

## Estradiol can modulate sensory processing with rapid and longer term consequences

Steroid hormones are derived from cholesterol. They are produced by the gonads and adrenal glands. For example, the testes secrete primarily testosterone and the ovaries secrete mainly estrogens (such as estradiol) and progesterone. More recent attention has focused on “neurosteroids”, or those produced in the brain. They can be synthesized from precursors in circulation – estradiol is produced in particular brain regions from testosterone, a reaction catalyzed by the aromatase enzyme. They also may be generated *de novo* in neural tissue from cholesterol.

Estradiol has numerous effects in the adult brain. It facilitates functions ranging from the display of sexual and aggressive behaviors to learning and memory. Recently, attention has turned to its role in sensory processing. Songbirds are particularly appropriate for these types of investigations, as they provide an opportunity to integrate across these functions. Songs are learned from adult male tutors, usually the father, during juvenile development (Williams 2004). They are used by males to attract mates, as well in more aggressive contexts in some species, such as the defense of a territory or guarding of a mate or nest site (e.g. Zann 1996). The Australian zebra finch has been a primary target of laboratory investigations, and in these animals (like other songbirds) a cortical region called the caudomedial nidopallium (NCM) is particularly responsive to auditory stimuli. Female zebra finches do not sing, but neurons in the NCM of males are stimulated particularly by a male’s own song. In both sexes, the region shows increased responses to conspecific compared to heterospecific songs and other auditory stimuli (Bailey *et al.* 2002; Mello *et al.* 2004).

The NCM contains aromatase (Saldanha *et al.* 2000). It also expresses both estrogen receptors  $\alpha$  and  $\beta$  (Bernard *et al.* 1999; Saldanha and Coomaringam 2005). This forebrain region can therefore synthesize and respond to estradiol. A recent report from Barney Schlinger’s lab elegantly documents specific and rapid increases in estradiol in the NCM of male zebra finches in response to presentation of a female and to playback of song (Remage-Healey *et al.* 2008). Testing the potential role of estradiol in song perception (or responsiveness to song) is also critical to advancing the understanding of mechanisms associated with a variety of critical behavioral processes. Further, it is important to examine this function in both males and females. A sizeable body of work in zebra finches has focused on the mechanisms regulating sex differences in the display of song and parallel structural dimorphisms (reviewed in Wade and Arnold 2004). The neural circuit controlling the learning and production of these vocalizations is greatly enhanced in males compared to females. However, accurate perception and interpretation of song is a critical function common to the two sexes.

In a series of elegant experiments recently published in the *Journal of Neuroscience*, Tremere *et al.* (2009) document that locally synthesized estradiol can rapidly modulate responses to auditory stimuli by suppressing GABA<sub>A</sub>-induced inhibition in NCM. The effect was not specific to song, but followed more general auditory stimulation. The authors went on to show that this estradiol contributes to the regulation of song-induced immediate early genes in the NCM. Importantly, however, the hormone alone was both necessary and sufficient for driving the expression of these target genes; acoustic input is not required for NCM neurons to change their activity. Finally, the authors commented that the results for males and females were equivalent in all of their studies. The work by Tremere *et al.* (2009) is technically sophisticated, integrative and thorough. Importantly, it tested not only the effect of exogenous estradiol, but also inhibiting the synthesis (with the aromatase inhibitor 1,4,6-androstatriene-3,17-dione [ATD]) and action (with the receptor blocker tamoxifen) of endogenous estradiol. The research solidly

**Keywords.** Communication; estrogen; songbird

demonstrates that estradiol can rapidly modulate the sensory experience of an individual by affecting local electrophysiological responses in NCM, as well as have longer term consequences via altering expression of multiple immediate early genes.

The recent paper by Tremere *et al.* (2009) thus extends a small, but growing, body of work on the role of estradiol in song responses in adult birds. Research on the hormonal regulation of song production has focused on males, whereas the role that steroids may play in modulating neural or behavioural responses to song has been primarily investigated in females. Early studies routinely treated females with estradiol prior exposing them to male songs with the goal of facilitating behavioural responses. However, effects were variable across, and even within, species (Searcy 1992). It was suggested that species that breed relatively easily in captivity, such as canaries and brown-headed cowbirds, do not require estradiol to produce full copulation solicitation (receptive) displays in response to song, whereas others that do not breed as easily in a lab environment, such as blackbirds and white-crowned sparrows, do require exogenous hormone administration (Searcy and Capp 1997).

More recent work in female songbirds has involved investigations of interactions between estradiol and song exposure on immediate early gene expression. In white-throated sparrows, estradiol appears to sharpen the response of the NCM and another region of the auditory cortex, the caudomedial mesopallium (CMM), by reducing expression of the immediate early gene *zenk* (one of the three tested in Tremere *et al.* 2009) following non-relevant acoustic stimuli. The response appears selective for song only when plasma estradiol approaches levels typically of the breeding season (Maney *et al.* 2006). Similar effects were seen in regions of the social behaviour network (Maney *et al.* 2008), suggesting additional circuits associated with interpretation of (or action on) these reproductive cues. In European starlings, breeding condition mediates the detection of phosphorylated tyrosine hydroxylase in regions involved in the regulation of social behaviours; labeling in areas including the ventromedial hypothalamus was lower in females in breeding condition that heard male song compared to those exposed to no song. The reverse pattern was detected in non-breeding females (Riters *et al.* 2007).

In zebra finches, estradiol can modify a variety of specific behavioural responses of adult females to the length or complexity of song (Vyas *et al.* 2008, 2009). However, in a study conducted in my lab, the hormone did not affect the behavioural preference for songs from males that had been tutored during juvenile development (high quality) versus those from untutored individuals (low quality) (Svec and Wade 2009). *Zenk* expression in both the NCM and CMM was equivalent in response to tutored song, untutored song, and silence, especially in estradiol treated individuals. In fact, the hormone may have reduced a substantial *zenk* induction following exposure to tutored song seen in control female zebra finches, although the effect was not statistically significant. Similar to our experiment, Tremere *et al.* (2009) did not see an estradiol-induced increase in NCM *zenk* following auditory stimulation, and suggest that song stimulation alone is sufficient to drive the expression to near maximal level. However, they did detect and increase in immediate early gene expression with estradiol alone, which we did not. Future work might assess the importance of the methodological differences between the two studies, including systemic estradiol treatment for one week prior to analysis of immediate early gene expression (Svec and Wade 2009) compared to unilateral infusion in NCM just prior to stimulus exposure (Tremere *et al.* 2009). Other factors include differences in presentation of particular auditory stimuli and the quantification of protein (Svec and Wade 2009) versus mRNA (Tremere *et al.* 2009). It is difficult to directly translate between plasma and neural levels of steroid hormones, particularly in songbirds whose forebrains produce high levels of estradiol. However, it is possible that longer term exposure to has an inhibitory effect that is not see with acute manipulations. In fact, in the ventromedial hypothalamus of females (a region commonly associated with receptivity), a week of peripheral estradiol decreased *zenk* expression (Svec and Wade 2009). This is in stark contrast to the increases seen with acute estradiol treatment alone in the NCM (Tremere *et al.* 2009).

The recent work by Tremere *et al.* (2009) and colleagues provides important new insights into the role of estradiol in modulating neural responses in perception of song. This function is a critical aspect of social communication in songbirds, and necessary for successful reproduction. Future work on differences obtained across species and experimental manipulations, both within song perception regions and those of the social behaviour network (Goodson *et al.* 2005; Newman 1999), will elucidate mechanisms important not only for the basic biology of passerine birds, but also those associated with perception, communication and neural responsiveness on a more general level.

## References

- Bailey D J, Rosebush J C and Wade J 2002 The hippocampus and caudomedial neostriatum show selective responsiveness to conspecific song in the female zebra finch; *J. Neurobiol.* **52** 43–51
- Bernard D J, Bentley G E, Balthazart J, Turek F W and Ball G F 1999 Androgen receptor, estrogen receptor  $\alpha$ , and estrogen receptor  $\beta$  show distinct patterns of expression in forebrain song control nuclei of european starlings; *Endocrinology* **140** 4633–4643
- Goodson J L, Evans A K, Lindberg L and Allen C D 2005 Neuro-evolutionary patterning of sociality; *Proc. R. Soc. London B.* **272** 227–235
- Maney D L, Cho E and Goode C T 2006 Estrogen-dependent selectivity of genomic responses to birdsong; *Eur. J. Neurosci.* **23** 1523–1529
- Maney D L, Goode C T, Lange H S, Sanford S E and Solomon B L 2008 Estradiol modulates neural responses to song in a seasonal songbird; *J. Comp. Neurol.* **511** 173–186
- Mello C V, Velho T A F and Pinaud R 2004 Song-induced gene expression; *Ann. N.Y. Acad. Sci.* **1016** 263–281
- Newman S W 1999 The medial extended amygdala in male reproductive behavior: A node in the mammalian social behavior network; *Ann. N.Y. Acad. Sci.* **877** 242–257
- Remage-Healey L, Maidment N T and Schlinger B A 2008 Forebrain steroid levels fluctuate rapidly during social interactions; *Nat. Neurosci.* **11** 1324–1334
- Riters L V, Oleson K M and Auger C J 2007 Evidence that female endocrine state influences catecholaminergic responses to male courtship song in European starlings; *Gen. Comp. Endocrinol.* **154** 137–149
- Saldanha C J and Coomaringam L 2005 Overlap and co-expression of estrogen synthetic and responsive neurons in the songbird brain – a double-label immunocytochemical study; *Gen. Comp. Endocrinol.* **141** 66–75
- Saldanha C J, Tuerk M J, Kim Y-H, Fernandes A O, Arnold A P and Schlinger B A 2000 Distribution and regulation of telencephalic aromatase expression in the zebra finch revealed with a specific antibody; *J. Comp. Neurol.* **423** 619–630
- Searcy W A 1992. Measuring responses of female birds to male song. In: Playback and studies of animal communication. McGregor P K (editor). New York, Plenum Press. pp 175–189
- Searcy W A and Capp M S 1997 Estradiol dosage and the solicitation display assay in red-winged blackbirds; *Condor* **99** 826–828
- Svec L A and Wade J 2009 Estrogen induces region-specific inhibition of ZENK but does not affect the behavioral preference for tutored song in adult female zebra finches; *Behav. Brain Res.* **199** 298–306
- Tremere L A, Jeong J K and Pinaud R 2009 Estradiol shapes auditory processing in the adult brain by regulating inhibitory transmission and plasticity-associated gene expression; *J. Neurosci.* **29** 5949–5963
- Vyas A, Harding C, Borg L and Bogdan D 2009 Acoustic characteristics, early experience, and endocrine status interact to modulate female zebra finches' behavioral responses to song; *Horm. Behav.* **55** 50–59
- Vyas A, Harding C, McGowan J, Snare R and Bogdan D 2008 Noradrenergic neurotoxin, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride (DSP-4), treatment eliminates estrogenic effects on song responsiveness in female zebra finches (*Taeniopygia guttata*); *Behav. Neurosci.* **122**
- Wade J and Arnold A P 2004 Sexual differentiation of the zebra finch song system; *Ann. Rev. N.Y. Acad. Sci.* **1016** 540–559
- Williams H 2004 Birdsong and singing behavior; *Ann. Rev. N.Y. Acad. Sci.* **1016** 1–30
- Zann R A 1996. *The zebra finch: A synthesis of field and laboratory studies* (Oxford: Oxford University Press)

JULI WADE

*Departments of Psychology and Zoology,  
Neuroscience Program, Michigan State University,  
East Lansing, MI 48824 USA  
(Email, wadej@msu.edu)*

ePublication: 14 August 2009