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Review article

Sex hormones and adult hippocampal neurogenesis: Regulation, implications, and potential mechanisms

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ABSTRACT

Neurogenesis within the adult hippocampus is modulated by endogenous and exogenous factors. Here, we review the role of sex hormones in the regulation of adult hippocampal neurogenesis in males and females. The review is framed around the potential functional implications of sex hormone regulation of adult hippocampal neurogenesis, with a focus on cognitive function and mood regulation, which may be related to sex differences in incidence and severity of dementia and depression. We present findings from preclinical studies of endogenous fluctuations in sex hormones relating to reproductive function and ageing, and from studies of exogenous hormone manipulations. In addition, we discuss the modulating roles of sex, age, and reproductive history on the relationship between sex hormones and neurogenesis. Because sex hormones have diverse targets in the central nervous system, we overview potential mechanisms through which sex hormones may influence hippocampal neurogenesis. Lastly, we advocate for a more systematic consideration of sex and sex hormones in studying the functional implications of adult hippocampal neurogenesis.

1. Introduction

The hippocampus retains substantial plasticity throughout the lifespan, and this malleability is essential to hippocampal function (Jessberger et al., 2007; Scharfman and Myers, 2015; Surget et al., 2011; Wainwright et al., 2015). Considerable research suggests that the hippocampus is compromised in multiple neuropsychiatric and neurodegenerative disorders, including depression (McKinnon et al., 2009) and dementia (Henneman et al., 2009). This is perhaps not surprising given the importance of the hippocampus in cognition (Sweatt, 2004) and mood regulation (Campbell and Macqueen, 2004). Importantly, the hippocampus is a region in which neurogenesis persists throughout the lifespan in a wide variety of species including humans (Eriksson et al., 1998; Gould et al., 1999b; Gross, 2000; Spalding et al., 2013).

The majority of research efforts devoted to understanding the functional implications of adult hippocampal neurogenesis have been focused on learning and memory (Yau et al., 2015) and mood regulation (Sahay and Hen, 2007). Indeed, alterations in hippocampal neurogenesis are reported in post-mortem tissue from patients with depression (Boldrini et al., 2012) and Alzheimer's disease (Crews et al., 2010; Jin et al., 2004), and in animal models of these disorders (Bessa et al., 2009; Green and Galea, 2008; Mu and Gage, 2011; Wainwright et al., 2011). Although we first expand on the role of the hippocampus in the neurobiology of depression and cognitive function in this review, we direct the reader to other reviews with a primary focus on these topics (Broadbent et al., 2010; Campbell and Macqueen, 2004; MacQueen and Frodl, 2011; Sweatt, 2004). The current review focuses on the influence of sex and sex hormones on adult hippocampal neurogenesis, and explores ramifications to cognition and mood in health and disease.

Robust sex differences exist in the incidence rates of depression, where at least twice as many women are affected than men

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(Gutiérrez-Lobos et al., 2002; Angst et al., 2002). Similarly, Alzheimer's disease is more prevalent in women than men (Baum, 2005), in contrast to other forms of dementia (Gao et al., 1998). Sex differences in these neuropsychiatric and neurodegenerative disorders extend beyond incidence rates. The manifestation of a disorder can differ by sex, where in the case of depression, women are more likely to be diagnosed with atypical depression, and to present with co-morbid anxiety (Angst et al., 2002; Silverstein, 2002; Young et al., 1990). The severity of disease is also linked to sex, as Alzheimer's disease follows a more severe progression in women relative to men (Irvine et al., 2012). It is beyond the scope of this review to delve into why these sex differences in disease incidence and severity exist, but the reader is directed to other reviews on this subject (Hammarström et al., 2009; Mielke et al., 2014; Vest and Pike, 2013). Beyond the context of disease, sex differences exist in certain domains of cognition, as reviewed in Hamson et al. (in press), and in neurogenesis, as reviewed in Galea et al. (2013). In instances where sex differences are observed in a phenotype of interest, whether it is in the context of health or pathology, it is essential to examine whether sex hormones are involved. The role of sex hormones in any given phenotype can arise from effects early in development, during the pubertal transition, throughout adulthood, or across a combination of developmental windows in both males and females.

In light of the sex differences in cognitive function and mood regulation in health and disease, and the potential role of neurogenesis in these domains, the influence of sex hormones on adult hippocampal neurogenesis is essential to consider and will be the focus of our current review. After giving a brief overview of neurogenesis in the adult hippocampus, we expand on the role of the hippocampus, and links to hippocampal neurogenesis, in the neurobiology of depression and learning and memory. We then discuss evidence indicating that sex hormones are potent modulators of neurogenesis within the dentate gyrus. We highlight the complexities of sex hormone modulation of neurogenesis, in how it may be affected as a function of sex, age, and reproductive history. Further, we discuss potential implications of sex hormone regulation of hippocampal neurogenesis, with particular attention to affective and cognitive functions in health and disease. Lastly, we highlight potential mechanisms through which sex hormones may mediate their effects on neurogenesis within the dentate gyrus.

2. Adult hippocampal neurogenesis

Altman first found neural stem cells in the brain of adult rodents more than fifty years ago (Altman, 1962) and neural stem cells have since been identified in a number of species, including humans (Eriksson et al., 1998). The production of new neurons in the adult brain is typically limited the subventricular zone (SVZ), which lines the lateral ventricles and sends newly generated cells along the rostral migratory stream to the olfactory bulb, and the subgranular zone (SGZ) of the hippocampus (Kaplan and Hinds, 1977). However, studies in humans indicate that adult neurogenesis may not occur in the SVZ, and is limited to the hippocampus (Sanai et al., 2011; Spalding et al., 2013). Multipotent neural stem cells are capable of producing multiple types of both neurons and glia and are located in the SVZ, while neural progenitor cells located in the SGZ divide more frequently, in a finite manner, and into a limited number of cell types, as they may only produce daughter cells of either a defined glial or neuronal lineage (Gage, 2000; Seaberg and van der Kooy, 2002, 2003; van der Kooy and Weiss, 2000).

Newly generated neurons may be identified through the administration of DNA-markers such as ^{3}H-thymidine, or a synthetic nucleoside such as 5-bromo-2-deoxyuridine (BrdU). Each marker is incorporated into the DNA of dividing cells during DNA synthesis, replacing thymidine nucleotides. The addition of BrdU into the DNA provides a unique epitope for antibody binding using immunocytochemistry. The controlled addition of the exogenous markers allows for a definitive timeline of neural development, as every cell undergoing DNA synthesis during the 2 h after injection will be labelled. Labelled cells may be examined at time points ranging from hours, weeks, or even years later depending on the research question (Dayer et al., 2003; Eriksson et al., 1998; Kempermann et al., 2003).

There are limitations, however, in the use of exogenous markers, as they become diluted as cells undergo mitosis and are only distinguishable from background for 4–5 divisions following administration, thereby limiting the population of cells that may be labelled (Prickaerts et al., 2004; Stone et al., 1965); however, this limitation also provides the benefit of generating a "time stamp" for the occurrence of cell proliferation. Factors such as dose, toxicity, or the permeability of the blood–brain barrier may also disrupt the detection of true cell counts when using exogenous markers of DNA synthesis (Taupin, 2007). Exogenous markers must also be used in conjunction with endogenous markers, such as neuronal nuclei (NeuN) for mature neurons or glial fibrillary acidic protein (GFAP) for glial cells, in order to phenotype newly-labelled cells with BrdU or ^{3}H-thymidine. It is therefore essential that BrdU or ^{3}H-thymidine labelled cells be assessed with endogenous markers in order to demonstrate that neurogenesis has occurred (Ming and Song, 2005; Wojtowicz and Kee, 2006).

The measurement of neurogenesis may also be achieved through the assessment of endogenous protein expression. Measurement of the Ki67 protein, which is expressed throughout the active phases of the cell cycle but absent in quiescent cells, may be used as a marker of cell proliferation (Kee et al., 2002). The use of Ki67 in the measurement of cell proliferation also precludes issues with toxicity encountered with exogenous markers, however Ki67 is limited by the short timeline of expression – approximately 24 h in rats, but is not limited to cells that will become neurons (Cameron and McKay, 2001; Kee et al., 2002). Endogenous markers may also be used to identify and characterize both immature and mature neurons. Doublecortin (DCX) is a neuron-specific protein that functions in the stabilization of microtubules in early mitotic neurons which may be used to measure immature neurons and assess immature neuronal morphology (Bechstedt et al., 2014), and in the rat hippocampus is expressed from a few hours to 21 days after the production of a new neuron (Brown et al., 2003). The NeuN protein is expressed by most mature neurons and functions in RNA splicing within the nucleus, and may be used in the characterization of mature neurons (Kim et al., 2009; von Bohlen und Halbach, 2011). It is worth noting that while NeuN is expressed in most neuronal cell types, it is not expressed in certain neuronal populations such as the cerebellar purkinje cells and retinal photoreceptor cells (Mullen et al., 1992). Importantly, expression patterns differ in the SVZ and in mice, with other species likely also differing from the rat (Ming and Song, 2005; Snyder et al., 2009).

It is important to note that neurogenesis, as defined here, requires the proliferation, migration, survival, and differentiation of newly generated cells into neurons (see Fig. 1). Any number of internal and/or external factors may independently affect the proliferation of progenitor cells, migration, their differentiation into neurons, or their survival rates; including stress, gonadal hormones, or pharmaceuticals (Kempermann et al., 1998; van Praag et al., 1999; Malberg et al., 2000; Barker and Galea, 2008; Burgess et al., 2008; Pariante and Lightman, 2008; Anacker et al., 2011; Surget et al., 2011; Wainwright et al., 2011). It is therefore essential to understand which aspects of neurogenesis are being examined, and when they are being examined, in relation to