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Review

Sex differences and rapid estrogen signaling: A look at songbird audition

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ABSTRACT

The actions of estrogens have been associated with brain differentiation and sexual dimorphism in a wide range of vertebrates. Here we consider the actions of brain-derived 'neuroestrogens' in the forebrain and the accompanying differences and similarities observed between males and females in a variety of species. We summarize recent evidence showing that baseline and fluctuating levels of neuroestrogens within the auditory forebrain of male and female zebra finches are largely similar, and that neuroestrogens enhance auditory representations in both sexes. With a comparative perspective we review evidence that non-genomic mechanisms of neuroestrogen actions are sexually differentiated, and we propose a working model for nonclassical estrogen signaling via the MAPK intracellular signaling cascade in the songbird auditory forebrain that is informed by the way sex differences may be compensated. This view may lead to a more comprehensive understanding of how sex influences estradiol-dependent modulation of sensorimotor representations.

1. Introduction

The recent forceful call to balance the study of both sexes in biomedical research (Clayton and Collins, 2014) reflects a resurgent interest in the biological understanding of sex differences. Sex differences in brain structure and function have been intimately linked to the synthesis and actions of estrogens in the central nervous system (CNS). A fundamental role for estrogens in shaping the differentiation of forebrain structures in particular is evident across vertebrates. Accumulating evidence shows that the nonclassical 'acute' actions of estrogens (~30 min) are different between the sexes and that the underlying mechanisms for acute actions may in fact themselves be differentially organized during development. Here, we consider these themes as they relate to the role of brain-derived estrogens in the regulation of the songbird brain, with a particular focus on sex differences in auditory function. The work synthesized here illustrates four broad themes. First, although the songbird brain is potently sensitive to the masculinizing effects of estrogens during development, brain estrogen levels (within the auditory forebrain) are not detectably different between males and females during the critical masculinization window. Second, neuroestrogen fluctuations occur in response to socially-relevant stimuli in the auditory forebrain of both males and females. Third, the acute, modulatory actions of estrogens on auditory representations in the songbird auditory forebrain are also similar in males and females. These findings indicate a broad conservation of mechanism between the sexes for the control of auditory representations by neuroestrogens. However, there is still evidence that auditory circuitry in the songbird is influenced by sex-specific mechanisms that are driven by neuroestrogens. We suggest that when considering the rapid 'nonclassical' signal transduction pathway(s), sex is likely an important factor that influences how cells respond to estrogens, drawing upon work in other model organisms and the parallels in songbirds. Taking into account the predominantly peripheral vs. central source of estrogens in zebra finches (females vs. males, respectively), acute estrogen signaling in the auditory forebrain and the molecular signaling pathways recruited are also likely to reflect mechanisms of compensation for (rather than further derivations of) sex differences. Below, we propose a working model for a nonclassical estrogen-dependent MAPK (mitogen-activated protein kinase) signaling pathway in the songbird auditory forebrain and how it can be used to test the mechanisms of compensation.

2. Sex differences in estrogen actions in vertebrates

Sexual differentiation of the brain has been intimately tied to the aromatization of androgens and the local actions of estradiol (E2) in neural circuits. Pioneering work in rodents established that exposure to pre and post-natal surges of testosterone masculinized sexual behavior (Phoenix et al., 1959) through the aromatization of testosterone into estradiol (Naftolin and Ryan, 1975). Following

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this proposed model for sexual differentiation, many other neural and behavioral sex differences have been attributed to estradiol's permanent or organizational effects early in development as well as the transient or activational role estradiol plays in adulthood. While these organizational effects can be explained in part by long-term genomic actions of estradiol interacting with nuclear estrogen receptors, a more unified view of sexual differentiation proposes that genetic differences attributable to sex chromosome complement interact with hormonal and environmental factors to direct masculine vs. feminine development (Arnold et al., 2004; McCarthy and Arnold, 2011). Previous reviews have considered how organizational effects of testosterone and estradiol direct sexual differentiation during critical periods in mammals (Forger and de Vries, 2010; McCarthy, 2010) as well as birds and lizards (Ball and Wade, 2013; Balthazart et al., 1996). Here, we consider how neuroestrogens may shape auditory processing differently in male vs. female songbirds, which relies on this foundational framework.

As noted by McCarthy and Konkle (2005), while the organizational/activational hypothesis has been a useful model to understand sex differences, the simplicity of the aromatization story for the reproductive diencephalon of the mammalian brain does not always hold true for other non-reproductive regions such as the hippocampus and cortex. In particular, observed differences between males and females may not be due to sex differences in the traditional, organizational sense, but rather molecular compensatory mechanisms of hormone signaling that contribute to sex "sameness". Here, we draw upon this perspective to consider how neuroestrogens are controlled both independently and in conjunction with gonadal steroids, and consider how downstream estradiol signaling mechanisms can inform our understanding of acute neuromodulation in sensory and sensorimotor cortex. This perspective keeps us cognizant of alternative molecular strategies between the sexes and how they may arrive at similar neuro-behavioral endpoints. This conceptual framework for the actions of estrogens can be considered part of a larger, growing appreciation for a sub-category of differentiated mechanisms that may compensate for sex differences in brain morphology and function to achieve similar behavioral ends in males and females (De Vries, 2004; McCarthy et al., 2012). Below, we review recent work on sexually dimorphic molecular mechanisms for the rapid actions of estradiol signaling and the control of auditory representations in the songbird brain.

3. Sex differences in acute effects of estrogens in the brain

Acute effects of estrogens in peripheral tissues have been well documented since the experiments of Szego and Davis (1967) on rat uteri. Kelly et al. (1976) first documented rapid estrogen effects in the hypothalamus of cycling females, demonstrating that acute estrogenic actions also occur in the brain. The acute effects of estradiol have been observed at multiple levels of biological organization, and it is therefore difficult to reach consensus for what classifies as an 'acute' effect. The initial observed acute effects in the brain were noted immediately after estradiol application (seconds) to the electrophysiological recording site (Kelly et al., 1976). Changes in kinase activity and phosphorylation occur over the time course of several minutes (Abraham et al., 2004; Boulware et al., 2007, 2005; Heimovics et al., 2012) and behavioral changes have been described in as little as 15 min to an hour (Cornil et al., 2006; Cross and Roselli, 1999; Fernandez et al., 2008; Phan et al., 2012; Taziaux et al., 2004; Trainor et al., 2008). For the purposes of this essay, we refer to acute events as changes in cellular physiology, signal transduction, or genetic expression that occur within 60 min, which is shorter than the canonical long-term effects initiated by nuclear estrogen receptors that can range from several hours to days after estradiol treatment (O'Malley and Means, 1974). It has been hypothesized that acute effects are initiated through estrogen interactions with extra-nuclear and/or membrane receptors (Blaustein et al., 1992; Milner et al., 2001; Revankar et al., 2005; Toran-Allerand et al., 2002), and there is ample evidence to support that membrane receptors can mediate acute effects (Filardo et al., 2000; Revankar et al., 2005; Srivastava and Evans, 2013). Here, we will focus on effects that are observable within a maximum time course of one hour and/or those that have been explicitly characterized by membrane associated mechanisms.

3.1. Electrophysiology in rodents

Estradiol can initiate cellular responses via membrane-associated actions in a variety of brain regions (Luine and Frankfurt, 2013; Meitzen and Mermelstein, 2011; Roepke et al., 2011; Srivastava et al., 2011), and sex differences have been reported since the very beginning of this literature. The initial findings in the hypothalamus were shown to fluctuate depending on the stage of estrus of female rats (Kelly et al., 1976), and slices from males and females exhibited different firing responses to testosterone and estradiol, depending on hormonal state (Teyler et al., 1980). The acute effects of estrogens have been extensively studied in the context of long-term potentiation (LTP) in the hippocampus, but few comparisons have been made between the sexes (as reviewed by McCarthy and Konkle, 2005). One exception is the observation that estradiol-induced LTP is more pronounced in intact females as compared to ovariectomized females and intact males (Vierk et al., 2012). However, the majority of experiments exploring these questions in vitro test either one sex or a mix of tissues without explicit comparisons between the sexes.

One major issue that has received recent attention is that many studies examine only one sex (primarily males), usually for the sake of simplicity. However, adding in both sexes to a research design can change the scope of the question as well as gain unforeseen insight to how these mechanisms are understood. An example of this is the 'instant classic' work of Huang and Woolley (2012) in which estradiol-dependent suppression of inhibitory hippocampal neurons was determined to be sex-specific. In this case, the acute effects of estrogens occur through a membrane version of the estrogen receptor (ERα) that is associated with a metabotropic glutamate receptor. This mechanism is in turn coupled to retrograde signaling of the endocannabinoid anandamide to ultimately suppress GABAergic inhibitory currents. After identifying this mechanism in slices from female hippocampus, Huang and Woolley then observed that E2 had no effect in gonadally intact or castrated males. Beyond the intriguing signaling mechanism for rapid E2 effects, this study is important because it illustrates the importance of including both males and females in a study design. If this study had focused on either sex exclusively, an important E2-dependent effect on inhibitory synapses would have gone unnoticed or the mechanism may have been assumed to be ubiquitous for E2-dependent changes in the hippocampus, which is a conclusion often drawn in single sex studies. Therefore, the necessity of continuing to focus our attention on potential sex differences in the acute effects of steroids like estrogens has become ever more apparent.

3.2. Intracellular estradiol-dependent effects

Some rapid intracellular signaling events initiated by estradiol actions at the cellular membrane are also sex specific in the female hippocampus (Meitzen et al., 2012). Specifically, actions at a membrane estrogen receptor have been shown to regulate cAMP response element binding protein (CREB) phosphorylation in