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Social behavior, hormones and adult neurogenesis

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ABSTRACT

A variety of experiences have been shown to affect the production of neurons in the adult hippocampus. These effects may be mediated by experience-driven hormonal changes, which, in turn, interact with factors such as sex, age and life history to alter brain plasticity. Although the effects of physical experience and stress have been extensively characterized, various types of social experience across the lifespan trigger profound neuroendocrine changes in parallel with changes in adult neurogenesis. This review article focuses on the influence of specific social experiences on adult neurogenesis in the dentate gyrus and the potential role of hormones in these effects.

1. Introduction

Adult neurogenesis in the dentate gyrus is sensitive to a large number of internal and external cues. The production and survival of new neurons (Fig. 1) can be modulated by growth factors, neurotransmitters and hormones, as well as by environmental conditions and specific experiences (see Song et al., 2012; Shors et al., 2012; Cameron and Glover, 2015 for reviews). While the regulation of adult neurogenesis by physical activity and stress has been extensively examined (Opendak and Gould, 2015), a smaller but emerging body of evidence has focused on social experience, particularly in the context of understanding the function of adult-generated neurons. Several studies have examined a variety of social experiences, including mating, social stress and parenting, on the production and survival of new neurons, with a particular emphasis on the functional consequences of such experience-induced changes. Social experiences have a strong influence on endocrine factors known to affect adult neurogenesis, suggesting several interesting potential connections. Additional findings have linked new neurons to social behavior itself. Taken together, these findings suggest that social experience may modulate adult neurogenesis through changes in hormones in order to shape the hippocampus so that it produces appropriate social behavior. This review article will consider studies that have explored the influence of specific social experiences on adult neurogenesis in the dentate gyrus, the potential role of hormones in these effects, as well as the impact such changes may have on behaviors associated with the hippocampus.

2. Sexual experience effects on adult neurogenesis

Social interactions can be stressful, rewarding, or a combination of the two. At least for some species, sexual experience may provide a straightforward example of a rewarding social interaction. Female hamsters form conditioned place preferences following sexual encounters (Meisel and Joppa, 1994), and male rats will readily form such preferences and learn to bar-press to gain access to a sexually receptive female (Everitt and Stacey, 1987; Tenk et al., 2009). For nonhuman primates as well, male and female rhesus monkeys will learn operant tasks to gain access to a receptive mate (Keverne, 1976; Michael and Keverne, 1968). In line with these results, sexual experience has been associated with activation of reward circuitry in the brain (Paredes, 2009). However, sexual experience is far from simple in terms of its effects on the brain and body, engaging an array of neural and hormonal systems. This complex and contingent behavior can exert profound effects on structural plasticity in the adult brain. For instance, transitioning from a reproductively suppressed subordinate to a dominant breeder in a hierarchy of naked mole rats produces robust changes in brain structure, including increased neurons in brain nuclei related to sexual behavior (Holmes et al., 2007). Sexual experience has been shown to increase the rate of adult neurogenesis in the hippocampus of young adult (Leuner et al., 2010b) and middle aged male rats (Glasper and Gould, 2013), as well as the number of dendritic spines on granule cells of the dentate gyrus (DG)

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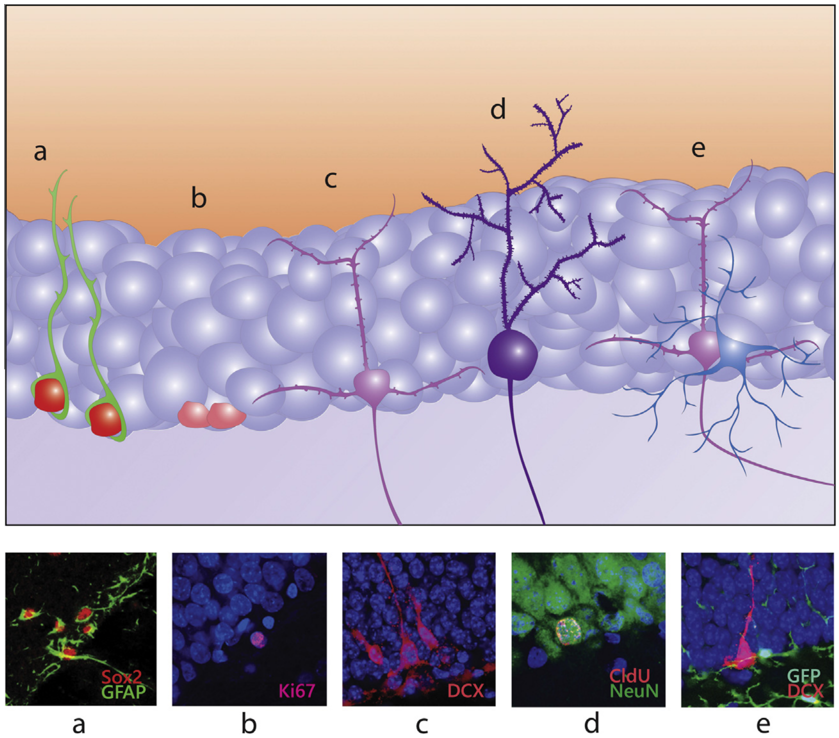

Fig. 1. Stages of adult neurogenesis in the dentate gyrus. Social interaction can affect the production of new neurons at one or multiple stages in their development. Top panel: Schematic diagram of adult neurogenesis in the granule cell layer of the dentate gyrus showing relevant cell types at different stages in the process. First, new neurons originate from precursor cells that have glial-like characteristics (A). These cells proliferate (B) and produce daughter cells that differentiate into immature neurons (C). Some of these immature neurons will survive and differentiate into mature neurons (D), while others will degenerate and their debris will be cleared by microglial phagocytosis (E). Bottom panel: confocal microscopic images of different cell types in the process of adult neurogenesis: (A) Glia-like precursor cells; Sox2 (red), Glial fibrillary acidic protein (GFAP) (green). (B) Proliferating precursor cells; Ki67 (red), Hoechst 33342 (blue). (C) Immature granule cells labeled with doublecortin (DCX) (red), Hoechst 33342 (blue). (D) Mature granule cells labeled with NeuN (green), CldU, a thymidine analog taken up by proliferating cells (red), Hoechst 33342 (blue). (E) Immature neuron near microglial cell, labeled with green fluorescent protein (GFP). DCX (red), GFP (green), Hoechst 33342 (blue).

of adult male rats (Glasper et al., 2015; Leuner et al., 2010b) (Fig. 1). Although the exact mechanisms through which these effects occur are unknown, several lines of evidence suggest the involvement of hormonal signals. The hippocampus is enriched with receptors for gonadal hormones, oxytocin, luteinizing hormone (LH), and prolactin, which may contribute to the effects of sexual experience on adult neurogenesis and dendritic spines in this brain region (Galea et al., 2013; Gimpl and Fahrenholz, 2001; Mak and Weiss, 2010).

Sexual experience provides a particularly useful paradigm through which to study experiential regulation of adult neurogenesis, as it can be reproduced readily in the laboratory and engages a variety of hormonal mechanisms that differ between sexes and across the lifespan. In young adult male rats, merely one sexual encounter is sufficient to stimulate cell proliferation in the hippocampus (Leuner et al., 2010a,b). Despite many possible candidates, a straightforward mechanistic description of this phenomenon remains elusive. Indeed, sexual experience is not defined by a unidimensional experience but rather comprises a complex combination of environmental, social and physiological cues and behaviors. Furthermore, the effects of reproductive hormones on adult neurogenesis may depend on species, sex differences, hormonal status, life history and social status. Indeed, even environmental cues associated with sexual experience, independently of mating itself, may induce changes in brain plasticity. Understanding the endocrinology underlying sexual experience may provide clues to the growth-promoting nature of this behavior.

2.1. Baseline differences in hormone levels

The effects of sexual experience on adult neurogenesis may depend on an animal's baseline endocrine status, which varies between males and females, as well as across species. Since endocrine systems are highly intertwined, a complete understanding of the role of hormones in the effects of sexual experience on adult neurogenesis requires a comprehensive view of multiple endocrine systems. However, in order to begin to understand the effects of hormones on adult neurogenesis in a naturalistic social context, it may be instructive to begin by examining what is known about individual hormone effects on adult neurogenesis.

Although no studies to date have examined the effects of sexual experience on adult neurogenesis in female rats, evidence exists that exposure to male pheromones stimulates adult neurogenesis in the dentate gyrus, as well as in the olfactory bulb of female mice (Mak et al., 2007). These findings strongly suggest that sexual contact, which naturally involves olfactory cues, would do the same. It is particularly interesting to note that stimulation of adult neurogenesis did not occur with exposure to pheromones of subordinate males, raising the possibility that while olfactory cues are sufficient to induce the effect when the male is dominant, actual mating behavior may be necessary to stimulate neuron growth when the male is subordinate (Mak et al., 2007). As will be discussed later in this review, social status appears to be a salient mediator of experience-dependent effects on adult neurogenesis.

It is likely that the hormonal state of the female is important for eliciting the stimulatory effects of sexual experience on adult