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Recent evidence for rapid synthesis and action of estrogens during auditory processing in a songbird

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Abstract

It is now clear that estrogens are not just circulating reproductive hormones, but that they also have neurotransmitter-like properties in a wide range of brain circuits. The view of estrogens as intrinsic neuromodulators that shape behavior has been bolstered by a series of recent developments from multiple vertebrate model systems. Here, we review several recent findings from studies of songbirds showing how the identified neural circuits that govern auditory processing and sensorimotor integration are modulated by the local and acute production of estrogens. First, studies using in vivo microdialysis demonstrate that estrogens fluctuate in auditory cortex (30-min time bin resolution) when songbirds are hearing song and interacting with conspecifics. Second, estrogens rapidly boost the auditory-evoked activity of neurons in the same auditory cortical region, enhancing auditory processing. Third, local pharmacological blockade of estrogen signaling in this region impairs auditory neuronal responsiveness as well as behavioral song preferences. Fourth, the rapid estrogen actions that occur within the auditory cortex can propagate upstream (transsynaptically) to sensorimotor circuits to enhance the neural representation of song. Lastly, we present new evidence that the receptor for the rapid actions of estradiol is likely in neuronal membranes, and that traditional nuclear estrogen receptor agonists do not mimic these rapid actions. Broadly speaking, many of these findings are observed in both males and females, emphasizing the fundamental importance of estrogens in neural circuit function. Together, these and other emergent studies provide support for rapid, brain-derived estrogen signaling in regulating sensorimotor integration, learning and perception.

Keywords

Neuroestrogen; neurosteroid; estradiol; electrophysiology; microdialysis

I. Introduction

This review emerged as part of a symposium on “Mechanisms of rapid regulation of behavior by estrogens” presented in February 2013, at the 7th International Meeting on Steroids and the Nervous System in Torino, Italy. Here, we consider recent developments and some unpublished data on the topic of acute synthesis and action of estrogens in the auditory cortex of songbirds. This review is therefore more limited in scope as compared to

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several recent reviews that are complimentary to and overlapping with information presented here, and these excellent sources should be consulted for more comprehensive treatment of this and related work (1-6).

The songbird brain contains a well-characterized network of nuclei that govern song learning, auditory processing, and the motor act of singing itself. These behaviors have overlapping representations in the songbird brain (i.e. the 'song system'), owing to the strong functional and anatomical links between learning, audition and song motor output (7-17). It is well established that the song system is highly sensitive to treatment with androgens and estrogens, and that the song system exhibits widespread expression of both androgen receptors and estrogen receptors (6, 18-26). The developmental maturation and seasonal activation of song system nuclei are each dependent on steroid hormone mechanisms, typically from peripheral androgen sources (21, 27-34). There is also increasing evidence that a substantial amount of estrogens can be synthesized directly in the songbird brain, especially in males. All of the enzymes necessary for the *de novo* production of estrogens from cholesterol are expressed in the 'song system' (20, 30, 35-42), and the brain itself is both the primary source and target of estrogens in male songbirds (43).

In songbirds, both anatomical and biochemical characterization of the aromatase enzyme, which synthesizes active estrogens from androgen precursors, show that some regions of the song system are capable of substantial estrogen production (36, 38, 41). In songbirds and other vertebrates, aromatase is expressed in neuronal cell bodies as well as in presynaptic boutons (41, 44, 45). This separation of aromatase into two subcellular compartments may have functional consequences for the way estrogen synthesis is controlled in neurons. It is clear that androgen precursors can be converted into estrogens for long-term seasonal or organizational actions, and this may be a primary role for the aromatase found in neuronal cell bodies. In some areas, the additional expression of aromatase in presynaptic boutons suggests that estrogens can be synthesized in a highly-restricted spatial and temporal manner at the level of individual synapses (41, 44, 45). This has raised the specter of a precise delivery mechanism for estrogens at 'synaptocrine' targets, although the extent of spatial and temporal specificity of this mechanism remains an open question (2, 4, 46).

Recent tests of this 'synaptocrine' signaling hypothesis have shown that presynaptic terminals in the songbird brain are capable of synthesizing estrogens (45, 47, 48). The mechanisms by which this 'synaptocrine' estrogen delivery mechanism is controlled have recently begun to emerge, based on convergent evidence in the songbird and quail model systems (49-51). Specifically, either glutamate- or potassium-evoked excitation of the auditory forebrain leads to acute suppression of local estradiol levels, as measured by *in vivo* microdialysis (52, 53). Second, in the presence of omega conotoxin (a specific presynaptic voltage-gated calcium channel blocker) the potassium-evoked suppression of local estradiol levels in the auditory forebrain is blocked (53). Third, in synaptosomes prepared from the songbird brain, the enzymatic activity of aromatase itself is rapidly suppressed by phosphorylating conditions, and more potently in the synaptosomal fraction than in the microsomal fraction (54). Therefore, in some cases estrogen signaling can be independently controlled at the level of presynaptic terminals to achieve very high temporal and spatial precision. This estrogen signaling mechanism at presynaptic terminals aligns well with the

precision of rapid actions of estrogens on neuronal activity and morphology. Notably among these is the well-documented rapid action of estrogens on dendritic spines in the rodent hippocampus (55-57). Below, we review a related line of work in birds showing that rapid estrogen signaling in the brain has direct consequences for auditory processing and sensorimotor integration.

II. Measurement of fluctuating brain estrogens

If estrogens can act as rapid, local modulators, then acute changes in estrogen synthesis or brain estrogen content should be detectable. As described above, one means of detecting rapid changes in estrogen synthesis is via measuring the enzymatic activity of aromatase (i.e., activity that directly reflects the biochemical conversion of androgen precursors into active estrogens). Several groups have presented evidence for the rapid regulation of aromatase in brain. In quail hypothalamic explants, the activity of aromatase is rapidly and reversibly inhibited by potassium-or glutamate-evoked excitation and calcium-dependent phosphorylating conditions (51, 58). There is also strong evidence that quail hypothalamic aromatase activity is rapidly regulated *in vivo* by sexual interactions (3, 59, 60) and acute stress (61-63). In territorial white-crowned sparrows, brief territorial challenges are associated with no changes in aromatase activity but lead to acute suppression of estradiol in several behaviorally-important brain regions (including hypothalamus and hippocampus), as assessed using tissue micropunches (64). In teleost fish, brain aromatase activity is suppressed during socially-induced changes in aggression and gonadal sex in bluebanded gobies (65) and rapid aromatization is associated with increased sexual motivation in goldfish (66). Lastly, pharmacological inhibition of aromatase in the brain can acutely disrupt sexual behavior in mice (67) and territoriality in songbirds (68). Therefore, evidence from several representative vertebrate species shows that acute changes in brain estrogen synthesis are associated with acute changes in behavior.

An alternative means of detecting rapid changes in estrogen synthesis is via measuring the fluctuations in brain estrogens directly. *In vivo* microdialysis for estradiol has been validated to quantify changes in estradiol levels in the CNS of awake, behaving songbirds (52). These experiments have focused primarily on a region of the songbird brain that is analogous to mammalian secondary auditory cortex, the caudomedial nidopallium (NCM). The NCM is relatively large, and is enriched in both somal and presynaptic aromatase expression (23, 41, 45), making it especially suited to *in vivo* microdialysis. Due to limits in detection, sampling intervals in published work to date has been limited to 30-min time bins for quantifying estradiol fluctuations. In male zebra finches, local levels of estradiol in the NCM increase during social interactions with females (when males are typically singing) and when males are exposed to artificial playback of zebra finch songs, but not control sounds (52).

Female zebra finches also exhibit a similar elevation in NCM estradiol levels when hearing male zebra finch song (69), suggesting that basic mechanisms of auditory processing are dependent upon the acute, local production of estrogens. Ongoing experiments are testing the extent to which the acute, song-dependent elevation in estradiol levels in NCM is dependent on social and/or contextual cues in both males and female zebra finches. Some 'classic' neuromodulators such as dopamine and arginine vasotocin (AVT) can encode the

salience or behavioral valence (i.e. positive vs. negative) of social stimuli (e.g., 70, 71), but it is unclear whether rapid fluctuations in brain estrogens are similarly sensitive to stimulus salience and/or valence. It is also unclear at present what mechanism may provide a 'stop signal' for rapid estrogen synthesis and release (in order to preserve the spatiotemporal fidelity of acute modulatory actions), similar to the reuptake/degradation mechanisms that have been identified for classical neuromodulators (72, 73).

III. Modulation of auditory processing and behavior by local estrogens

The acute fluctuations in local levels of estrogens in the songbird NCM stimulated interest in the rapid actions of estrogens on NCM neuronal activity, as well as behaviors supported by NCM. Electrophysiology and immediate early gene studies have identified the NCM as an auditory processing region, specifically analogous to supragranular layers of the auditory cortex in mammals (74-79). To test for rapid actions of estrogens on NCM neurons, two complimentary approaches have been used to manipulate estrogen signaling, reverse dialysis and pressure delivery, and each of these have been coupled with extracellular recordings of the activity of nearby neurons within the NCM (80)(81). Findings using these independent approaches have been largely convergent, in that rapid elevations in NCM estrogens cause rapid increases (5-30 min) in the auditory-evoked activity of NCM neurons, in both male and female zebra finches (69, 80-82). Importantly, reverse dialysis or pressure infusion of aromatase antagonists cause acute decreases in the auditory-evoked activity of NCM neurons. Therefore, endogenous estrogen signaling appears to exert acute, enhancing effects on auditory processing in NCM.

Similar manipulations of estrogen signaling in NCM have been carried out while male zebra finches were engaged in auditory preference behavioral tasks. These tasks rely on the expression of phonotaxis (physical proximity to a speaker) for familiar songs as compared to unfamiliar songs in adult zebra finches (83, 84). Reverse dialysis of the aromatase inhibitor fadrozole (FAD) into the left hemisphere NCM resulted in a complete block of the behavioral preference for passive playback of familiar songs within 30 min, whereas control aCSF dialysis had no effect on song preference prior to, or following the FAD treatment (81). Similarly, intracranial injection of the aromatase inhibitors FAD or ATD reduced song preferences within 30 min, whereas behavioral preferences for calls (simpler acoustic signals) were unaffected (82). Together, these convergent pieces of evidence show that acute and local estrogen signaling within the NCM improves auditory processing and can guide behavioral song preferences.

IV. Transynaptic modulation of sensorimotor representations by estrogens

The rapid actions of NCM estrogens on auditory preference behavior could depend entirely on local effects on NCM itself, or to rapid effects of estrogens that propagate from NCM to downstream targets (or some combination of these mechanisms). Since auditory processing is distributed among multiple sensory and sensorimotor circuits in the zebra finch brain (7, 9, 11, 77, 85-92), it is reasonable to expect that estrogen-dependent modulation of auditory processing in NCM is both influential and dependent upon the functional outputs of downstream targets.

One nucleus downstream from NCM is HVC (used as a proper name), which is essential for both song perception and song production (93-97). HVC is a sensorimotor nucleus at the juncture of the auditory pathway for song processing and the premotor pathway that directly governs song output. Individual HVC neurons are activated both when a male hears a rendition of his own song and when he is singing that same song (98), and HVC neurons have inherent 'selectivity' for the bird's own song relative to other stimuli (13, 85, 92, 99-106). This selective property of HVC neurons is considered essential for HVC's role in the feedback sensitivity and sensorimotor integration of singing behavior.

Using dual extracellular recordings coupled to retrodialysis in males, we recently reported that estrogens delivered to NCM can acutely enhance the responses of HVC neurons to the male's own song (107). This enhancement is stimulus-specific, since the responses of HVC neurons to conspecific songs are unaltered by estrogens acting in NCM. By contrast, as we had initially reported, the auditory-evoked activity of NCM neurons is enhanced for all song stimuli in response to estrogens acting in NCM. Therefore, estrogens in NCM influence the selectivity of HVC neurons for certain song features via an as yet unidentified, transsynaptic, modulatory signal. Similar experiments using reverse dialysis show that the aromatase inhibitor FAD into NCM causes a rapid suppression of the selectivity for the male's own song in HVC neurons (107). Therefore, rapid estrogen signaling can be transmitted and filtered as it propagates between two information processing nuclei, NCM and HVC. Our current hypothesis is that rapid estrogen signaling in NCM can enhance the production or perception (or both) of song via indirect modulation of HVC response properties. These recent findings are therefore consistent with the idea that acute estrogen production in the cortex is essential for ordinary cognitive function through actions on individual nodes within distributed networks.

V. Possible receptor mechanisms

The rapid actions of estrogens in the songbird auditory NCM suggest that they may be mediated by a non-classical receptor mechanism. One means to test membrane-specific effects of estrogens is to use conjugated molecules that prevent diffusion of steroids across the cellular membrane, such as biotinylated-estradiol (E6biotin). In other systems, E6biotin appears to restrict rapid estrogen signaling to membrane-specific events (108-110). In recent tests in the songbird auditory forebrain, E6biotin was found to be an effective mimic for the rapid actions of estrogens on NCM auditory processing (69, 107), indicating that these actions are likely mediated by a membrane-specific effect. The nature of the specific receptor mechanism for putative membrane-mediated rapid actions of estrogens in NCM is not well understood. We report below on preliminary experiments to explore this mechanism.

It is now clear that many rapid actions of estrogens can be mediated by the classical estrogen receptors (ERs) ER α and ER β (e.g., 111, 112), possibly via nuclear receptors transiently docked in neuronal membranes (109, 113-117). Recent progress has been enabled by commercially-available drug ligands that are highly specific for ER α (propyl-pyrazole-triol; PPT) vs. ER β (diarylpropionitrile; DPN), and that can have differential rapid actions in the brain (118-120). NCM neurons express ER α and ER β (19, 23, 121), raising the possibility

that the rapid actions of estrogens on NCM auditory processing are mediated by either of these nuclear receptor subtypes.

Rapid actions of estrogens can also be mediated by membrane receptors, including a formerly orphaned g-protein coupled receptor GPR30 (122) which has been renamed GPER1 (G-protein coupled estrogen receptor-1). Estrogen-dependent actions through the GPER1 receptor can be acute and specific in the brain (114, 123, 124). The GPER1 was recently characterized and protein expression was evaluated in juvenile and adult zebra finches (125). The expression levels of GPER1 are highest during the posthatching song learning period and are reduced in adulthood. Even still, GPER1 expression in adults is modestly elevated in the NCM region, raising the possibility that rapid estrogen signaling in the NCM occurs through GPER1 in neuronal membranes.

We have recently generated unpublished results from experiments testing the role of these candidate estrogen receptor subtypes in mediating the rapid actions of estrogens in NCM. Using the ER-selective agonists DPN or PPT with robust sample sizes ($n = 7-9$) and at comparable doses to estradiol itself ($77 \mu\text{M}$ (PPT); $125 \mu\text{M}$ (DPN)), we have been unable to detect a significant recapitulation of the rapid actions of estradiol on the auditory-evoked activity in NCM in adult males (Fig. 1). In more limited experiments with the combination of DPN + PPT ($n = 2$; data not shown), we are also unable to detect a significant recapitulation of the rapid actions of estradiol in NCM. While the specificity of PPT and DPN for zebra finch ER α and ER β , respectively, have not been characterized in brain tissue, it is important to note that these same agonists are effective at mimicking the actions of estradiol in another avian species (quail copulatory behaviors; 110). Based on these initial findings, we conclude that the rapid actions of estrogens on NCM auditory processing are mediated by a non-classical receptor. Moreover, in addition to the GPER1 mentioned above, two other candidate non-classical estrogen receptor mechanisms have been identified in mammalian systems that may be involved in the songbird NCM. First, a Gq-coupled membrane receptor (Gq-mER) has been identified that is responsive to estrogens and a non-steroidal drug, STX, in several neurobiological preparations (114, 126-130). Second, a membrane associated estrogen receptor (ER-X) has been identified that has markedly different binding characteristics for many of the estrogenic agonists and antagonists (131). The involvement of GPER1, Gq-mER or ER-X in the songbird auditory forebrain has now become an active area of research interest.

VI. Conclusions

This review summarizes recent work describing how estrogens are rapidly synthesized in the songbird brain in response to social and environmental cues, and how estrogens can have acute, modulatory actions on sensory encoding, sensorimotor integration and behavioral preferences. This perspective highlights the brain itself as a source and target for estrogens, and that this signaling mode can be on a timescale consistent with neuromodulation. With this perspective in mind it is important to consider the many ways that estrogens can influence brain function and behavior in parallel over much longer timescales, including seasonal and developmental events (22, 25, 29, 34, 64, 132-138). Because steroids are lipid-soluble and can readily cross the blood-brain-barrier, the steroid environments within the

CNS vs. outside the CNS should not be considered independent (e.g., 139, 140). It is currently unclear to what extent the rapid, neuromodulatory actions of estrogens are dependent on more protracted changes in circulating steroids (141), although there is increasing evidence that the rapid actions of estradiol on behavior (142) and cell signaling pathways (143) are influenced by long-term seasonal events. Thus, this work has now set the stage for studies to explore the interactions between changes in circulating steroids (e.g., estrogens and androgen precursors) and the modulatory fluctuations in estrogens within the brain.

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Figure 1.

The rapid actions of estradiol on NCM auditory processing are not mimicked by selective nuclear receptor agonists. In adult male zebra finches, acoustic playback of the bird's own song (BOS), conspecific song (CON), reverse BOS (REV), and to a lesser extent white noise (WN) each elicit an increase in the firing rate of NCM neurons relative to baseline conditions (i.e., responses are > 0 in the aCSF condition in panels A & B). Unlike responses to estradiol (as described in refs 69, 81, 107), the selective $ER\alpha$ agonist PPT (A; $n = 9$ birds) has no significant effect on NCM responses to playback stimuli (repeated measures ANOVA $F = 0.57$; $p = 0.47$). Similarly, the selective $ER\beta$ agonist DPN ($N = 7$ birds) has no significant effect on NCM responses to playback stimuli (repeated measures ANOVA $F = 2.86$; $p = 0.17$). The Z-score is Z-transformation of the evoked spiking activity in NCM that is used to standardize comparisons among playback stimuli. The Z-score is a numerical difference between the mean response during the playback stimulus minus the mean response during the baseline period, divided by the SD of the difference between the stimulus and baseline periods. S. Jeon, N. R. Joshi, and L. Remage-Healey, unpublished observations.