebrate species

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(Martinez-Vargas et al., 1976; Morrell and Pfaff, 1978). Steroid receptors were localized to many of the same areas across a broad range of taxa, suggesting that the different vertebrate groups possess a common set of core brain structures that coordinate a variety of steroid-dependent behaviors. In mammals, most of these brain regions are now known to comprise a “social behavior network,” which consists of six, bidirectionally connected nodes — the extended medial amygdala (i.e., the medial amygdala and the medial bed nucleus of stria terminalis, BSTm), the lateral septum (LS), the preoptic area (POA), the anterior hypothalamus (AH), the ventromedial hypothalamus (VMH) and midbrain areas such as the periaqueductal gray (PAG) and various regions of the tegmentum. Each of these areas is involved in multiple forms of social behavior, including aggression and sexual behavior (Newman, 1999).

In birds, recent tracing studies demonstrate reciprocal connectivity throughout the same suite of steroid-sensitive areas (identically named, with the exception of the avian medial amygdala, which is known as the nucleus taeniae) (Balthazart and Absil, 1997; Balthazart et al., 1994; Briganti et al., 1996; Cheng et al., 1999; Montagnese et al., 2004; Ritters and Alger, 2004), and a variety of functional data are now available regarding their roles in overt aggression, agonistic communication, appetitive and consummatory sexual behavior, parental behavior, and non-sexual affiliation (Absil et al., 2002; Balthazart et al., 1998; Charlier et al., 2005; Goodson and Evans, 2004; Goodson et al., 1999, 2005; Ritters and Ball, 1999; Ritters et al., 2004; Ruscio and Adkins-Regan, 2004; Thompson et al., 1998). These functional studies have established extensive similarities with other taxa. For instance, investigations of immediate early gene responses in birds (using antibodies for Fos and Zenk, also known as *egr-1*) have shown that birds and mammals exhibit similar patterns of activation following agonistic encounters (Goodson and Evans, 2004), appetitive sexual behavior and copulation (Ball et al., 1997; Charlier et al., 2005; Meddle et al., 1997, 1999; Ritters et al., 2004; Tlemçani et al., 2000). Notably, recent studies have provided much-needed information on various behavioral functions of the avian PAG and adjacent tegmentum (Charlier et al., 2005; Maney and Ball, 2003; Shaw, 2000). These tracing and functional studies have been conducted concomitantly with a large number of immunocytochemical studies, particularly focused on the distribution of neuropeptides and/or their regulation by sex steroids (Aste et al., 1991, 1995, 1997, 1998a; Goodson et al., 2004a; Panzica et al., 1998, 1999b; Plumari et al., 2004). Overall, the data strongly support the proposal that birds possess a “social behavior network” that is homologous to the network identified for mammals (Goodson, 2005; for a more general consideration of the avian forebrain, see Reiner et al., 2004).

Vasotocin, sex steroids, and aggression

A peptidergic component of the social behavior network that has been intensively studied is the arginine vasotocin

(AVT) system of the BSTm and LS, and the data generated thus far have both confirmed and extended multiple findings in mammals (review: Goodson and Bass, 2001). As in mammals (which express a homologous neuropeptide, arginine vasopressin), the AVT neuronal population of the BSTm is often sexually dimorphic and innervates the LS in a male-biased fashion (Jurkevich et al., 1999; Viglietti-Panzica et al., 1992, 1994). In most species examined, this system is strongly regulated by testosterone (T) (Aste et al., 1997; Panzica et al., 1999a; Plumari et al., 2004; Viglietti-Panzica et al., 1992; Voorhuis et al., 1988), and data from Japanese quail (*Coturnix japonica*) show that T regulates AVT primarily via its aromatization to estradiol (E₂) (Viglietti-Panzica et al., 2001). Also similar to mammals, AVT acts within the septum to modulate stress responsivity and agonistic behavior (Goodson, 1998a; Goodson and Evans, 2004).

Studies of birds have yielded multiple novel insights into this system, as well. For instance, AVT modulates overt male–male aggression in a species-specific manner (Goodson, 1998a,b; Goodson and Adkins-Regan, 1999; Goodson et al., 2004b), and AVT infusions into the septum have been shown to exert context-specific effects on territorial behavior: AVT facilitates spontaneous, agonistic dawn song in male field sparrows (*Spizella pusilla*), but inhibits overt male–male aggression (Goodson, 1998a). These species- and context-specific effects likely reflect the fact that AVT acts most strongly on LS responses to stress, not agonistic stimuli per se, as recently shown for male song sparrows (*Melospiza melodia*) (Goodson and Evans, 2004). In these experiments, AVT receptor blockade was combined with presentation of a severe non-social stressor and/or simulated territorial intrusion (STI), followed by analyses of Zenk responses within specific chemoarchitectonic subdivisions of the LS (which are very similar to LS subdivisions in rats; see Goodson et al., 2004a). The results indicate that AVT’s effects on agonistic behaviors are secondary to its modulation of broader affective states (e.g., stress or anxiety); thus species differences in AVT’s effects may reflect a context-specific relationship between stress and aggression.

Sexual behavior, the POA, and aromatase

Birds also offer distinct advantages for the study of male sexual behavior, and a large amount of information is now available on the functional properties of the avian POA, which is essential for male sexual behavior, and its neuroendocrine constituents such as aromatase (Balthazart et al., 1996, 1998; Castagna et al., 1999; Foidart et al., 1994; Ritters and Ball, 1999; Ritters et al., 1998, 2004). In both mammals and birds, aromatase (estrogen synthetase) mRNA is localized to a variety of areas in the social behavior network, but is most dense within the POA (Aste et al., 1998b; Balthazart et al., 1990b,c; Foidart et al., 1995; for a review of both the mammalian and avian literatures, see Balthazart et al., 2004). However, some aspects of

aromatase function may be more easily addressed in birds: although it is difficult to compare findings generated using different assays (and in different vertebrate groups), the data demonstrate that there is higher aromatase activity in the avian diencephalon compared to mammals. Perhaps because of this relative abundance, aromatase immunolocalization has proven easier in birds, permitting a more detailed cellular inspection of the role of aromatase in sexual behavior (see Balthazart et al., 2004).

Birds also exhibit patterns of appetitive and consummatory sexual behavior that are easily quantified. In quail, these components of sexual behavior are dependent upon different subregions of the medial preoptic nucleus (Balthazart et al., 1998), a sexually-dimorphic structure of the POA (Adkins-Regan and Watson, 1990; Panzica et al., 1996). Quail therefore offers good opportunities to investigate specific components of sexual behavior in relation to specific subdivisions of the POA. Both appetitive and consummatory sexual behavior are T-dependent in quail and require the aromatization of T to E₂ (Balthazart et al., 1995, 1997), and the POM is an essential target for the activation of behavior (e.g., Ritters et al., 1998; for reviews, see Balthazart et al., 2004; Panzica et al., 1996). In addition, recent studies show that pharmacological blockade of aromatase activity produces deficits in both appetitive and consummatory sexual behavior within 15–45 min (Cornil et al., 2003; also see Ball and Balthazart, 2004; Balthazart et al., 2004).

Neural and neuroendocrine correlates of sociality

Unlike other vertebrate groups, in which species-typical group size (“sociality”) is typically confounded with other behavioral and ecological variables (e.g., mating system, patterns of parental care, and habitat; see Goodson, 2005), birds offer the opportunity to study sociality while controlling for most other relevant factors. Recently, this advantage has been exploited to determine how differences in species-typical group size relate to immediate early gene activity within the social behavior network (Goodson et al., 2005). Four estrildid finch and waxbill species (one territorial, one modestly gregarious and two highly colonial) were exposed to a same-sex conspecific (or a control condition) in a paradigm that elicited little overt social behavior, thereby allowing an examination of Zenk and Fos responses that are related primarily to social perception and/or motivation. Responses of the extended medial amygdala (nucleus taeniae and BSTm) were negatively correlated with sociality, and showed stepwise variation across species. In addition, the territorial species showed significantly greater responses in the ventrolateral LS, AH and lateral VMH than did all three gregarious species. Importantly, the *pattern* of response that distinguishes the territorial species is characteristic of animals (birds and mammals) that are exposed to aversive or stressful social stimuli (for discussion, see Goodson, 2005).

Finally, multiple peptidergic systems may coordinate these species-specific responses. Recent experiments (which

include an additional territorial species) show that receptor distributions for corticotropin-releasing factor, vasoactive intestinal polypeptide, and AVT parallel social structure within numerous brain regions. These include three of the areas listed above — the LS, VMH and BSTm (J.L. Goodson, A.K. Evans and Y. Wang, unpubl. obs.).

Environmental effects on avian brain and behavior: tractability and diversity

An issue relevant to all of the topics presented here is the major influence of environmental factors (e.g., changing photoperiod) on brain and behavior (Ball et al., 2002; Dawson et al., 2001). Indeed, the activity of steroid-sensitive circuits (first section above), brain steroidogenesis (next section), and processes related to neural plasticity (second section below) are all seasonally regulated. Although steady advances in our understanding of the environmental regulation of avian behavior and physiology have occurred since pioneering work in the 1920s (Rowan, 1925), recent progress has been particularly remarkable.

Photoperiodic states

Birds undergo pronounced annual changes in physiology, morphology, and behavior that facilitate survival and reproduction in varying environments (Murton and Westwood, 1977). This results from both changing external environmental cues and changing internal responsiveness to those cues (Ball, 1993; Dawson et al., 2001). Seasonally breeding birds pass annually through three physiological states that underlie annual reproductive cycles: *sensitivity*, *stimulation*, and *refractoriness* (Ball and Hahn, 1997). Brains of *sensitive* birds can mount a reproduction-related neuroendocrine response to environmental cues. Lack of stimulatory external cues in early winter, in combination with sex steroid feedback, hold reproductive development in check (Cockrem, 1995). In late winter and early spring, external cues *stimulate* the secretion of gonadotropin releasing hormone (GnRH) and gonadotropin (Follett, 1984). *Refractoriness* to stimulatory cues causes gonadal collapse and declines in reproductive behavior (Ball et al., 2002; Nicholls et al., 1988). Although large changes in behavior, gonadal physiology, and peripheral endocrine physiology occur in a variety of animals, birds are unusual in the degree to which these changes can be underlain by similarly dramatic changes within the neuroendocrine machinery itself. During *absolute photorefractoriness*, the down-regulation of the septo-infundibular GnRH system is profound (Ball and Hahn, 1997; Dawson et al., 2001; Hahn et al., 1997). In the few temperate zone taxa that do not become absolutely photorefractory (i.e., Japanese quail, crossbills; Hahn et al., 2004; Robinson and Follett, 1982), down-regulation of the GnRH system does not occur, even though the birds may be *relatively refractory* (Foster et al.,

1987; Pereyra et al., in press; see Nicholls et al., 1988). Stimulation of the reproductive axis can enhance activity of the GnRH system (e.g., Saldanha et al., 1994a), but the most pronounced changes occur during development and dissipation of absolute refractoriness (Ball and Hahn, 1997; Hahn et al., 1997; Sharp, 1996).

The medial–basal hypothalamus, brain deiodinase, and photoperiodism

The avian medial–basal hypothalamus (MBH) plays an important role in transducing environmental cues into reproductive signals (Davies and Follett, 1975; Juss, 1993; Sharp and Follett, 1969), and recent evidence indicates that the clock responsible for circadian measurement of day-length is located in the MBH of Japanese quail (Ball and Balthazart, 2003; Yasuo et al., 2003). Although clock genes are expressed rhythmically in the quail SCN and pineal, only in the MBH does the rhythm remain constant under experimental light–dark regimes. The critical role of the MBH in avian photoperiodism (Ball and Balthazart, 2003) is further underscored by the facts that (1) this region probably also contains the deep-brain photoreceptors that are responsible for reproductive photoinduction (Saldanha et al., 1994b, 2001; Silver et al., 1988), and (2) the MBH exhibits significant Fos responses to photic cues (Meddle and Follett, 1997).

The MBH also figures prominently in the effects of thyroid hormones in avian photoperiodism. Thyroid hormones may act either directly (cf. Wilson and Reinert, 1995, 2000) (cf. Bentley et al., 1999) in photoinduction, photorefractoriness, or both (see Dawson et al., 2001). Central effects (Wilson and Reinert, 2000) likely depend on production of physiologically active thyroid hormone, 3,5,3'-triiodothyronine (T_3), which occurs in the MBH (Yoshimura et al., 2003). Light pulses during the photo-inducible phase specifically activate transcription of the gene *Dio2*, which codes for the type 2 iodothyronine deiodinase enzyme responsible for catalyzing conversion of thyroxine (T_4) to T_3 in the quail MBH. Numerous lines of evidence, including photoinduced changes in MBH T_3 and T_4 levels, intraventricular infusion of thyroid hormones, and central blocking of the T_4 to T_3 conversion, all point to a MBH-mediated role of thyroid hormones in avian photoperiodism (Yoshimura et al., 2003).

These findings also dovetail nicely with evidence supporting a role for glia in avian photoperiodism, given that astroglia (specifically, astrocytes, and tanycytes) express *Dio2* in mammals (Garcia-Segura and McCarthy, 2004; Garcia-Segura et al., 1996). Astroglia may therefore be key in the conversion of T_4 to T_3 in the avian MBH. Furthermore, in the quail median eminence, glial endfeet apparently create greater separation between GnRH terminals and the basal lamina during short days than during long days, suggesting that the glia may obstruct GnRH secretion (Yamamura et al., 2004). Earlier studies on European

starlings (*Sturnis vulgaris*) suggest that glia may affect synaptic input to GnRH neurons as well (Parry and Goldsmith, 1993).

Diversity of photoperiodism

Although quail have served as a proving ground for many ideas in avian behavioral endocrinology (Balthazart and Ball, 1995), including mechanisms of photoperiodism (e.g., Ball and Balthazart, 2003; Follett, 1984), exploration of the diversity of avian reproductive cycles, from strictly seasonal through temporally opportunistic, is required to clarify the adaptive significance of a given mechanism. For example, seasonal plasticity of the GnRH system is greater in taxa that become absolutely photorefractory, such as European starlings and house finches (*Carpodacus mexicanus*), than in those that do not, such as quail and crossbills (*Loxia* sp.) (Cho et al., 1998; Foster et al., 1987, 1988; MacDougall-Shackleton et al., 2001; Pereyra et al., in press). These differences are correlated with the degree of reproductive flexibility displayed (Hahn et al., 1997; MacDougall-Shackleton et al., 2005). Comparisons among taxa that vary in reproductive flexibility, and in the form of refractoriness that develops, may help reveal the extent to which processes such as glial ensheathment and deiodinase activity contribute to short-term modification of GnRH release versus long-term down-regulation of GnRH production. Studying temporally opportunistic taxa (cf. Hahn et al., 1995), such as crossbills, that rely heavily on non-photoc cues to time changes in reproductive condition (Hahn, 1995; Hahn et al., 1995, 2005) should clarify whether mechanisms underlying processing of photic cues apply to other kinds of cues, such as food supply, as well.

Neural steroidogenic enzymes: intracrinology and neurosteroids

The central nervous system has traditionally been considered to be a receiver of sex steroids produced by the gonads and adrenals. Over time, this idea has been modified, with increasing emphasis on the brain's ability to synthesize sex steroids independently. Such considerations have important consequences for interpreting correlations (or lack thereof) between behavior and plasma sex steroid levels, and interpreting effects (or lack thereof) of castration on behavior.

Aromatase

Aromatase catalyzes the conversion of AE to E_1 and of T to E_2 (Fig. 1). Aromatase was initially characterized in the ovary and then detected in multiple areas of the basal forebrain in mammals (Naftolin et al., 1971, 1972), raising the hypothesis that some effects of gonadal T on sexual and aggressive behavior are dependent upon local conversion of

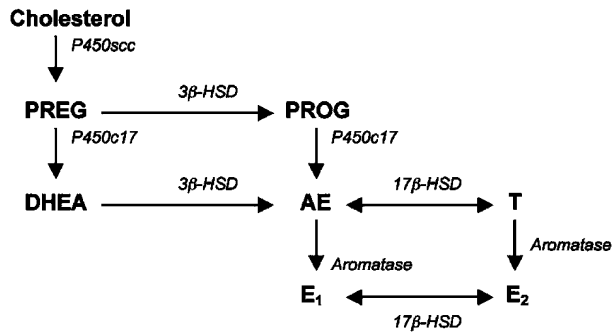


Fig. 1. Simplified diagram of sex steroid synthesis. Steroids are in bold; enzymes are in italics. Steroids: PREG = pregnenolone; PROG = progesterone; DHEA = dehydroepiandrosterone; AE = androstenedione; T = testosterone; E₁ = estrone; E₂ = 17 β -estradiol. Enzymes: P450scc = Cytochrome P450 side chain cleavage; P450c17 = Cytochrome P450 17 α -hydroxylase/C17,20 lyase; 3 β -HSD = 3 β -hydroxysteroid dehydrogenase/isomerase; 17 β -HSD = 17 β -hydroxysteroid dehydrogenase; Aromatase = Cytochrome P450 aromatase.

T to E₂ by brain aromatase. Indeed, a variety of data now show that brain aromatase is a key mediator of the link between T and behavior, and research on birds has provided seminal insights into (1) the cellular localization of aromatase protein and mRNA in neurons (Balthazart et al., 1990c; Shen et al., 1994), (2) the presence of aromatase at the synapse (Naftolin et al., 1996; Schlinger and Callard, 1989; Peterson et al., submitted for publication), (3) hippocampal aromatase expression (Saldanha et al., 2000; Vockel et al., 1990), (4) the expression of aromatase in glia (Schlinger et al., 1994), (5) the regulation of aromatase by endocrine and environmental factors (Balthazart et al., 1990a; Hutchison et al., 1986; Schlinger and Callard, 1990), and (6) behavioral functions of aromatase (Adkins, 1975; Adkins and Nock, 1976; Schumacher et al., 1984; and see first section).

Several examples of recent work demonstrate that avian studies continue to make novel contributions to this field. First, most studies of aromatase focus on the brain, but aromatase was recently detected in the spinal cord of quail (Evrard and Balthazart, 2004a; Evrard et al., 2000). Interestingly, spinal cord aromatase modulates nociception in quail, indicating a novel function for this enzyme (Evrard and Balthazart, 2004a,b). Second, studies in quail also indicate that aromatase activity is rapidly regulated within minutes by calcium-dependent phosphorylation (Balthazart et al., 2001a,b, 2003). Traditionally, aromatase has been thought to be regulated on a longer time scale, involving gene transcription. Rapid modulation opens new directions for research and has major implications for understanding the functions of aromatase. Third, in songbirds, recent ultrastructural studies have examined the regulation of aromatase in terminals within the hippocampus, hypothalamus, and song nuclei (Peterson et al., submitted for publication; Saldanha et al., 2000). Such studies are critical to understanding the function of aromatase at the synapse, which has remained enigmatic. Importantly, this line of

inquiry is greatly facilitated by the relatively high levels of aromatase in the avian nervous system.

Intracrinology

The “aromatase hypothesis” no longer portrayed the brain as a passive recipient of gonadal sex steroids, but in general researchers still assumed that the brain could only aromatize T that was produced in the gonad. However, it is becoming increasingly clear that the adrenal glands can play a major role in supplying sex steroids to the nervous system. For example, the sex steroid precursor dehydroepiandrosterone (DHEA; Fig. 1) and its sulfated ester (DHEA-S) are secreted in abundant quantities by the human adrenal cortex (Thijssen and Nieuwenhuys, 1999). Circulating DHEA can be locally metabolized to sex steroids within peripheral target tissues (e.g., prostate, skin), a phenomenon Labrie et al. termed “intracrinology” (Labrie, 1991). Interestingly, DHEA metabolism to sex steroids also occurs within the human brain (Milewich et al., 1991) and rodent brain (Jellinck et al., 2001; Zhao et al., 1991; Zwain and Yen, 1999).

Recent studies in birds suggest that DHEA plays an important role in the control of territorial aggression. For example, in field studies of male song sparrows, territorial behavior is robustly expressed during non-breeding season (autumn and early winter) (Soma and Wingfield, 1999; Wingfield and Hahn, 1994), although plasma T, 5 α -DHT, AE, E₂, and E₁ are non-detectable at this time (Soma and Wingfield, 1999; Wingfield and Hahn, 1994). The testes are also completely regressed during the autumn (Soma and Wingfield, 1999) and castration does not decrease aggression in the non-breeding season (Wingfield, 1994). In contrast, aromatase inhibition does decrease aggression in autumn (Soma et al., 1999, 2000a,b), despite the fact that plasma levels of aromatizable androgens (AE and T) are non-detectable (<0.1 ng/ml). However, plasma levels of DHEA are detectable (on average ~0.8 ng/ml, up to 1.7 ng/ml) (Soma and Wingfield, 2001), and DHEA levels in the adrenals and regressed testes are also high. In autumn, DHEA treatment increases territorial singing and the size of the song nucleus HVC, similar to the effects of T and E₂ (Soma et al., 2002, 2004b; Tramontin et al., 2003). DHEA treatment, unlike T, does not stimulate growth of the cloacal protuberance, a peripheral secondary sex character (Soma et al., 2002), and does not suppress immune function in non-breeding sparrows (Owen-Ashley et al., 2004).

Recently, DHEA metabolism by 3 β -HSD (Fig. 1) in songbird brain has been characterized in zebra finches (Soma et al., 2004a). In song sparrows, brain tissue metabolizes DHEA to AE and estrogen, and DHEA metabolism is higher in autumn than spring across several forebrain regions (K. Soma, D. Wacker, J. Wingfield and B. Schlinger, unpub. obs.). Interestingly, brain 3 β -HSD activity is rapidly modulated (Soma et al., 2004a), similar to brain aromatase (see above). Taken together, these data support the hypothesis that non-breeding song sparrows combine

adrenal and/or gonadal DHEA synthesis with neural DHEA metabolism to maintain territorial behavior in the absence of gonadal T secretion. Moreover, it remains possible that the brain itself is a significant site of DHEA synthesis (see below).

Similar results have been obtained in field studies of the spotted antbird (*Hylophylax n. naevioides*), a tropical bird in which both sexes aggressively defend territories year-round. Spotted antbirds have basal plasma T levels throughout the year, but nonetheless, a combined treatment of aromatase inhibitor plus androgen receptor antagonist decreases male aggression in the breeding season (Hau et al., 2000). In the non-breeding season, both sexes show high levels of aggression, primarily to intruders of the same sex (Hau et al., 2004). Both males and females have elevated levels of plasma DHEA in the non-breeding season, and in males, plasma DHEA levels are positively correlated with aggressive vocalizations and/or the length of territorial intrusions (Hau et al., 2004). These data suggest that DHEA regulates aggression in this tropical species, possibly in both males and females.

Neurosteroids

Groundbreaking studies by Baulieu et al. suggested that the brain can synthesize DHEA and other steroids de novo from cholesterol (designated as “neurosteroids”) (Corpechot et al., 1981). Despite great advances in understanding the biochemistry of neurosteroid synthesis, much remains unknown regarding the physiological functions of neurosteroids and the selective forces that favor evolution of such local endocrine signaling.

Recent studies in birds suggest that sex steroids can be synthesized entirely within the brain, both during development and adulthood. Studies by Tsutsui et al. have identified P450scc, P450c17, and 3 β -HSD (Fig. 1) in the brain of quail (Tsutsui and Yamazaki, 1995; Tsutsui et al., 2003). These novel experiments have successfully combined measurements of enzyme mRNA, protein, and activity with measurements of steroids in plasma and brain tissue. Regional analyses of neural steroidogenic enzymes reveal high expression in the telencephalon and diencephalon, as well as Purkinje neurons of the cerebellum (Matsunaga et al., 2002; Ukena et al., 1999). The functions of neurosteroids in Purkinje neurons are currently under investigation.

In the zebra finch (*Taeniopygia guttata*), profound male-biased sex differences in the telencephalic song control system (Nottebohm and Arnold, 1976) arise during early development (Gurney and Konishi, 1980). Estrogen treatment of female zebra finches during development masculinizes the song system (Gurney and Konishi, 1980), but experimental manipulations that produce functional testes in genetic females do not masculinize the song system (Wade and Arnold, 1996). Recent data suggest that neurosteroids, but perhaps not gonadal steroids, are important for the development of a male pathway from the song nucleus HVC

to the robust nucleus of the arcopallium (RA) in the song circuit (Holloway and Clayton, 2001; Schlinger et al., 2001). In organotypic slice cultures from developing animals, innervation of the song nucleus RA by HVC neurons occurs in slices from males but not females (Holloway and Clayton, 2001), and treatment of male slices with an aromatase inhibitor reduces the innervation of RA. This is striking because the slices were cultured in a medium with low sex steroids. In addition, measurements of E₂ in the conditioned medium indicate that estrogen is produced de novo in the slices, with higher E₂ production in male slices than female slices. Studies in vivo demonstrate neural expression of mRNA for P450c17 during development, although no sex differences in P450c17 mRNA were detected in brain (London et al., 2003). Taken together, these studies suggest that neurosteroids regulate formation of the HVC-RA pathway in males, but the role of neurosteroids in song nucleus size dimorphism requires further investigation (Arnold, 2004).

Adult neurogenesis and steroid-mediated neuroplasticity: bird is the word

Although overt changes in adult neuron number and morphology were previously relegated to the realm of “lower” vertebrates, the realization that such changes occur in mammals has rejuvenated inquiry into the structural reorganization of the CNS. This perspective has increased our appreciation of the structural indices whereby stimuli (including hormones) alter neurons and neuronal networks. Here, we discuss the contribution of avian models to our understanding of how changes in the size, number, and projections of neurons may modulate adult CNS function.

Adult neurogenesis

Although neurogenesis was reported in the brains of adult mammals beginning in the early 1960s, these studies were viewed with considerable skepticism (see Gould and Gross, 2002, for review). However, based on ultrastructural, peptidergic, and electrophysiological characteristics, several landmark studies later reported abundant neurogenesis in the brains of adult canaries (*Serinus canaria*; Alvarez-Buylla and Nottebohm, 1988; Goldman and Nottebohm, 1983; Paton and Nottebohm, 1984). These observations changed our appreciation of plasticity in the adult vertebrate brain: not only was the abundance of these mitotic neurons higher than previously suggested, but more rigorous criteria were used to support the inference that the mitotic cells were truly neurons (see above). In only two decades, we have learned that precursor cells located in the subventricular zone (SVZ; Goldman and Nottebohm, 1983; Goldman et al., 1996) give rise to radial glia and neurons within the SVZ itself (Alvarez-Buylla et al., 1990). These new neurons migrate along radial glia (Alvarez-Buylla and Nottebohm, 1988)

into HVC, a pallial song control nucleus critical for sensorimotor integration (Goldman et al., 1993). The observation that precursor cells from adult canaries can differentiate into neurons (Goldman, 1990; Goldman et al., 1992), migrate along radial glia (Goldman et al., 1993) and become functionally active (Goldman and Nedergaard, 1992) *in vitro*, strongly underscores the inherently robust nature of adult neurogenesis in birds. Indeed, *in vivo*, the canary HVC exhibits an orchestrated balance of neuronal turnover with peaks of cell death in August–September and January, each of which is followed by peaks of neurogenesis in October and March (Kirn et al., 1994). Although the precise functional role of neuronal replacement remains enigmatic, it is clear that newly born neurons in the adult canary brain project from HVC to RA (Kirn and Nottebohm, 1993) and may underlie changes in song learning and production (Alvarez-Buylla et al., 1990; Kirn et al., 1994). Presumably, this rich history of adult neurogenesis in passerines and other birds will provide important touchstones for the developing topic of adult neurogenesis in mammals, including humans. In particular, the balance between cell death and neurogenesis, and the possible modulation of cell birth by cell death (Scharff et al., 2000) provide exciting avenues of research that are easily applicable to clinical situations in humans.

Seasonal adult neuroplasticity in the song system

The dynamic nature of the avian brain is perhaps most obvious in the oscine suborder of the family Passeriformes, which contains the true songbirds (i.e., perching birds that are known to learn their songs). Specific portions of the adult songbird brain undergo dramatic changes in volume across seasons. These changes have been exhaustively described in nuclei of the song circuit (Tramontin and Brenowitz, 2000) and to a lesser extent in the hippocampus (Smulders et al., 1995; 2000). Several photoperiodic passerines from different families demonstrate increases in the volume of the song nuclei HVC, RA, Area X, and MAN in the summer relative to the winter. These changes are not subtle: HVC volume changes 2-fold in some songbirds. Changes in song nuclei do not reflect non-specific changes in the size of the telencephalon, and for most of these brain nuclei, the volume increase is due to a combination of increased cell number, cell size, cell spacing, dendritic arborization, and/or synaptic density. These changes are believed to underlie the considerable increase in singing behavior observed in the summer and may mediate vernal changes in song structure and repertoire in some species (Nottebohm, 2004).

Circulating steroids, particularly T, are implicated in the regulation of song circuit plasticity. Administration of T, or its metabolite E₂, increases neuronal number and size in HVC and Area X in song sparrows, white-crowned sparrows (*Zonotrichia leucophrys gambelii*), and dark-eyed juncos (*Junco hyemalis*), and increases neuron size in RA (Gulledge and DeViche, 1995; Soma et al., 2004a,b;

Tramontin et al., 2003). The arborization of neurons within RA is profoundly affected by E₂ in the adult canary, with the number of dendrites and synaptic profiles increasing with steroid administration (DeVoogd and Nottebohm, 1981). Surprisingly, the steroidal influence on the song system can be extremely rapid, as significant increases in HVC neuron number are detectable within a week of T administration (Brenowitz, 2004). Importantly, non-steroidal factors also influence neuroplasticity within the adult song circuit. For instance, Gulledge and DeViche (1998) described independent effects of steroids and photoperiod on the growth of HVC in the juvenile junco. Melatonin, a photoperiodically regulated indoleamine, inhibits the growth of HVC in European starlings (Bentley et al., 1999), demonstrating that non-steroidal hormones can also affect the plasticity of the avian brain. Thus, the response of the adult passerine brain to hormones is rapid and robust, as exemplified by the recruitment of new neurons into specific neural circuits during adulthood.

Hippocampal plasticity

Although less dramatic, recruitment of neurons into the adult hippocampus is also observed for food caching songbirds, and the hippocampus is critical for accurate cache retrieval (Sherry et al., 1989). Scatter-hoarding species are found within a number of songbird families, including the Corvids (crows and jays), Parids (tits and chickadees), and Sittids (nuthatches; Krebs, 1990), and of these, the neuroanatomy of the black-capped chickadee (*Poecile atricapillus*) has been studied the most. In this species, mitotic neurons are known to migrate into the adult hippocampus (Barnea and Nottebohm, 1996), thereby increasing hippocampal volume via changes in neuron number, not neuron size (Smulders et al., 1995; 2000; but see Hoshoooley and Sherry, 2004). Interestingly, in contrast to what is observed in the song system, new neurons invade the passerine hippocampus during the autumn and winter. This suggests the possibility that different parts of the adult songbird brain recruit new neurons in a season- and behavior-specific manner. Indeed, of chickadees examined in October, February, or June, cell number in the hippocampus (which is necessary for food retrieval) is maximal in October, whereas cell numbers in HVC and Area X (necessary for singing) are maximal in June (Saldanha et al., 2004). Although the endocrine mediators of hippocampal plasticity are unknown, its marked seasonal nature suggests the involvement of hormones. These combined data on the song system and hippocampus point to the exaggerated capability of the adult passerine brain to reorganize behaviorally relevant circuitry during adulthood.

Responses to neural injury

Hormone-mediated neural reorganization is also revealed in pathological conditions. In mammals and birds, recent

studies on the role of cell-specific hormone production in response to neural injury reveal a critical role for steroids in the mitigation of damage. Brain damage results in an upregulation of aromatase in reactive glia, a cell-type that does not express aromatase in the intact homeotherm brain (Garcia-Segura et al., 1999, Peterson et al., 2001, 2004). These data suggest that glia switch on the ability to synthesize E_2 in response to neural injury and indicate a functional role for the glial aromatase expression that was first described in cell cultures of songbird telencephalon (Schlinger et al., 1994). Indeed localized administration of an aromatase inhibitor increases neural damage and increases apoptosis relative to localized saline administration (Wynne and Saldanha, 2004) an effect rescued by replacement with E_2 in the zebra finch (Saldanha et al., in press). These data point to the clinical relevance of avian studies and highlight important similarities between avian and mammalian neurophysiology.

Multi-system integration: birdsong and neuroendocrine cascades

Perhaps more than any other vertebrate group, birds offer the opportunity to conduct examinations of behavioral neuroendocrinology in a manner that integrates components of appetitive and consummatory behavioral states, environmental regulation, and neuroplasticity — with each component being mediated by a diversity of endocrine mechanisms (e.g., by actions of gonadal, adrenal and thyroid hormones, neuropeptide modulators, intracrine processes, and/or de novo steroid synthesis in the brain).

Birdsong in particular provides an excellent window into mechanistic integration (Ball et al., 2002), and in many male birds that breed and display song seasonally, the cascade of mechanistic events that initiates vernal song can be traced back to an increase in photoperiod. Increasing photoperiod is detected by the MBH (Meddle and Follett, 1997; Saldanha et al., 1994b, 2001), and gonadal recrudescence is subsequently triggered by release of GnRH and gonadotropin (Follett, 1984; Dawson et al., 2001). The accompanying rise in circulating T coordinates a variety of processes in the brain, many of which require that T be aromatized to E_2 . These include, but are not limited to, increased expression of neuropeptides (e.g., AVT within the BSTm-LS system) (Plumari et al., 2004; Viglietti-Panzica et al., 2001), dramatic restructuring and growth of telencephalic song nuclei (Nottebohm, 2004; Tramontin and Brenowitz, 2000), and an increase in aromatase activity within the VMH and POA (Vockel et al., 1990).

While the rise in circulating hormones directly influences the song circuitry, it can also influence singing via components of the social behavior network that are involved in sexual and aggressive behaviors (see first section). These areas express sex steroid receptors (Balthazart et al., 1992; Metzdorf et al., 1999), and a variety of data show that they

participate in the control of song. For instance, lesions of the medial preoptic nucleus (POM) decrease courtship singing in starlings (Riters and Ball, 1999), and the expression of song is correlated with POM size, Zenk immunoreactivity, and Fos immunoreactivity (Riters et al., 2000, 2004); the midbrain central gray may additionally play a role in territorial singing (see below). The social behavior network also plays a role in the selection of *what* to sing: in male field sparrows, AVT infusions into the septum selectively promote the use of an agonistic song type, but do not influence the use of a multipurpose song type (Goodson, 1998a).

This influence of the social behavior network on the telencephalic song system may be mediated by a variety of connections, particularly those through the midbrain central gray. All forebrain components of the social behavior network project to the midbrain central gray, as do preoptic aromatase neurons (Absil et al., 2001; Cheng et al., 1999; Montagnese et al., 2004; Riters and Alger, 2004). The central gray in turn provides direct input to the telencephalic song system (i.e., monosynaptic projections are observed to HVC and RA) (Appeltants et al., 2000). Neurons in the central gray exhibit a significant Fos response to agonistic challenge in free-living male song sparrows, and the number of songs sung correlates positively with the number of Fos-immunoreactive neurons (Maney and Ball, 2003).

Importantly, the central gray is a major site of catecholamine production, and the catecholaminergic innervation of HVC and RA is modulated by T (Appeltants et al., 2003). Recent data from Japanese quail (a non-songbird) also demonstrate that catecholamine neurons of the central gray are responsive to sexual interactions (Charlier et al., 2005). Thus, the combined findings suggest that the midbrain central gray integrates a variety of inputs, and then influences the song system in a manner that is appropriate to the behavioral, hormonal, seasonal, and motivational context.

It is important to note how many components of this multifaceted cascade are exceptionally pronounced in birds, such as the degree of neuroplasticity and the expression of aromatase. At the same time, these variables can be studied within a context that is meaningful for a wide range of taxa, given that other vertebrates (1) often coordinate their social behavior and reproductive physiology based upon the same environmental variables (e.g., photoperiod and food availability) and (2) possess neuroendocrine and social behavior circuits of the basal forebrain and midbrain that are strongly evolutionarily conserved. In songbirds, these features are juxtaposed to a highly derived system that is dedicated to the learning and production of song. While a “song system” is obviously absent in other vertebrates, songbirds offer highly tractable opportunities to study the conserved aspects of behavioral regulation (i.e., functions dependent upon the social behavior network) as they relate to the telencephalic coordination of learning and performance (functions that are served by the song system). Hence, song can be viewed as a

proxy for many kinds of complex behavior, and by examining the interactions between the song system and other steroid-sensitive circuits, we should obtain much information that is novel, important, and broadly relevant.

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