

Chapter 2

Hormone-Dependent Plasticity of Auditory Systems in Fishes

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Abstract Fishes, the most species-rich group of living vertebrates, present remarkable opportunities to investigate neural mechanisms underlying the sense of hearing. While the sound-producing and hearing abilities of fishes have long been known, it was not until the turn of this century that the influence of hormones on audition was first reported for fish. This discovery has led to numerous studies in multiple species using a range of methodological approaches to investigate underlying cellular and molecular mechanisms. Here, we review these findings within behavioral, hormonal, ecological, and evolutionary contexts. As shown, fishes share a large suite of behavioral and neurohormonal characters with tetrapods and offer distinct advantages as experimental models, in part, because of easy accessibility to the peripheral and central auditory systems.

Keywords Androgen • Aromatase • Auditory efferent • BK channels • Cichlid • Damselfish • Dopamine • Estrogen receptor • GnRH • Hair cell • Hawaiian sergeant damselfish • Inner ear • Midshipman fish • Sacculle • Teleost

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2.1 Introduction: Why Study Hormones and Hearing in Fish?

The past decade has witnessed a number of new studies highlighting the potent influence of hormones on the hearing abilities of fish, in particular among teleosts that are a clade of ray-finned fishes (Actinopterygii) and the most species-rich group of living vertebrates (Nelson 2006). Why might one study fish, and more specifically teleosts, to identify behavioral and neural mechanisms of hearing shared across vertebrate lineages and, in turn, the influences of hormones on those mechanisms? First, psychophysical studies show that teleosts “behave as if they have perceptual dimensions similar to pure-tone pitch, periodicity pitch, roughness, and timbre as defined in studies on humans” (Fay and Simmons 1999). Second, teleosts share the same general pattern of ascending brainstem auditory pathways with tetrapods, including sites of auditory-vocal integration (McCormick 1999; Bass et al. 2005). Third, the auditory hair cell epithelium and brainstem auditory centers share neurophysiological encoding mechanisms with tetrapods and are readily accessible for experimental investigation (Bass and McKibben 2003; Fay and Edds-Walton 2008).

The main focus of this chapter is on fish species that, like all major lineages of tetrapods, generate acoustic signals for the purposes of social communication (Fig. 2.1a, b) (Bass et al. 2015). Such species have provided additional advantages for studies of

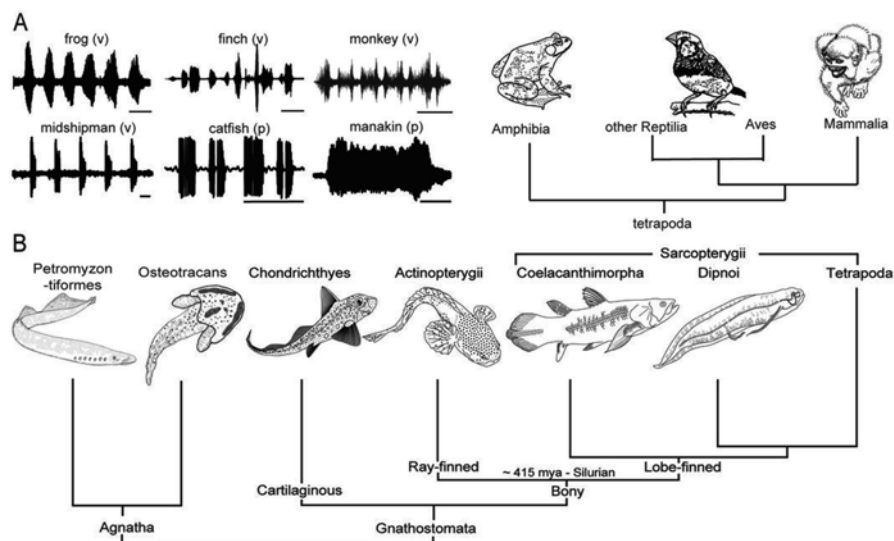


Fig. 2.1 Vertebrate acoustic communication signals and phylogeny. (A) Sample vocalizations of bullfrog, *Lithobates catesbeianus* (bar scale represents 1 s), zebra finch, *Taeniopygia guttata* (250 ms), squirrel monkey, *Simia sciurea* (200 ms), plainfin midshipman fish, *Porichthys notatus* (500 ms), catfish, *Platydoras armatulus* (250 ms) and club-winged manakin, *Machaeropterus deliciosus* (100 ms). Vocal (v) and pectoral-sonic (p) mechanisms indicated. (B) Cladogram indicates relationships among jawless (Agnatha, e.g., Petromyzontiformes: lamprey) and jawed (Gnathostomata) vertebrate radiations (Osteostracans are an extinct agnathan group with pectoral fins). Modified from Bass and Chagnaud (2012)

hearing, especially for revealing hormonal influences on underlying neural mechanisms. First, the simplicity of their pulsatile acoustic signals is easily mimicked using computer methods and hence enables the design of behaviorally relevant acoustic stimuli whose properties can be readily manipulated for behavioral and neurophysiological studies (Bass and McKibben 2003). Second, like the auditory system of mammals and other tetrapods that communicate using acoustic signals, auditory neurons in sound-producing fish encode both amplitude variations in the temporal envelope of vocal signals, such as duration and modulation rate, as well as the temporal fine structure, in other words, the time course of the waveform beneath the envelope (Bass and McKibben 2003; Bass et al. 2005). Third, there is strong evidence for steroid receptors in, and neuromodulatory inputs to, the peripheral and central auditory systems like those observed in tetrapods (e.g., Fergus and Bass 2013; Forlano et al. 2014). Fourth, neurophysiological studies demonstrate hormone-dependent plasticity in the encoding of acoustic information (Sisneros et al. 2004a; Maruska and Tricas 2011).

2.2 Peripheral and Central Auditory Systems

A brief overview of the peripheral and central auditory systems of fishes provides background for the remaining sections of this chapter. The inner ear of teleosts includes three non-otolithic end organs (the semicircular canals) and three otolithic end organs (the utricle, the saccule, and the lagena) (Fig. 2.2) (Popper and Fay 1999). Some teleost species also have a non-otolithic sensory epithelium of unknown function called the macula neglecta, which has an auditory function in sharks (e.g., Fay et al. 1974; Corwin 1977). Unlike tetrapods that have a non-otolithic end organ dedicated to hearing (cochlea, amphibian papilla, basilar papilla) (Manley 2000), many species of teleosts have adapted the saccule to serve mainly an auditory function, although the utricle and lagena can also be sensitive to sound (Bass and Lu 2007; Maruska and Mensinger 2015). The saccule has been the focus of most recent studies of cellular and molecular mechanisms and, hence, is the focus here as well.

The auditory saccule's sensory epithelium extends along the long axis of the otolith and is innervated by the saccular branch of the VIIIth nerve. In species like the plainfin midshipman fish (*Porichthys notatus*), the epithelium and nerve are easily accessible because they lie lateral to the brain and just below the surface of the skull (Fig. 2.2). Saccular afferents, originating from VIIIth nerve ganglion cells, and efferents, originating from a rostral hindbrain nucleus known as the octavolateralis efferent nucleus, synapse directly on hair cells (Lanford et al. 2000; for more complete review see Koppl 2011). The efferent nucleus innervates all divisions of the inner ear ("octavo") and the lateral line organs (e.g., Highstein and Baker 1986; Tomchik and Lu 2005).

The general organization of central auditory pathways is similar among teleosts and tetrapods (McCormick 1999; Bass and Lu 2007). The most information is available for brainstem and thalamic targets of the ascending auditory system; telencephalic auditory centers in fishes are the least studied and remain important targets for future investigation (see McCormick 1999; Bass et al. 2005). Figure 2.3 portrays the pattern of connectivity for midshipman fish. For more comprehensive neurophysiological reviews, see Bass and Lu (2007) and Fay and Edds-Walton (2008).

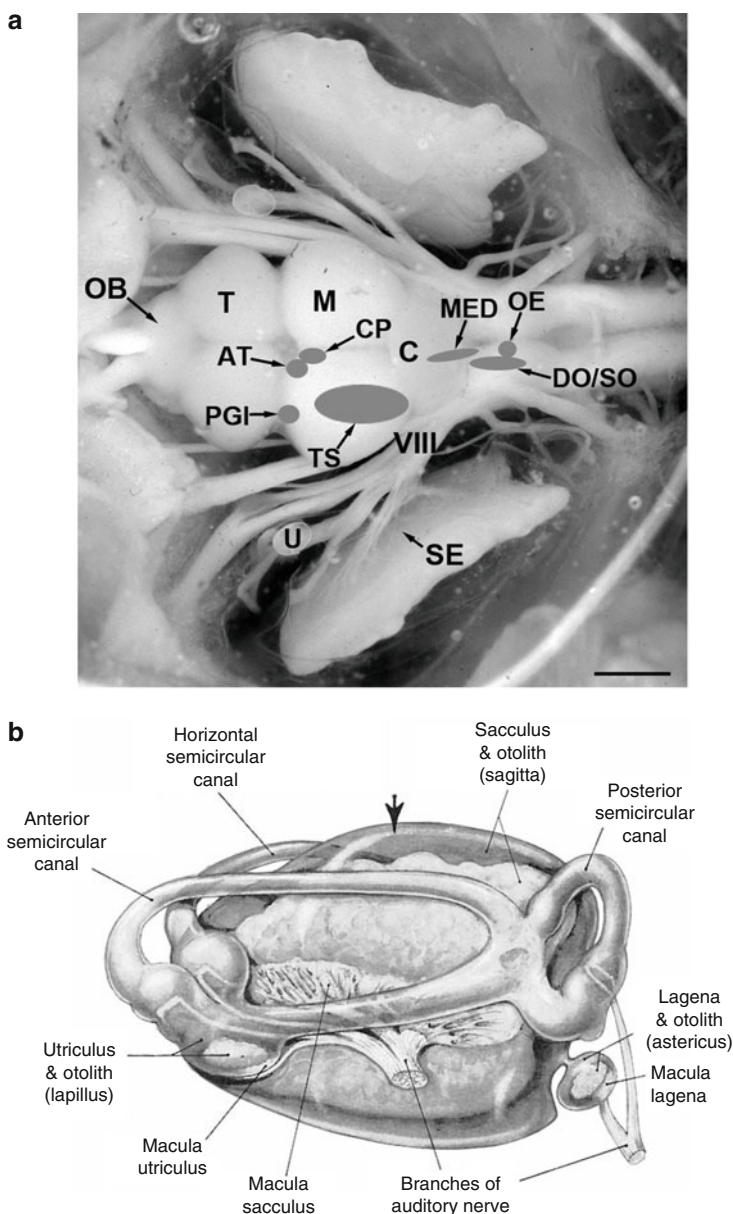


Fig. 2.2 Dorsal view of an exposed brain and inner ear of midshipman fish, *Porichthys notatus*. (a) Shaded areas indicate relative location of auditory nuclei. (b) Drawing of the medial view of the right inner ear in the midshipman. AT anterior tuberal nucleus, C cerebellum, CP central posterior nucleus of the thalamus, DO descending octaval nucleus, M midbrain, MED medial octavolateralis nucleus, OB olfactory bulb, OE octavolateralis efferent nucleus, PGI lateral division of nucleus preglomerulosus, SE sacculus epithelium of the inner ear, SO secondary octaval nucleus, T telencephalon, TS torus semicircularis, U utricle, VIII eighth nerve. Scale bar = 1.5 mm. (a) Adapted from Bass et al. (2000) and Forlano et al. (2015b); (b) adapted from Cohen and Winn (1967)

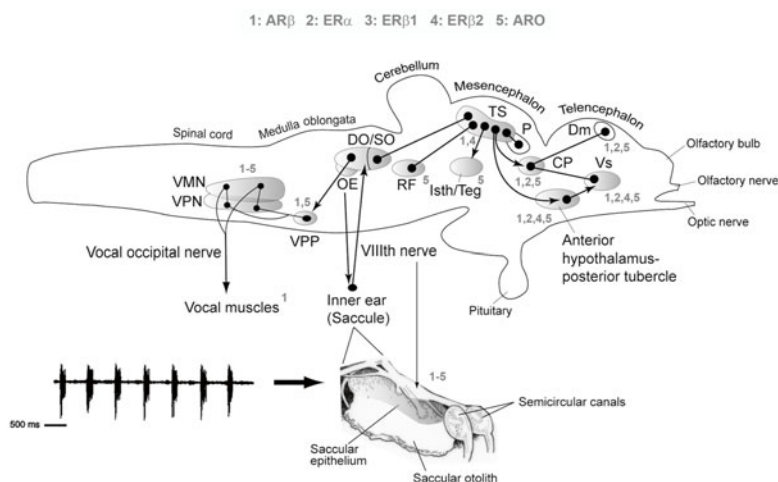


Fig. 2.3 Peripheral and central auditory systems of vocal teleosts. Side view of the brain shows connectivity and sites of steroid hormone receptors and aromatase (estrogen synthase) in the auditory system of batrachoid fish (midshipman fish, *Porichthys notatus*, and Gulf toadfish, *Opsanus beta*). Solid dots represent somata and lines represent axonal projection pathways. Two connected dots indicate reciprocal connections. Numbers indicate localization of: (1) androgen receptor beta ($AR\beta$) mRNA; (2) estrogen receptor alpha ($ER\alpha$) mRNA; (3) estrogen receptor beta 1 ($ER\beta1$) protein; (4) estrogen receptor beta 2 ($ER\beta2$) protein; (5) aromatase (ARO) mRNA and protein. Nuclei with catecholaminergic innervation are shaded. Vocalizations (e.g., grunt trains) are detected by the auditory saccule within the inner ear, which projects via the VIIIth nerve to auditory nuclei in the hindbrain that innervate the auditory midbrain torus semicircularis (TS). Shown are nuclei interconnected with TS. A dorsal thalamic nucleus (central posterior nucleus, CP) contains reciprocal connections to dorsal (dorsomedial, Dm) and ventral (supracommisural, Vs) divisions of the telencephalon; Vs receives input from the anterior hypothalamus-posterior tubercle (for nomenclature see Braford and Northcutt 1983). TS and CP also connect to forebrain (anterior hypothalamus, POA) and midbrain (PAG, isthmal/tegmentum) vocal sites, while auditory-recipient hindbrain nuclei connect to the vocal central pattern generator (CPG). The vocal CPG includes topographically separate vocal prepacemaker (VPP), pacemaker (VPM) and motor (VMN) nuclei. VMN projects via occipital nerves to vocal muscles (see also Chagnaud et al. 2011). A hindbrain octavolateralis efferent nucleus (OE) directly innervates the inner ear and lateral line organs. Modified from Forlano et al. (2010) and Fergus and Bass (2013); also see Forlano et al. (2014) and references within for catecholaminergic innervation

2.3 Sound-Producing Fishes

A detailed discussion of sound production in fishes is far beyond the scope of this chapter, especially given several recent collections of reviews (e.g., Ladich et al. 2006; Ladich 2015). Nonetheless, some essential background information is needed given that several studies identifying the auditory system as targets of steroid hormone modulation were carried out in the context of sound production.

2.3.1 *Sonic and Vocal Fish*

Sound production among fishes has long been known, but the middle of the last century witnessed several reports that especially brought attention to underlying biomechanical and neural mechanisms (see collection of papers in Tavolga 1977 for historical overview and biomechanics; see Bass and Zakon 2005 for neurobiology). Sonic behavior is widespread among fishes (e.g., Fish and Mowbray 1970; Ladich et al. 2006). Teleosts, in particular, have evolved a range of peripheral mechanisms to produce sound (Ladich et al. 2006; Ladich 2015). The term ‘sonic’ was adopted early on to describe these fishes (Fish 1948; Fish and Mowbray 1970). One of the more widespread sonic mechanisms depends upon the contraction of a pair of muscles attached either directly (intrinsic) or indirectly (extrinsic) to the lateral walls of the swim bladder (Ladich and Fine 2006).

The most intensely studied group of sonic teleosts for audition is toadfishes (order Batrachoidiformes, family Batrachoididae), which includes 25 genera and 78 species with intrinsic swim bladder muscles and species generally referred to as toadfish and midshipman fish (Greenfield et al. 2008; Rice and Bass 2009). More recently, the term ‘vocal’ has been adopted in studies of sound production mechanisms of toadfishes, in part, to draw one’s attention to the many similarities they share with the vocal behavior and underlying mechanisms of tetrapods (e.g., midshipman fish, Fig. 2.1a) (Bass et al. 1994; Bass 2014).

Another mechanism for teleost sound production depends on the use of some part of the pectoral appendage (e.g., catfish, Fig. 2.1a) (Tavolga 1962; Ladich and Fine 2006). This is yet another sonic character that teleosts share with some tetrapods (Bass and Chagnaud 2012). Such species differ from those with dedicated sonic mechanisms (e.g., swim bladder) in that pectoral muscles serve other functions (e.g., locomotion) and hence it is appropriate to simply refer to them more generally as sonic. Using this classification scheme, sonic would be inclusive of vocal species.

2.3.2 *Vocal Central Pattern Generator (CPG)*

A major reason why vocal teleosts have provided important models for audition and showing how hormones can directly modulate the neural basis of behavior is the direct translation between the output of a hindbrain vocal CPG and the physical attributes of natural vocalizations. The acoustic signals of many fish species exhibit extreme temporal precision on a millisecond timescale. A 1:1 relationship between the pattern of motor nerve activity, sonic muscle contraction rate, and natural sound pulse repetition rate (PRR) allows one to define the relationship between individual neuron activity and the physical attributes of natural vocalizations in a vertebrate preparation (Fig. 2.4a, b). Toadfishes, the main focus of such studies, have a vocal CPG composed of three topographically separated populations of hindbrain neurons activated by descending input from forebrain-midbrain vocal centers (Fig. 2.4c, d)

(Kittelberger et al. 2006; Chagnaud et al. 2011). A vocal prepacemaker nucleus (VPP) codes for sound duration and innervates downstream vocal pacemaker neurons (VPNs) that code for PRR (Fig. 2.4c, d) (Chagnaud et al. 2011; Chagnaud and Bass 2014). The VPN provides dense bilateral input to paired vocal motor nuclei (VMN) that contribute to the coding of sound amplitude (Fig. 2.4c, d) (Chagnaud et al. 2012). Recent studies used transcriptome sequencing to identify a suite of candidate genes underlying the intrinsic and network properties of the VMN (Feng et al. 2015), setting the stage for comparable studies of auditory-vocal integration sites.

The vocal CPG shares multiple characters with comparable circuitry in tetrapods, including a vocal corollary discharge circuit (Bass 2014). Studies in midshipman fish specifically identify duration-encoding VPP neurons as the source of a corollary discharge signal to the octavolateralis efferent nucleus that directly innervates the auditory saccule (Weeg et al. 2005; Chagnaud and Bass 2013). This finding draws attention to the impact of self-vocalization on auditory encoding (Chagnaud and Bass 2013), as well as the salient role of sound duration in auditory discrimination tasks central to behavioral mechanisms of conspecific recognition in midshipman fish (Bass and McKibben 2003).

2.4 Seasonal Changes in Hearing Sensitivity

Seasonal changes in behavioral phenotypes are one form of biological rhythm (Nelson 2011). Several studies during the late 1970s and early 1980s launched widespread interest in this topic among neuroethologists that has continued over the past four decades. Nottebohm and colleagues demonstrated sexual dimorphisms and seasonal increases in the volume of telencephalic song nuclei in male canaries that were related to seasonal changes in song production (Nottebohm and Arnold 1976; Nottebohm 1981). These findings inspired comparable studies of the electrosensory and electro-motor systems of teleosts (Meyer and Zakon 1982; Bass and Hopkins 1983) and elasmobranchs (Sisneros and Tricas 2002). In the acoustic modality, underwater playback studies in midshipman fish revealed seasonal, reproductive state-dependent changes in positive phonotaxis toward social acoustic signals (McKibben and Bass 1998). These findings led, in turn, to the demonstration of steroid-dependent, seasonal plasticity in frequency encoding by saccular auditory afferents (Sisneros and Bass 2003; Sisneros et al. 2004a). As reviewed in the following sections, other studies soon followed with a new focus on seasonal changes in auditory hair cells.

2.4.1 Auditory Plasticity in Midshipman Fish

It is now well established in fish that vocal motor phenotypes and the performance of vocal behaviors that function in mate attraction and localization vary with reproductive state (Amorim et al. 2015; Bass et al. 2015). Although observations of seasonal

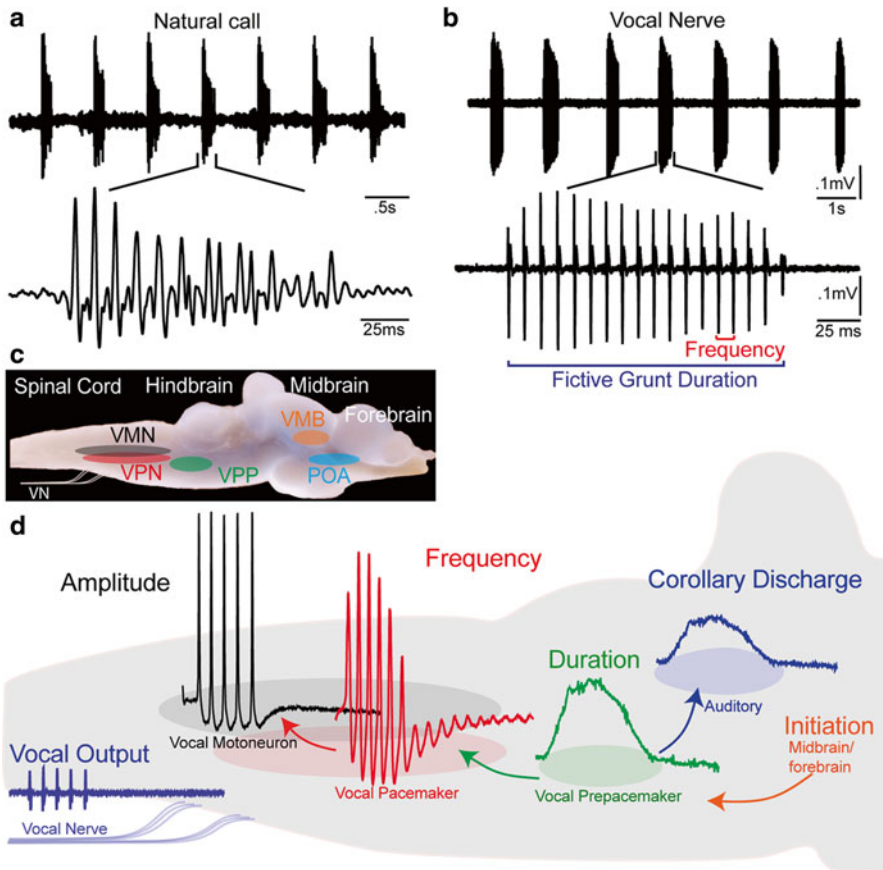


Fig. 2.4 Vocal central pattern generator (CPG) directly determines vocal behavior in fish. **(a) Top:** Hydrophone record of a series (“train”) of agonistic grunts from the nest of a type I male midshipman fish, *Porichthys notatus*. **Bottom:** Single grunt on an expanded time scale. **(b)** Vocal nerve activity mimics natural grunts. **Top:** Recording of spontaneously generated vocal nerve volley from a type I male. **Bottom:** A single burst of vocal nerve activity on expanded time scale. **(c)** Sagittal view of brain of midshipman fish maps the central vocal motor network. Vocal midbrain (VMB) neurons gate descending input from the preoptic area (POA) that activates the vocal central pattern generator (CPG) comprised of vocal prepacemaker (VPP), pacemaker (VPN), and motor (VMN) nuclei. **(d)** Schematic sagittal view of hindbrain summarizing vocal CPG neurophysiology. The vocal CPG generates a vocal nerve motor volley that determines natural call properties including duration and the pulse repetition rate (PRR), which also sets the fundamental frequency in fish. Vocalization duration, PRR, and amplitude are coded by VPP, VPN, and VMN neurons, respectively. The vocal CPG (VPP) transmits a corollary discharge that informs auditory hindbrain populations, including efferent (octavolateralis) neurons that directly innervate saccular hair cells (see Fig. 2.3) about call duration. Modified from Chagnaud et al. (2011) and Bass and Chagnaud (2012).

changes in bird vocalizations date back to Aristotle (for translation of Aristotle’s original text, see Balme 2002), the first reported observation of a natural seasonal cycle in hearing sensitivity was for midshipman fish (Sisneros and Bass 2003). Midshipman fish rely extensively on acoustic communication during the breeding

season for successful reproduction and have two male reproductive morphs (Bass 1996). Type I males build nests under rocky shelters in the intertidal zone from where they acoustically court gravid females carrying mature eggs at night using a multiharmonic advertisement call known as a hum (Brantley and Bass 1994; McIver et al. 2014). Type II males exhibit an alternative reproductive tactic; they neither build nests nor engage in acoustic courtship but rather steal fertilizations from nesting type I males (Brantley and Bass 1994). Each male morph and females show divergent profiles of circulating plasma levels of 17β -estradiol (E_2), testosterone (T), and 11-ketotestosterone (11-KT) that figure prominently in mechanisms of peripheral auditory plasticity (Sect. 2.5). More complete reviews of the neurobiology and behavior of the two male morphs in the broader context of reproductive plasticity are available elsewhere (Bass 1996; Bass and Grober 2009).

The hum functions as an advertisement call (Brantley and Bass 1994; Forlano et al. 2015a). The fundamental frequency of the hum hovers close to 100 Hz at 14–16 °C (increasing by about 5 Hz per 1 °C) with several prominent harmonics that range up to approximately 800 Hz, and the harmonics contain most of the signal's total energy (Brantley and Bass 1994; McIver et al. 2014). Behavioral studies of underwater acoustic playbacks show that both male morphs and gravid females exhibit positive phonotaxis to natural or synthetic hums, though females show the most robust responses. This unconditioned phonotactic response of gravid females is unambiguous and results in precise localization of the sound source (McKibben and Bass 1998; Zeddies et al. 2010). In contrast, recently spawned females void of eggs neither exhibit phonotaxis nor show any interest in natural or synthetic advertisement calls (McKibben and Bass 1998, 2001a).

Recognizing the robust behavioral results from the underwater playbacks, Sisneros and Bass (2003) tested the hypothesis that seasonal variation in reproductive state can modulate the neurophysiological response properties of saccular nerve afferents. Up until that time, saccular afferents were mainly characterized in type I males held in captivity through the non-breeding season (McKibben and Bass 1999, 2001b). Sisneros and Bass (2003) compared afferent response properties between reproductive females recently collected from intertidal nest sites and non-reproductive females recently collected during the winter months from deeper offshore sites. Responses were measured in terms of spike rate and accuracy of phase-locking (vector strength of synchronization, VS), a metric used to characterize frequency encoding. Reproductive individuals displayed robust frequency encoding (measured by VS) up to 340 Hz, whereas non-reproductive fish displayed comparable frequency encoding only up to 100 Hz. Reproductive females also showed increases in best frequency (BF, frequency that evoked the greatest spike rate or highest VS value to the auditory stimuli), VS values at BF, and maximum evoked spike rate at BF compared to non-reproductive females. In sum, reproductive females were best adapted to encode the higher harmonic components of the male advertisement hum during the breeding season.

Recognizing that type I males also, though less frequently, exhibit positive phonotaxis to hum playbacks (McKibben and Bass 1998), Rohmann and Bass (2011) showed that the auditory thresholds of saccular hair cells were lower (or more sensitive) in reproductive compared to non-reproductive type I males.

This study also independently confirmed the dependency of enhanced saccular sensitivity in females on their being in reproductive condition, as first reported by Sisneros (2009). Together, these studies showed that the saccular hair cells of reproductive females and type I males were approximately 2.5–4.5 times more sensitive than those of non-reproductive fish to frequencies corresponding to the dominant harmonics in the male advertisement call. The hearing sensitivity of reproductive type II males is like that of type I males and females (Fig. 2.5a); pilot studies showed comparable seasonal changes as well (Whitchurch and Sisneros 2011).

The most recent midshipman fish studies focused on mechanisms underlying the seasonal plasticity of frequency encoding by the sacculus. Rohmann et al. (2013) reported that variation in frequency sensitivity by saccular hair cells could be accounted for by seasonal changes in the abundance of large-conductance, calcium-activated potassium (BK) channels, which underlie a primary outward current and influence hair cell tuning in reptiles and birds (Fettiplace and Fuchs 1999). Using iberiotoxin, a specific antagonist to BK channels, Rohmann et al. (2013) effectively showed that BK channels alone could account for nearly all seasonal transformations in the sacculus's neurophysiological phenotype that is shared by both sexes (Fig. 2.5b).

The highly conserved, pore-forming α subunits of BK channels are encoded by duplicates of the *slo 1* gene, *slo 1a* and *slo 1b* in midshipman fish and other teleost fish (Rohmann et al. 2009). Using an antibody against a conserved region of the *slo 1* duplicate genes, BK channel expression was mainly localized to the apical neck and basal surfaces of saccular hair cells (Rohmann et al. 2013). Rohmann et al. (2013), using quantitative (q) PCR, went on to show that the expression of *slo 1a* and *slo 1b* mRNA transcripts increased nearly threefold in the saccular epithelia of reproductive versus non-reproductive fish; mRNA transcript levels varied inversely with individual auditory thresholds. Together with the pharmacological experiments (Fig. 2.5b), the results were consistent with the earlier studies in reptiles (turtle) and birds (chicken) showing that increased BK channel expression in auditory hair cells underlies higher resonant frequencies and improved encoding of higher frequency sounds (Fettiplace and Fuchs 1999). Rohmann et al. (2013) proposed that the plasticity in BK ion channel expression represents an evolutionarily labile solution for shaping the sensory bandwidth of auditory hair cells to maximize the detection of conspecific social signals during reproductive cycles among vertebrates in general.

Coffin et al. (2012) identified seasonal, reproductive state-dependent increases in saccular hair cell density and decreases in hair cell death in midshipman fish (Fig. 2.6a–e) that were independent of body size (age) and not observed for other otolithic end organs of the inner ear, the lagena and utricle. For reproductive females, these changes were concurrent with increases in the magnitude of the evoked saccular potentials and decreases in saccular auditory thresholds. These authors concluded that the correlated seasonal plasticity of hair cell addition and auditory sensitivity contributes to the overall seasonal enhancement of hearing sensitivity in midshipman fish.

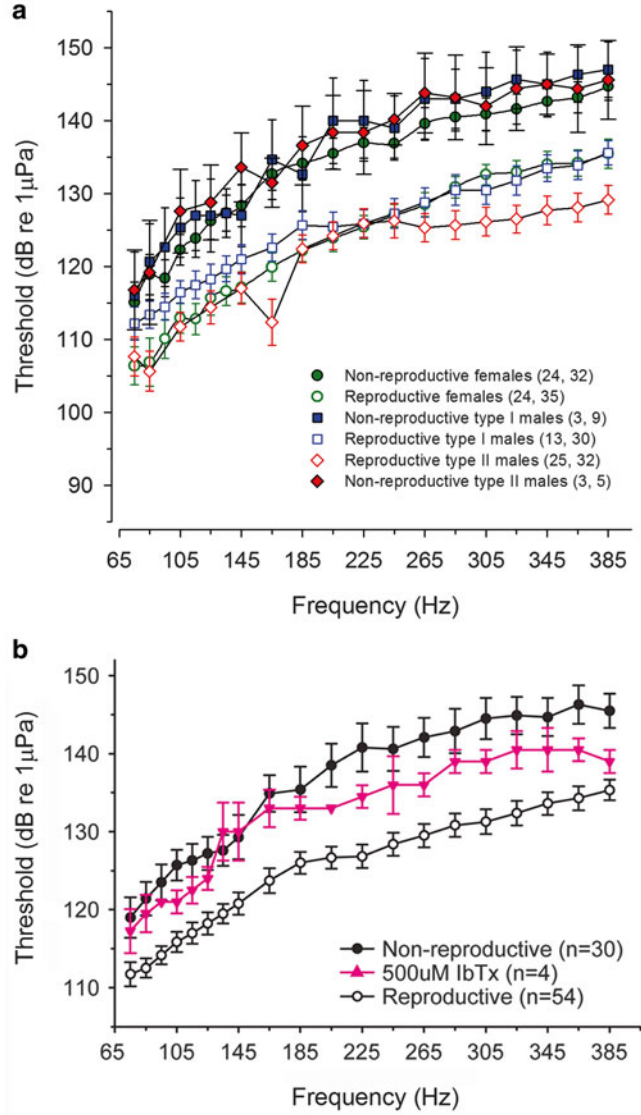


Fig. 2.5 Frequency sensitivity of hair cells of the saccular epithelium in the midshipman fish, *Porichthys notatus*. (a) Depicted here are auditory threshold tuning curves based on evoked potential recordings from the saccular epithelium of all three adult midshipman morphs in reproductive (females, type I males, and type II males) and non-reproductive (females, type I males, and type II males) condition. All data are plotted as mean $\pm 95\%$ confidence limit and the number of animals and records are indicated in parentheses. (b) Delivery of the specific BK channel antagonist iberitoxin (IbTx) to the saccule of reproductive type I males shifts their thresholds to a non-reproductive like state (reproductive phenotype included to facilitate comparisons). Adapted from Rohmann et al. (2013)

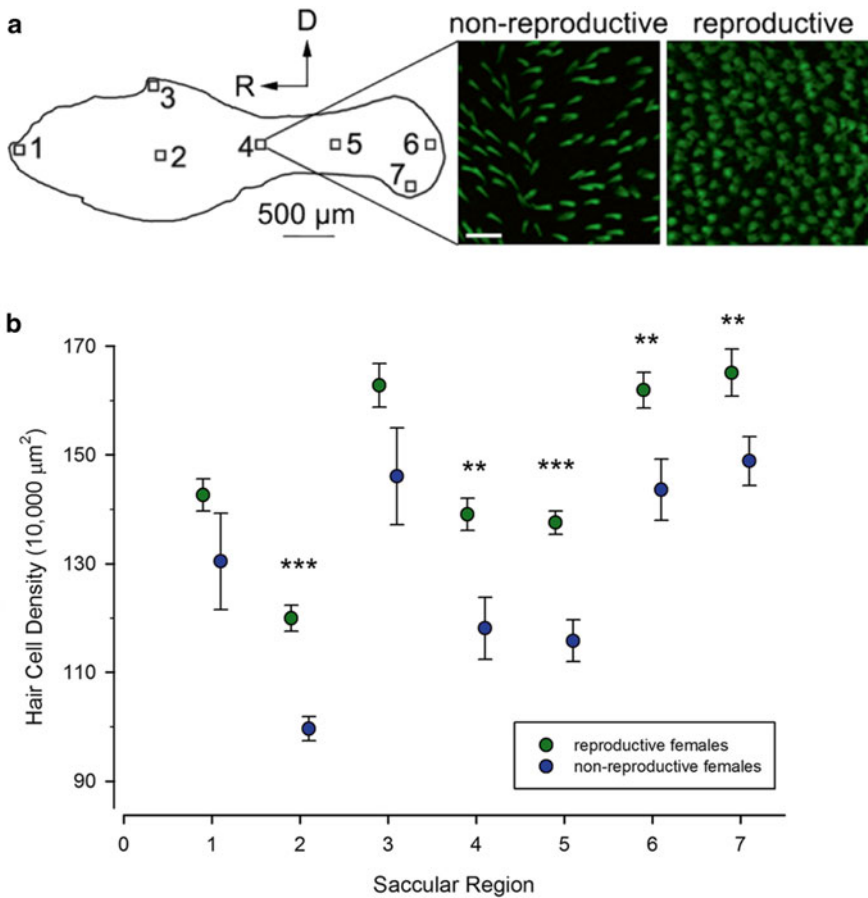


Fig. 2.6 Seasonal differences in hair bundle density and in the number of small hair bundles in the saccule of female midshipman fish, *Porichthys notatus*. **(a)** Phalloidin-labeled hair bundles were counted in 10,000 µm² areas from seven regions across the saccule, as indicated by the numbered boxes on the line drawing (top left). Two micrographs (top right) show representative images from the middle of the saccule of non-reproductive and reproductive females. **(b)** Hair bundle quantification shows significantly more hair cells in several regions of the saccule of reproductive (green circles) compared to non-reproductive (blue circles) females (** $p < 0.01$; *** $p < 0.001$). **(c)** Confocal brightest point projection and **(d)** scanning electron micrograph showing a small, immature-like bundle (small arrow) adjacent to larger, mature hair bundles (arrowheads). Scale bars: C, 2 µm; D, 1 µm. **(e)** Small hair bundles were counted in seven 15,380 µm² regions of ten saccules from both reproductive (green circles) and non-reproductive (blue circles) females. There were significantly higher densities of small hair bundles in reproductive compared to non-reproductive females in regions 1–4 of the saccule (* $p < 0.05$; ** $p < 0.01$). Data from Coffin et al. (2012)

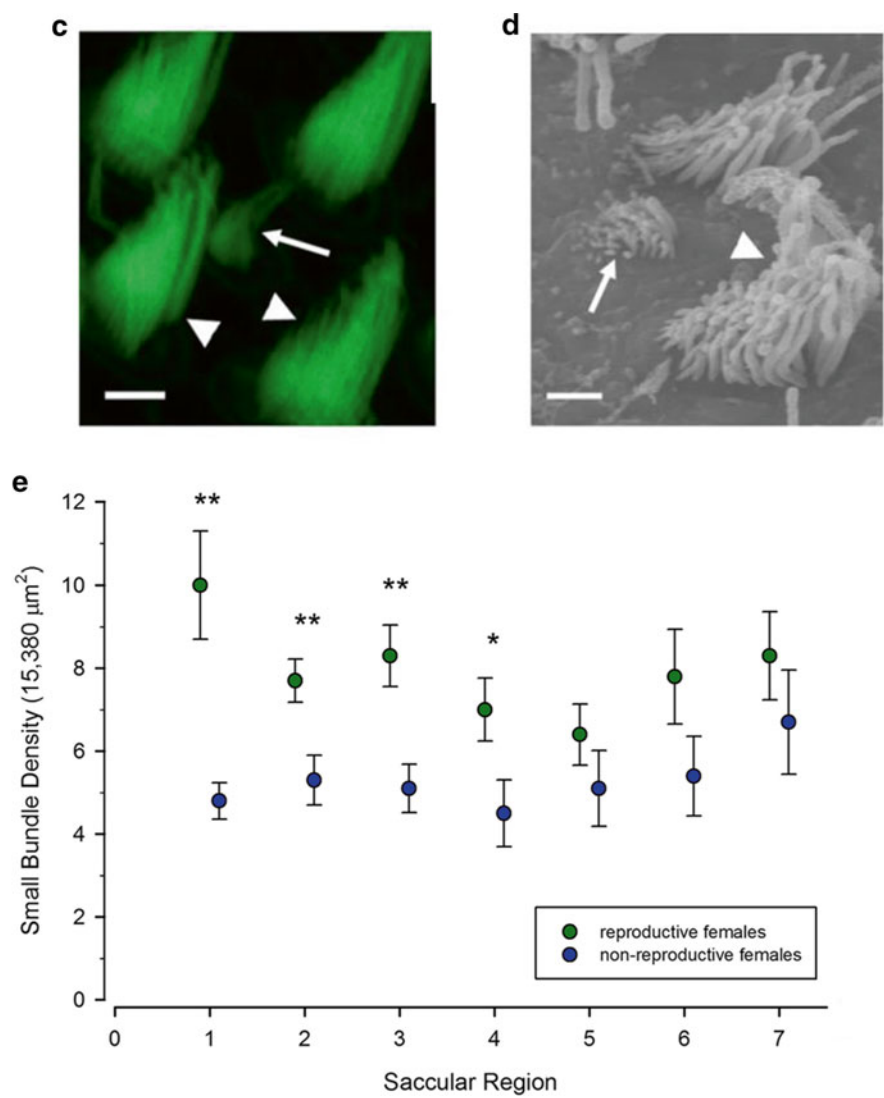


Fig. 2.6 (continued)

What might be the adaptive/functional significance of reproductive-related seasonal changes in hearing sensitivity? In considering midshipman fish, the functional significance may be to increase the probability of detection and localization of the nesting male's advertisement call in shallow-water environments where the propagation of acoustic signals is greatly affected by water depth and substrate composition (Rogers and Cox 1988; Bass and Clark 2003). Sisneros and Bass (2003) proposed that seasonal enhancement of the higher frequency harmonics in the male

advertisement call by receptive females would effectively increase their detection range and aid in mate localization. Support for this hypothesis comes from McKibben and Bass (2001b), who showed that saccular afferent encoding of pure tones at or near the fundamental frequency of the advertisement call improved when additional tones similar to the call's harmonics were added to the presentation stimuli. These results suggest that the dominant higher harmonics of the advertisement call may also affect the encoding of the call's fundamental frequency when the receiver is near or close to the sound source (i.e., calling male).

In sum, the seasonal increase in auditory saccular sensitivity may represent an adaptive plasticity of the midshipman fish auditory system for improved detection and localization of vocalizing conspecifics in shallow-water environments during the breeding season.

2.4.2 Hearing, Hormones, and Changing Reproductive State in Cichlids

In addition to the seasonal and steroid-induced auditory plasticity seen in teleosts like toadfishes that rely heavily on acoustic communication during reproduction, there is emerging evidence that hormones also influence hearing in other sonic fish species (Maruska and Sisneros 2015). One such example is the African cichlid fish, *Astatotilapia burtoni*, in which dominant males produce pulsed (~2–19 pulses), broadband (peak frequency range: ~120–900 Hz) sounds during body quivers as part of their courtship behavior to attract and lead gravid females back into their territory for spawning (Maruska et al. 2012). Playback experiments suggest that females gain some valuable information from these male-generated acoustic signals that facilitates mating decisions (Maruska et al. 2012).

Astatotilapia burtoni differs from the seasonally breeding midshipman fish because it breeds year-round in its equatorial East African habitat in Lake Tanganyika, but it does undergo social status and reproductive-state variations in hormones and peripheral auditory sensitivity. Females cycle between a gravid receptive phase and a mouth-brooding parental phase in which they care for developing young inside of the buccal cavity for about 2 weeks (Fig. 2.7a). Gravid females have higher circulating androgen (T and 11-KT) and E_2 levels (Maruska and Fernald 2010). These reproductive-state changes in hormone cycling, coupled with the knowledge that dominant males produce courtship sounds that females attend to, suggest that

Fig. 2.7 (continued) and *asterisks* indicate statistical differences ($p < 0.05$). The *gray line* represents the power spectrum of a representative male courtship sound for comparison. **(c)** Schematic summary of relationships between hearing thresholds, circulating sex steroids, and steroid receptor mRNA levels in the saccule across the female *A. burtoni* reproductive cycle. In gravid receptive females, plasma steroid levels are high, hearing sensitivity to low frequencies is improved (lower thresholds), and mRNA levels of some steroid receptors in the saccule are low. In parental mouth-brooding females, these relationships are primarily opposite in relative value. Modified from Maruska and Sisneros (2015)

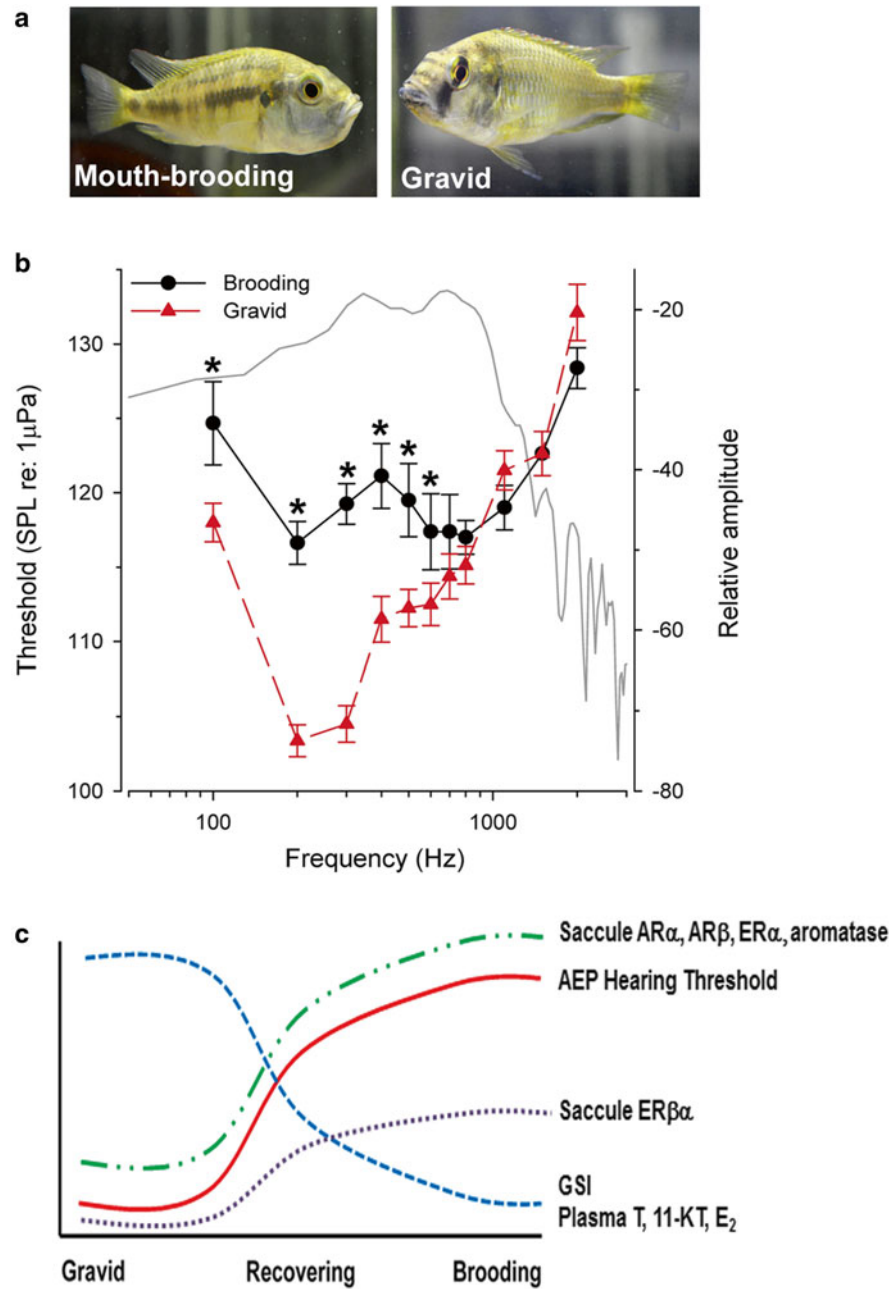


Fig. 2.7 Reproductive-state plasticity in the auditory system of the cichlid fish, *Astatotilapia burtoni*. (a) Photographs of a reproductively receptive, gravid female and a parental care phase, mouth-brooding female. (b) Hearing thresholds measured via auditory evoked potentials from gravid females compared to mouth-brooding females show lower thresholds from 100 to 600 Hz, which overlap the spectral content of male courtship sounds. Data are plotted as mean \pm SE (left axis)

steroid-induced auditory plasticity exists in this species as in the distantly related toadfishes that include midshipman fish (Sect. 2.5).

Since auditory sensitivity changes with reproductive state in both fishes and tetrapods (Caras 2013; also see Wilczynski and Burmeister, Chap. 3; Caras and Remage-Healey, Chap. 4; Chong and Liu, Chap. 6), Maruska et al. (2012) used auditory evoked potentials (AEP) to test whether hearing sensitivity also differed between female reproductive states in *A. burtoni*. Gravid receptive females had lower hearing thresholds (~5–15 dB SPL re 1 μ Pa lower) at low frequencies (100–600 Hz) compared to mouth-brooding, non-receptive females (Fig. 2.7b). This two- to five-fold improvement in auditory sensitivity is within the spectral range of courtship sounds produced during male quiver behaviors and may allow females to better distinguish the quality of individual males within the population, to detect courting males at greater distances, and to make more informed mating decisions. Enhanced sensitivity to courtship signals and choosing a high quality male is important in this species because spawning is followed by costly mouth-brooding and parental care in which there is a switch from self-promoting to offspring-promoting behavior and physiology. Females with better auditory sensitivity also had higher gonadosomatic indices (GSI, ratio of total gonad mass to body mass) and levels of circulating T and E₂ (Fig. 2.7c) (Maruska et al. 2012). In sum, as a female *A. burtoni* approaches spawning readiness and searches for a courting male, her circulating sex steroid levels increase and overall hearing sensitivity is improved, which may depend, in turn, on changing levels of steroid receptors (see Sect. 2.5). While direct tests of steroid influences on auditory sensitivity and processing like those performed in midshipman fish (Sect. 2.5.1) are still needed, it is evident that reproductive-related plasticity exists in this species. Whether this plasticity is mediated via changes in central processing, peripheral processing, or both, however, remains unknown. As exemplified by *A. burtoni*, hormone effects on auditory perception likely also exist in many fishes that use acoustic signals as part of more complex multisensory (vision, chemoreception, mechanoreception) communication behaviors during reproduction (Maruska and Fernald 2014).

In addition to midshipman fish and cichlids, studies in other species, such as the round goby (*Neogobius melanostomus*), show condition-dependent auditory sensitivity, in this case correlated with reproductive readiness and circulating E₂ levels in females but not in males (Zeyl et al. 2013). Females displayed lower auditory thresholds than males in response to natural vocalizations and pure tones from 300 to 600 Hz, and females had a higher density of hair cells in the sacculus. Thus, the results by Zeyl et al. (2013) also demonstrate a sex difference in auditory sensitivity that may be based, at least partially, on differences in circulating steroid levels.

2.5 Peripheral Studies of Hormone Modulation

Auditory plasticity related to reproductive readiness and steroid hormones is now known to be widespread among vertebrates, including humans (Wilczynski and Burmeister, Chap. 3; Caras and Remage-Healey, Chap. 4; Maney and Rodriguez-Saltos, Chap. 5; Chong and Liu, Chap. 6; Frisina and Frisina, Chap. 8) and fishes.

2.5.1 Steroid-Mediated Plasticity of Fish Auditory Systems

Androgens and estrogens fluctuate seasonally with the reproductive cycle in teleosts (Brantley et al. 1993; Oliveira 2009). Midshipman fish, like closely related species of toadfish, exhibit seasonal changes in circulating steroids that parallel changes in reproductive state (Fig. 2.8) (Sisneros et al. 2004b and references therein). Four seasonally defined periods were recognized based on field collections across reproductive and non-reproductive time periods (Fig. 2.8) (Sisneros et al. 2004b). Dramatic increases in female E_2 levels in the spring led Sisneros et al. (2004a) to test the hypothesis that T and E_2 (a metabolite of T) were responsible for the observed seasonal changes in auditory sensitivity among females (Sisneros and Bass 2003). Both E_2 and T separately improved the phase-locking accuracy of sacral afferents and enhanced the encoding of frequencies corresponding to the dominant, higher harmonic components of the mate call. RT-PCR also confirmed the presence of estrogen receptor alpha ($ER\alpha$) in the saccular epithelium, suggesting a direct effect of steroids on the peripheral auditory system of a teleost. Rohmann and Bass (2011) provided comparable physiological support for reproductive type I males. They further proposed that elevated androgen and/or estrogen levels act via long-term (i.e., days to weeks) signaling pathways to upregulate BK channels (Sect. 2.4.1) that underlie higher resonant frequencies and lower acoustic thresholds of auditory hair cells. This hypothesis remains to be tested.

2.5.1.1 Hormone Targets of the Peripheral Auditory System

Since elevating either T or E_2 in non-reproductive, ovariectomized females could induce a reproductive physiological phenotype, a predominantly estrogenic effect was predicted since T can be metabolized into E_2 by the enzyme aromatase. The search for estrogen receptors (ERs) in the saccule began with $ER\alpha$, the best characterized ER at the time (Toran-Allerand 2004). Estrogen receptor α was found to be expressed in saccular epithelia (Sisneros et al. 2004a), although $ER\alpha$ mRNA was not expressed in either ganglion or hair cells, but rather just outside the hair cell layer over unidentified cell types (Forlano et al. 2005).

While most vertebrates express two ER subtypes, $ER\alpha$ and $ER\beta$, teleosts express two distinct $ER\beta$ s, $ER\beta1$ and $ER\beta2$, for a total of three types of known “classical” (i.e., nuclear) receptor subtypes (Hawkins et al. 2000; Menuet et al. 2002), although these have also been localized to the cytoplasm. Fergus and Bass (2013) localized $ER\beta1$ and $ER\beta2$ to saccular hair cells (and the central auditory system) of midshipman fish (Fig. 2.9a–d). These results provided strong support for estrogen having direct effects on hair cell physiology. $ER\beta2$ was broadly, but variably, found throughout the cytoplasm of hair cell somata, while $ER\beta1$ was localized only on the apical surface of hair cells at the base of the hair cell bundle (Fergus and Bass 2013). The location of $ER\beta2$ in the hair cell cytoplasm suggests a membrane receptor-type mechanism that may be involved with ion channel regulation (Rohmann et al. 2013), while $ER\beta1$ may function in modifying mechanotransduction properties.

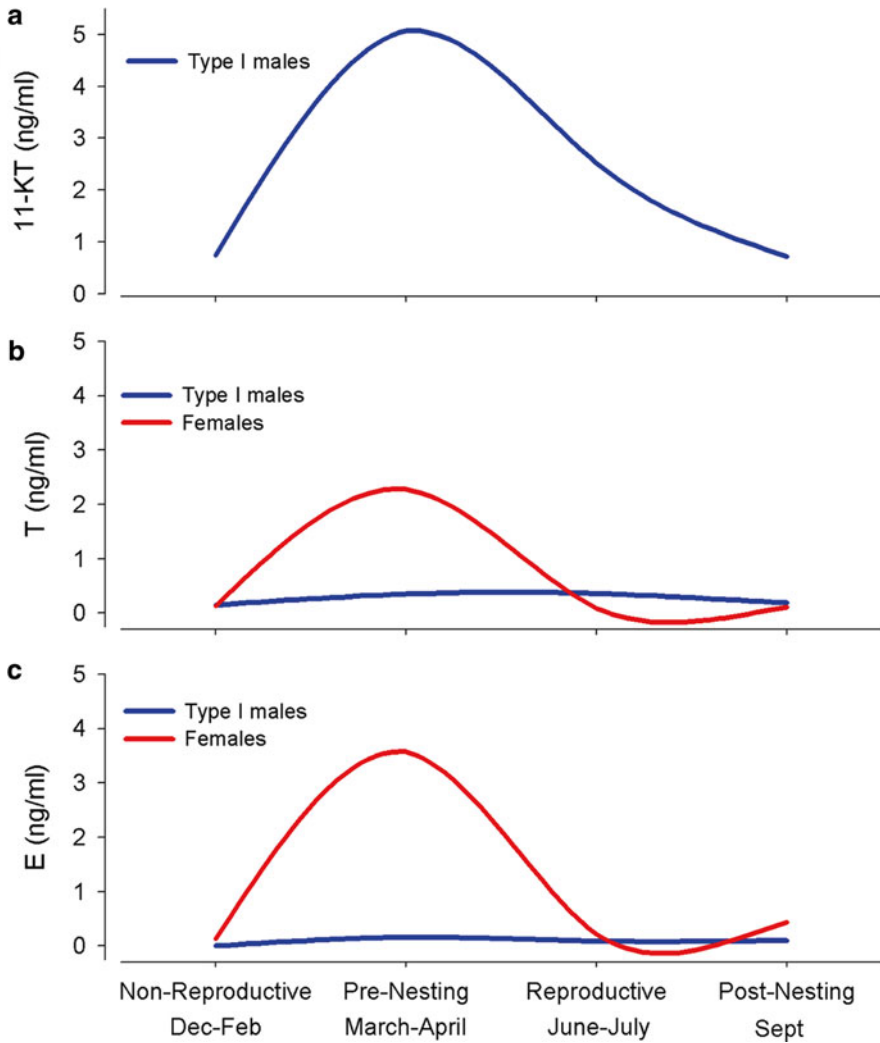


Fig. 2.8 Schematic portrayals of plasma levels of 11-ketotestosterone (11-KT), testosterone (T), and estradiol (E) are shown in (a)–(c), respectively, for wild-caught female and type I male mid-shipman fish, *Porichthys notatus*, collected from Monterey Bay and Tomales Bay, CA. Fish were collected during four time periods between March 2001 and July 2002. December–February: winter, non-reproductive months when both sexes remain offshore, and GSI and steroid levels remain low; March–April: spring, pre-nesting months when both sexes begin their inshore migration from deep offshore sites and exhibit wide variation in GSI as circulating steroid levels increase; June–July: summer, nesting months when females have a relatively high GSI; T and E₂ levels are low, although advertisement calling (humming) type I males exhibit significantly higher 11-KT levels than non-humming males (Genova et al. 2013); September: fall, post-nesting time period when both sexes are offshore again and have very low GSIs and steroid levels. Modified from Sisneros et al. (2004b)

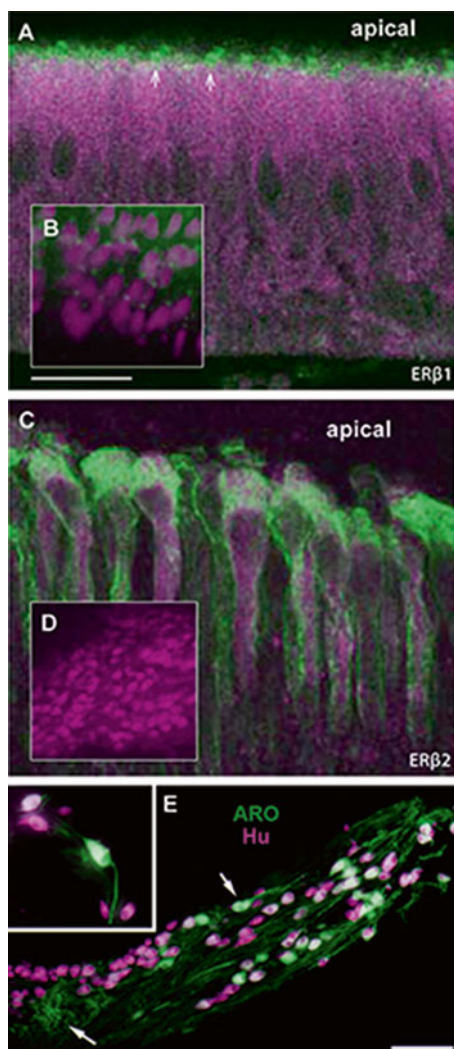


Fig. 2.9 Expression of ER β 1, ER β 2, and aromatase in the sacculus of the inner ear in the midshipman fish, *Porichthys notatus*. (A) Saccular hair cells are stained robustly throughout the cell body with the hair cell-specific (HCS-1) antibody (magenta); ER β 1 staining (green) is limited to the apical surface. (B) Co-label of hair cells with phalloidin (magenta), which stains actin filaments of hair cell bundles, and ER β 1 antibodies (green) show ER β 1 protein localized near the base of each bundle. (C) Co-label with ER β 2 (magenta) and HCS-1 (green) antibodies show ER β 2 label throughout the hair cell, although expression levels vary widely among cells. (D) ER β 2 is also present in ganglion cells of the saccular branch of the VIIIth nerve. (E) Double-label immunofluorescence using aromatase (green) and neuronal-specific Hu (magenta) antibodies reveals aromatase in ganglion cell somata (green-white) and their processes (green) in the saccular division of the VIIIth nerve (e.g., arrows). Inset is a high magnification of aromatase expression in bipolar ganglion cells (green-white) and processes (green) (center and upper left). (A) and (D) are from a sacculus that was frozen-sectioned (30 μ m); (B) and (C) are images from whole-mount sacculi. Scale bar in (A)=20 μ m for (A) and (C); 40 μ m for inset (B); 200 μ m for (D). Scale bar in (E)=100 μ m and 50 μ m in inset. (A–D) is from Fergus and Bass (2013); (E) is modified from Forlano et al. (2005)

Heterogeneous expression of ER β 2 may be related to different populations of hair cells with variable encoding properties that are estrogen sensitive. An increase in hair cell number in the reproductive season in females (see Coffin et al. 2012) may reflect differential targets of estrogen. Transcript levels for ER α , ER β 1 and ER β 2, and aromatase were found to be similar among the three reproductive morphs (Fergus and Bass 2013), consistent with shared patterns of seasonal auditory plasticity (Fig. 2.5).

Since saccular ganglion cells express ER β 2 (Fig 2.9d), they appear to be important players in estrogen-dependent plasticity in peripheral auditory function. Saccular ganglion cells also express aromatase (Fig. 2.9e). Together, these results support the hypothesis that estrogen is synthesized and acts locally in the auditory periphery from circulating androgen precursors (Forlano et al. 2005).

The androgen receptor (AR) in teleosts also has undergone gene duplication, resulting in two subtypes, AR α and AR β (Guerriero 2009; Ogino et al. 2009). In midshipman fish, AR β mRNA was found in a similar position as ER α mRNA, just outside the hair cell layer (Forlano et al. 2010). While localization of steroid receptors directly in hair cells implies direct action on the most peripheral level of auditory encoding, the role of steroid receptors residing within the epithelium, but not in hair cells, is more speculative. Such action could: (1) modulate either primary afferent response properties and/or efferent-afferent interactions; (2) be involved in seasonal hair cell neurogenesis (e.g., Coffin et al. 2012); or (3) maintain endolymph ionic homeostasis (Lee and Marcus 2001) when seasonal regulation may be important for migrating species, such as midshipman fish, when variable concentrations of saltwater are experienced.

Gravid female cichlids, *A. burtoni*, have higher circulating androgen (T, 11-KT) and E₂ levels and lower mRNA levels of AR and ER subtypes (AR α , AR β , ER α , ER β 1) in the saccule compared to mouth-brooding females (Fig. 2.7c) (Maruska and Fernald 2010). Furthermore, steroid receptor levels were negatively correlated with circulating androgen and E₂ levels, suggesting downregulation of ARs and ERs by elevated steroids produced from the ovaries as females approach spawning.

Expression of ERs in the inner ear appears to be a conserved vertebrate character since, outside of fishes, it has been demonstrated previously in mouse, rat, and human, and more recently in zebra finch, *Taeniopygia guttata* (Hultcrantz et al. 2006; Noirot et al. 2009). In contrast, AR expression in auditory sensory epithelia has not yet been studied outside of teleosts. Evidence for aromatase in the inner ear was also demonstrated in the zebra finch (Noirot et al. 2009) but not investigated in other species to date, although other steroidogenic enzymes are found in rat cochlea (Lecain et al. 2003). The functional significance of steroid hormone action in the inner ear of tetrapods is largely unknown, but evidence in mice suggests a role for ER β in acoustic trauma protection (Meltser et al 2008) and normal inner ear development (Simonoska et al. 2009). Outside of the classical ERs, recent evidence has found estrogen-related receptor gamma (ERR γ) expressed in the inner ear of both zebrafish (*Danio rerio*) and mice and appears to be necessary for normal inner ear development and hearing (Nolan et al. 2013; Tohme et al. 2014).

2.5.1.2 Hormone Targets of the Central Auditory System

Seasonal and steroid hormone influences on central auditory circuitry have not been investigated in fishes, although neuroanatomical evidence points to multiple sites as potential targets of steroid action (Fig. 2.3, Table 2.1). Unlike the periphery, where aromatase is expressed in VIIIth nerve ganglion cells, central expression is exclusively glial (Forlano et al. 2001; Diotel et al. 2010). No study has localized ERs and ARs (and aromatase) to the auditory hindbrain, which, therefore, does not appear to be a direct target of steroid hormones in midshipman fish (Forlano et al. 2015a). This is in stark contrast to mice in which ER α and ER β are documented throughout hindbrain auditory

Table 2.1 Distribution of androgen receptor (AR), aromatase (ARO, estrogen synthase), estrogen receptor alpha (ER α), beta 1 (ER β 1) and beta 2 (ER β 2) in the plainfin midshipman fish, *Porichthys notatus*

Anatomical location	AR ^a	ARO ^b	ER α ^c	ER β 1 ^d	ER β 2 ^e
Ventral telencephalon					
Olfactory bulb (OB)	–	+	+	–	–
Ventral nucleus (Vv) AUDITORY	–	+	+	–	+
Supracommissural nucleus (Vs) AUDITORY, VOCAL	+	+	+	–	+
Postcommissural nucleus (Vp) AUDITORY	+	+	+	–	–
Dorsal nucleus (Vd)	+	+	–	–	+
Intermediate nucleus (Vi)	+	+	–	–	–
Dorsal telencephalon					
Central zone (Dc)	+	+	+	–	–
Central medial division of medial zone (Dm-cm)	+	+	+	–	–
Posterior division of medial zone (Dm-p)	+	+	+	–	–
AUDITORY, VOCAL					
Dorsal posterior zone (Dp)	–	+	+	–	–
Preoptic area					
Anterior parvocellular (PPa) AUDITORY, VOCAL	+	+	+	+	+
Posterior parvocellular (PPp) AUDITORY, VOCAL	+	+	–	–	+
Magnocellular (PM/PMg)	+	+	+	+	–
Ventral hypothalamus					
Anterior tuberal (AT) AUDITORY, VOCAL	+	+	+	–	+
Ventral tuberal (vT) AUDITORY, VOCAL	+	+	–	–	–
Periventricular (Hv/Hd)	+	+	+	–	+
Thalamus					
Central posterior nucleus (CP) AUDITORY	+	+	+	–	–
Dorsal posterior (DPo)	+	+	+	–	–
Nucleus preglomerulosus (PGl/m) AUDITORY	+	+	–	–	–
Periventricular nucleus of posterior tuberal (TPp)	+	+	+	–	+
Posterior tuberal nucleus (TP)	+	+	–	–	+
Pineal	–	+	+	–	–

(continued)

Table 2.1 (continued)

Anatomical location	AR ^a	ARO ^b	ERα ^c	ERβ1 ^d	ERβ2 ^e
Brainstem					
Periaqueductal gray (PAG) VOCAL	+	+	–	+	+
Mesencephalic tectum (TeM)	+	–	+	–	–
Medial longitudinal fasciculus (MLF) (peri)	+	+	–	–	–
Nucleus of medial longitudinal fasciculus (nMLF)	+	+	+	–	–
Periventricular cell layer of TS (Pe) AUDITORY	+	–	–	–	+
Griseum central (GC)	+	+	–	–	–
Medial octavolateralis nucleus (MED) LATERAL LINE	+	–	–	–	–
Vagal motor nucleus (Xm)	+	+	–	+	+
Vocal prepacemaker (VPP) VOCAL	+	–	–	–	–
Vocal motor nucleus (VMN) VOCAL	+	+	+	+	+
Peripheral tissues					
Saccular epithelium (inner ear) AUDITORY	+	+	+	+	+
Vocal muscle VOCAL	+	–	–	–	–

Identification as central nodes of auditory and/or vocal networks is indicated

+/– presence/absence of mRNA or protein

For full descriptions see

^aForlano et al. (2010)

^bForlano et al. (2001)

^cForlano et al. (2005)

^{d,e}Fergus and Bass (2013)

nuclei (Charitidi and Canlon 2010). Interestingly, the lateral line-recipient medial octavolateralis nucleus shows robust ARβ expression (Forlano et al. 2010). Given the evidence in midshipman fish that lateral line afferents encode frequencies within the spectrum of vocalizations (Weeg and Bass 2000, 2002), androgens may indeed influence responses to social acoustic cues at the level of the hindbrain.

Estrogen receptors (ERs) are found in the midbrain in midshipman fish (Forlano et al. 2005; Fergus and Bass 2013), including the torus semicircularis, the principal midbrain auditory nucleus. This is the same named region in amphibians (Wilczynski and Burmeister, Chap. 3) and birds (Caras and Remage-Healey, Chap. 4; Maney and Rodriguez-Saltos, Chap. 5) and a homologue of the mammalian inferior colliculus (see McCormick 1999; Chong and Liu, Chap. 6). In general, forebrain auditory nuclei in teleosts express steroid receptors, including multiple auditory-vocal integration sites in midshipman fish (Fig. 2.3, Table 2.1) (Forlano and Bass 2011).

2.6 Hormone Modulation of Central Auditory Physiology

Hormone modulation of central auditory processing occurs in several brain regions in mammals (Hurley et al. 2002; Chong and Liu, Chap. 6), amphibians (Wilczynski and Burmeister, Chap. 3), and birds (Caras and Remage-Healey, Chap. 4; Maney

and Rodriguez-Saltos, Chap. 5) and is often associated with reproductive state- or context-dependent auditory perception. Hormones such as E_2 , for example, can rapidly modulate auditory neuron activity in the brain (Caras and Remage-Healey, Chap. 4). This modulation of auditory perception then allows animals to fine tune their behaviors on a moment-by-moment basis by integrating external sensory inputs with their internal physiological state. Thus, hormonal influences on central auditory physiology are an important aspect of acoustic communication across vertebrates.

In contrast to tetrapods, however, neurophysiological studies on hormone modulation of central auditory neurons are limited in fishes. The only documented example is the study of the effects of gonadotropin-releasing hormone (GnRH) on the response properties of auditory neurons in the TS of the Hawaiian sergeant damselfish (*Abudefduf abdominalis*) (Maruska and Tricas 2011). GnRH1 is a decapeptide that is best known for its control of the reproductive system via release to the pituitary gland, but many vertebrates including fishes have other GnRH forms (GnRH2, GnRH3) that are widely distributed in the brain and can function as neuromodulators (Abe and Oka 2011; Karigo and Oka 2013). GnRH is present in many sensory-processing regions, including auditory nuclei, leading to the hypothesis that it might function to modulate audition (Maruska and Tricas 2007, 2011). To test this hypothesis, Maruska and Tricas (2011) used the sonic Hawaiian sergeant damselfish to determine how GnRH influenced response properties of auditory midbrain neurons. This is a colonial, benthic-spawning species that produces low-frequency pulsed sounds during reproductive and territorial behaviors (Maruska et al. 2007) and shows seasonal changes in GnRH innervation to the auditory midbrain (Fig. 2.10) (Maruska and Tricas 2011). Exogenous application of GnRH affects several auditory response properties (spike rates, response latency, thresholds). The effects were most pronounced within the spectral region of courtship sounds (~80–200 Hz) produced by males, which is also the region of best hearing sensitivity for this species (Fig. 2.10). The results suggested disinhibition of midbrain auditory processing to facilitate reproductive-related acoustic communication.

Several studies demonstrate that neurons in the mammalian inferior colliculus (TS homologue) can be modulated by neuroactive substances such as serotonin and steroid hormones (Saalmann et al. 2006; Hurley and Sullivan 2012). Similar to the colliculus, the TS of fishes contains inputs and receptors for hormones, neurotransmitters, and neuromodulators (Sect. 2.7), suggesting that future examination of hormone effects on central physiology in the TS are warranted. The TS in fishes is an important site for integration of auditory information with other senses (McCormick 1999; Bass et al. 2005), thus serving as a substrate for modulation of auditory information depending on the animal's reproductive state and behavioral context. Compared to tetrapods, relatively little is known in fishes about the response properties of auditory neurons in higher processing regions of the forebrain (diencephalon and telencephalon), and nothing is known about how hormones might modulate audition in these important, decision-making nuclei. The expression of several modulatory substances and their receptors in forebrain auditory nuclei in fishes, however, suggests that central hormone modulation of audition is conserved across vertebrates.

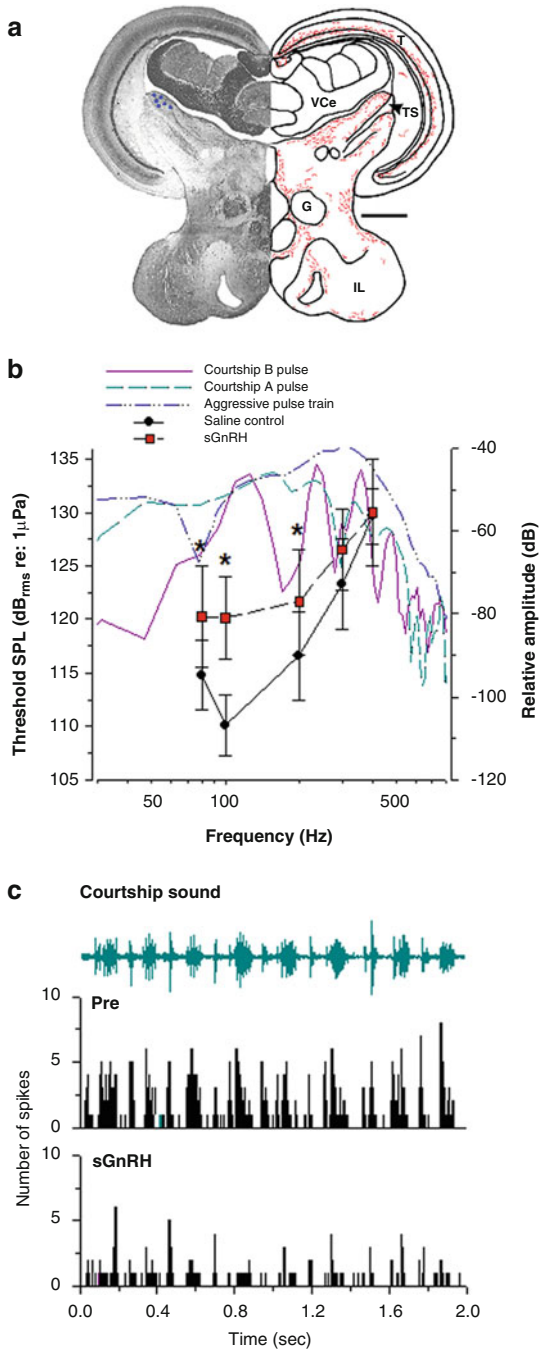


Fig. 2.10 Gonadotropin-releasing hormone (GnRH) increases auditory-evoked thresholds in midbrain neurons of the Hawaiian damselfish *Abudefduf abdominalis*. **(a)** Labeled recording sites and distribution of GnRH-immunoreactive axons in the midbrain torus semicircularis (TS).

2.7 Catecholamines and Hearing

While it is well established that steroid hormones, such as estrogen, drive seasonal peripheral auditory plasticity in midshipman fish in order to better encode the male's advertisement call (Sect. 2.5), neuromodulators downstream of steroids are unexplored, and little is known of the neural substrates that underlie the motivation and coordinated behavioral response to auditory social signals. Catecholamines, which include dopamine and noradrenaline, are good candidates for this function as they are well-documented regulators of motivation, attention, and arousal, as well as modulators of motor and sensory systems across vertebrates (Hurley et al. 2004; Riters 2012). Importantly, it has been proposed from multiple studies in songbirds that seasonal changes in steroid hormones may regulate brain catecholamines that, in turn, increase incentive salience of conspecific vocalizations (see Maney 2013; Maney and Rodriguez-Saltos, Chap. 5). Summarized below are recent studies in midshipman fish that have established direct innervation and seasonal plasticity of catecholamines throughout the auditory system. These studies, in addition to evidence that catecholaminergic (CA) neurons are activated in type I males subjected to playbacks of hums of other males (Petersen et al. 2013), support catecholamines, in particular dopamine, as important modulators of seasonal, steroid-dependent acoustic behaviors (Forlano and Sisneros 2016).

2.7.1 Catecholaminergic Innervation of the Auditory System

Recently, Forlano et al. (2014) mapped catecholaminergic (CA) innervation in the auditory system of midshipman fish. Importantly, neural tract tracing combined with a marker for catecholamines demonstrated innervation on and around neurons directly connected with the ascending auditory system. Much of the CA innervation of the auditory hindbrain appears to originate from dopaminergic (DA) neurons in the periventricular posterior tuberculum (TPp) in the diencephalon. This includes the octavolateralis efferent nucleus (OE), which contains the densest input of CA axons in the brain and directly innervates the auditory sacculle (Sect. 2.2) that is a target of TPp axons as well (Fig. 2.11a–c) (Forlano et al. 2014, 2015b). Only a small

←
Fig. 2.10 (continued) *Left side* shows a transverse, cresyl-violet stained section to illustrate the location of representative recording sites (*blue dots*) within the TS. *Right side* shows the distribution of GnRH-immunoreactive axons (*red lines*) in the same cross section. Scale bar = 1 mm. **(b)** Auditory tuning curves for TS neurons in response to tone burst stimuli from 80 to 400 Hz after application of saline control solution (*black circles, solid line*) and 100 nM sGnRH (*red squares, dashed line*). Tuning curve data are plotted as means \pm SD and referenced to the left axis. Asterisks indicate a significant difference ($p < 0.05$) in mean threshold level at 80–200 Hz between saline and sGnRH treatments. Power spectra (128 point FFT, Hanning window) of courtship and aggressive sounds are overlaid and plotted as relative amplitude in dB (right axis). **(c)** Representative responses of TS neurons to playback of a courtship sound show a decrease in spike rate after GnRH application. Peri-stimulus time histograms before (pre) and after sGnRH application are shown. *Top trace* shows the stimulus waveform. Modified from Maruska and Tricas (2011)

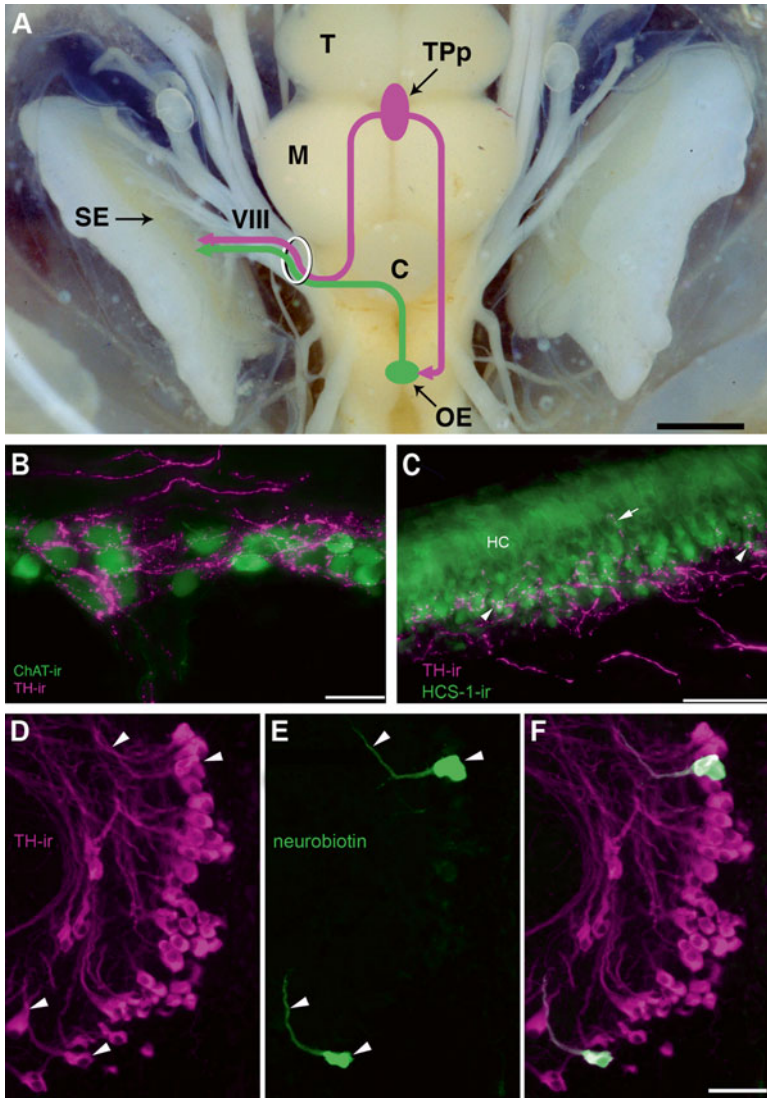


Fig. 2.11 Dopaminergic (DA) innervation of the saccule and octavolateralis efferent nucleus (OE) in midshipman fish, *Porichthys notatus*. (A) Dorsal view of midshipman brain and inner ear depicting the DA periventricular posterior tuberculum (TPp) (magenta) in the diencephalon and the cholinergic OE (green) in the rostral hindbrain that project to the saccular epithelium (SE). C cerebellum, M midbrain, OB olfactory bulb, T telencephalon, U utricle, VIII eighth nerve. (B, C) Fluorescent micrographs depict tyrosine hydroxylase (TH)-ir innervation of OE and saccule. (B) Punctate TH-ir fibers extensively wrap around OE neurons (green, identified with antibody for choline acetyltransferase). (C) TH-ir fibers (magenta) enter the base of the SE where they form punctate swellings (white arrowheads) around the base of hair cells (HC, green, identified with otoferlin-binding hair cell specific antibody HCS-1). (D–F) Neurobiotin backfills of the saccule combined with TH immunofluorescence identify the source of TH-ir efferents to the SE from large, pear-shaped cells in the TPp. (D) TH-ir cells in the TPp medial to the medial forebrain bundle, and lateral and dorsal to the paraventricular organ. (E) Three neurobiotin labeled-neurons (two adjacent cells on top) after a SE backfill. (F) Overlay of images in (A) and (B). Arrowheads indicate same cells and filled axons. All neurobiotin backfilled cells in this region are also TH-ir. Scale bars = 1.5 mm in (A), 50 μ m in (B) and F, 25 μ m in (C). (A–C) Adapted from Forlano and Sisneros (2016); (D–F) adapted from Forlano et al. (2014)

number (5–10 % of ~300) of TPp neurons are the source of DA input to the saccule (Fig. 2.11d–f) (Forlano et al. 2014) and likely project to other inner ear end organs and the lateral line (see Zottoli and Van Horne 1983; Bricaud et al. 2001).

Another TPp-DA target is the auditory-recipient midbrain periaqueductal gray (PAG) (Forlano et al. 2014; Petersen et al. 2013) that connects downstream to the vocal CPG, the dorsal thalamic auditory nucleus (CP, Figs. 2.2a and 2.3) and other nodes within the vocal-acoustic network (Goodson and Bass 2002; Kittelberger and Bass 2013). In the auditory midbrain, the TS is a known target of the locus coeruleus and, therefore, likely receives mixed CA input composed of both DA and noradrenergic (NA) fibers (Ma 1994; Forlano and Sisneros 2016). Together, the data available point to a key role for catecholamines in the modulation of auditory networks in fish.

2.7.2 Catecholaminergic Innervation of the Auditory System Varies with Reproductive State

As summarized in Sect. 2.4.1, midshipman fish exhibit a dramatic seasonal change in frequency encoding and sensitivity at the level of the saccule that is mediated, in part, by a change in circulating steroid hormones (Sisneros et al. 2004b), levels of BK channel expression (Rohmann et al. 2013), and possibly hair cell number (Coffin et al. 2012). Centrally, DA neurons in the TPp are positioned to directly modulate peripheral and central auditory sensitivity as well as coordinate the behavioral response to acoustic social signals (Forlano et al. 2015a). Importantly, the TPp is a brain area replete with ERs, AR, and aromatase (Table 2.1) and, therefore, is a prime target for steroid hormone-regulated auditory plasticity (Forlano et al. 2015a). Although hindbrain auditory nuclei do not express steroid receptors, they may be modulated indirectly through seasonal or hormone-regulated neurotransmitter systems such as dopamine.

In support of seasonal CA modulation of audition in female midshipman fish, Forlano et al. (2015b) demonstrated differences in CA innervation of the central and peripheral auditory system in reproductive (gravid) summer females collected from nests versus non-reproductive females with regressed ovaries collected in offshore waters. Relevant to the discussion of OE circuitry in Sect. 2.7.1, summer females had significantly more CA fiber innervation on the somata and dendrites of the OE (Fig. 2.12a–d), while winter, non-reproductive females had larger and greater numbers of DA terminals in the saccular epithelium (Fig. 2.12e–h). The influence of seasonal plasticity in DA innervation on auditory neurophysiology (e.g., Fig. 2.5) remains to be investigated.

Overall, these findings support a role for catecholamines as important modulators of auditory plasticity and behavior that varies with reproductive state in female midshipman fish. Further studies will be required to determine the contribution of the NA system to the CA fiber densities in central auditory nuclei. A NA-specific marker may uncover further neurotransmitter-specific seasonal differences in areas, such as the TS, that receive a mixture of DA and NA input. Seasonal changes in central auditory

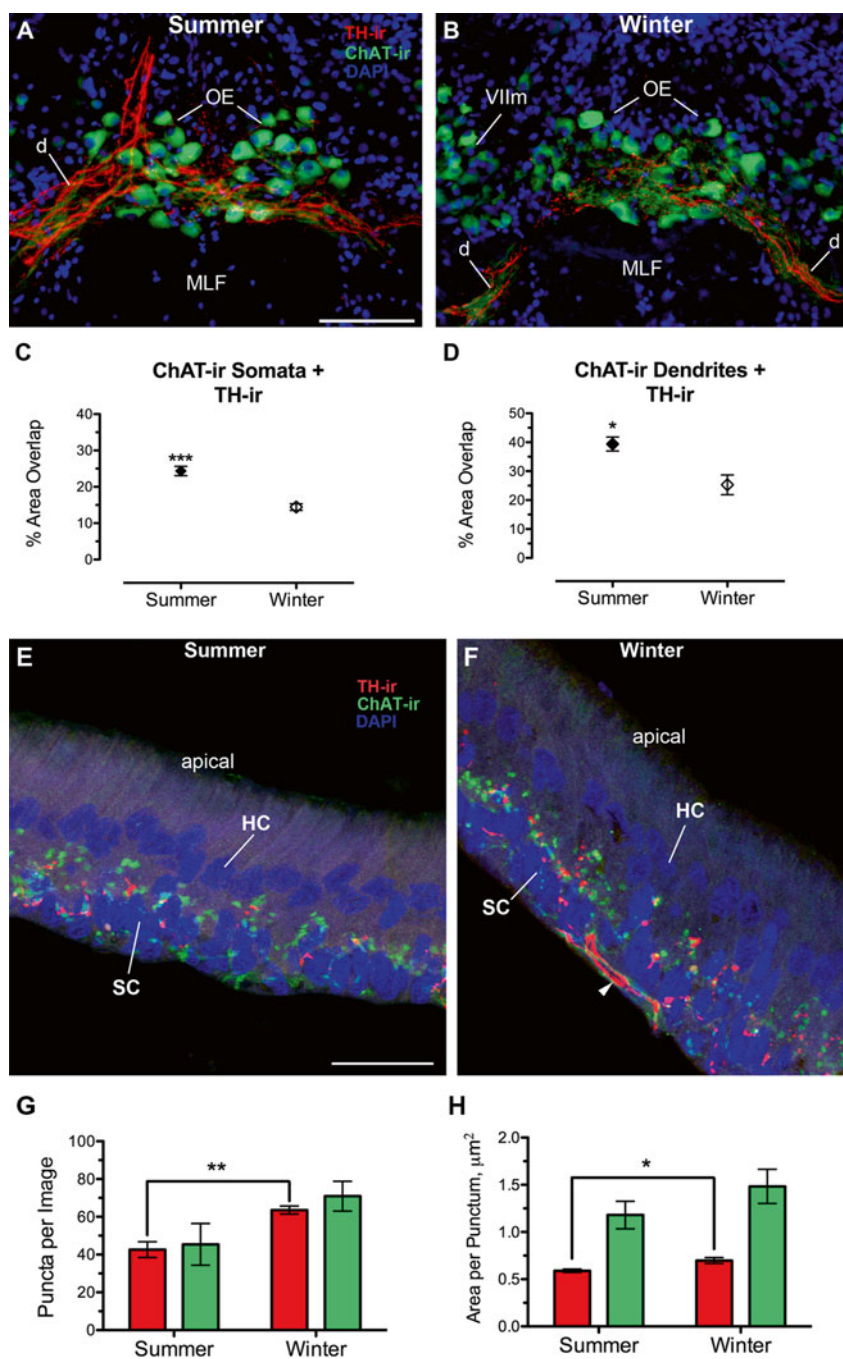


Fig. 2.12 Seasonal difference in tyrosine hydroxylase (TH)-ir innervation of the cholinergic octavolateralis efferent nucleus (OE) and saccule of midshipman fish, *Porichthys notatus*. (**A**, **B**) Transverse sections through the rostral OE showing TH-ir fibers and terminals on somata and

response properties are unknown at this time, but differences in CA innervation in forebrain and hindbrain auditory and lateral line recipient areas (see Bass et al. 2000) may provide a modulatory substrate for such central physiological plasticity.

Importantly, seasonal changes in DA innervation of the saccule and OE (Forlano et al. 2015b) are coincident with known seasonal and hormone-induced plasticity in the auditory periphery (Sect. 2.5). Thus, DA neurons are anatomically positioned to seasonally modulate the sensitivity of the inner ear directly, at the level of the hair cell or primary afferents, or indirectly, via the OE (Fig. 2.11). To date, studies on the effects of DA pharmacology on inner ear physiology have only been conducted on various rodents, such as guinea pig, rat, and mouse (e.g., Ruel et al. 2007; Valdes-Baizabal et al. 2015). If similar in fishes, DA would have a largely inhibitory effect on auditory nerve physiology. A simple interpretation of Forlano et al. (2015b) would be that a decrease in the number of DA terminals in the sensory macula in the summer reproductive season may confer reduced DA inhibition and, therefore, increase overall sensitivity of the saccule, consistent with seasonal physiological data recorded from primary afferents (Sisneros and Bass 2003). This mechanism would be similar to that proposed for GnRH modulation of the TS in Hawaiian sergeant fish (Sect. 2.6) (Maruska and Tricas 2011). However, as seen in rodents, a complex scenario of pre- and post-synaptic interactions of dopamine in the inner ear may result from the expression of multiple dopamine receptor subtypes (see Garrett et al. 2011; Maison et al. 2012). The cholinergic OE is documented to have an inhibitory effect on auditory hair cells in the fish saccule (Furukawa 1981). Therefore, if DA innervation has an inhibitory effect on efferent firing, this would result in release of cholinergic inhibition in the saccule in the summer, and again, increased sensitivity in the reproductive season (Forlano et al. 2015b). Precise receptor subtype localization and neurophysiological experiments combined with pharmacology are necessary to support the above hypotheses.

The functional significance of opposing plasticity in CA input at primary versus higher auditory processing centers is unclear, but modulatory roles may involve optimization of signal detection as proposed for cholinergic efferents (Tomchik and Lu 2006; Smith and Kiel 2015). This function would be adaptive in the acoustically complex summer nesting grounds of midshipman fish (McIver et al. 2014). In addition to increasing perception, catecholamines may prove to be essential for modulating the

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Fig. 2.2 (continued) dendrites (d) of OE neurons labeled by choline acetyltransferase (ChAT)-ir. (C, D) Percent area of ChAT-ir in the OE that is covered by TH-ir fibers (mean ± SE). * $p=0.01$, *** $p=0.0001$. (E, F) Transverse sections through the saccular epithelium. TH-ir and ChAT-ir puncta are largely concentrated at the base of hair cells and within the support cell layer. Arrowhead in (F) indicates an example of a thick, varicose TH-ir fiber along the base of the SC layer that was excluded from the puncta analysis. HC and SC labels point to DAPI-stained nuclei of individual hair cells and support cells, respectively. The rest of the hair cell is unlabeled and is a light purple background. Stereocilia (unlabeled) are located at the apical end of the hair cells. Quantification of numbers (G) and size (H) of putative TH-ir and ChAT-ir terminals (puncta) in the saccule (mean ± SE). Colors in the graphs match TH-ir and ChAT-ir in the micrographs. * $p=0.017$, ** $p=0.001$. Other abbreviations: *MLF* medial longitudinal fasciculus, *VIm* facial motor nucleus. Scale bar = 100 μm in (A) and (B) and 25 μm in (E) and (F). Adapted from Forlano et al. (2015b)

salience of male vocalizations (Maney 2013; Maney and Rodriguez-Saltos, Chap. 5) and, ultimately, the coordination of auditory responsiveness with the decision and subsequent motor response to localize a potential mate's nest or engagement in male-male competition for females (Forlano et al. 2015b).

2.8 Summary

Reports of hormonal influences on vocal behavior in fishes date back to a report for the satfinfin shiner, *Cyprinella analostana* (formerly *Notropis analostanus*), close to the middle of the last century (Winn and Stout 1960). By contrast, the first comparable observation for the sense of hearing in a fish species, namely the highly vocal midshipman fish extensively discussed in this review, was not until the beginning of this century (Sisneros and Bass 2003). Studies of hearing in fishes have often been hindered by a poor understanding of the behavioral relevance of any one species' range of hearing, namely what it is used for in natural habitats. Sonic species allow researchers to investigate the sense of hearing in more easily identified behavioral, ecological, and evolutionary contexts. Moreover, like many vertebrate species that have seasonal and daily cycles of breeding, changes in vocal phenotypes among teleosts are correlated with increasing circulating levels of steroid hormones. The identification of hormone-sensitive vocal phenotypes naturally led to investigations of seasonal, steroid-dependent plasticity in audition.

As reviewed here, since the initial demonstration of peripheral auditory plasticity in midshipman fish, subsequent studies in that species and other sound-producing species identified neuroanatomical, neurophysiological, and molecular signaling pathways underlying the influence of steroids, catecholamines and peptides on auditory-guided behaviors. Highlighted is the seasonal, steroid-dependent plasticity in the frequency sensitivity of the hair cell epithelium and ganglion cells of the sacculus, the main auditory division of the inner ear in many species of fish, including midshipman fish. This mechanism represents an example of adaptive plasticity that likely underlies seasonal improvement in the detection of conspecific vocalizations during the breeding season. Other studies now strongly imply an important role for diencephalic dopaminergic neurons in such plasticity. Dopaminergic neurons directly innervate saccular hair cells and, together with input from hindbrain cholinergic neurons, are likely to influence neurophysiological properties of the auditory periphery. The latter would include modulation of a recently demonstrated hind-brain vocal-auditory corollary discharge pathway.

The importance of the auditory sense in the life history of midshipman fish is clearly related to its predominantly nocturnal activity pattern. Comparable neuro-behavioral mechanisms for diurnal species are exemplified by investigations of the cichlid fish and Hawaiian sergeant damselfish discussed in this review in which the effects of steroids and peptides (GnRH), respectively, on auditory perception are likely to function together with other sensory modalities to guide the performance of communication behaviors during reproduction. These studies have only just

begun to uncover neuro-hormonal mechanisms underlying the remarkable diversity of reproductive tactics among fishes (e.g., Bass and Grober 2009), the most species-rich group of living vertebrates.

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