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Review article

The effects of hormones and physical exercise on hippocampal structural plasticity

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ABSTRACT

The hippocampus plays an integral role in certain aspects of cognition. Hippocampal structural plasticity and in particular adult hippocampal neurogenesis can be influenced by several intrinsic and extrinsic factors. Here we review how hormones (i.e., intrinsic modulators) and physical exercise (i.e., an extrinsic modulator) can differentially modulate hippocampal plasticity in general and adult hippocampal neurogenesis in particular. Specifically, we provide an overview of the effects of sex hormones, stress hormones, and metabolic hormones on hippocampal structural plasticity and adult hippocampal neurogenesis. In addition, we also discuss how physical exercise modulates these forms of hippocampal plasticity, giving particular emphasis on how this modulation can be affected by variables such as exercise regime, duration, and intensity. Understanding the neurobiological mechanisms underlying the modulation of hippocampal structural plasticity by intrinsic and extrinsic factors will impact the design of new therapeutic approaches aimed at restoring hippocampal plasticity following brain injury or neurodegeneration.

1. Introduction

Neurogenesis in the mammalian adult brain, including humans, has been widely studied for the last few decades (Altman, 1962; Altman and Das, 1965; Cameron et al., 1993; Eriksson et al., 1998; Kaplan and Hinds, 1977). Given its putative role as a modulator of cognitive function (Bruel-Jungerman et al., 2007; Gould et al., 1999a; Jessberger et al., 2009; Kee et al., 2007; Winocur et al., 2006), the study of adult neurogenesis has focused not only on mechanisms underlying the birth of new neurons but also in the structural and functional features of these newly generated cells and their relationship with the pre-existing neural circuitry (Kee et al., 2007; Toni et al., 2007). Furthermore, since alterations in adult hippocampal neurogenesis may underlie, at least in part, the cognitive deficits associated with several neurodegenerative diseases (Thompson et al., 2008; Winner et al., 2011) and given the increasing incidence of these disorders in the world population (Ferri et al., 2005; Prince et al., 2013), the elucidation of factors that modulate adult hippocampal neurogenesis and neuronal plasticity is a recognized priority (Gómez-Pinilla, 2008; Hillman et al., 2008; Yau et al., 2014a).

The hippocampus is a key structure in learning and memory (Anderson et al., 2007) and one of the few regions in the brain that

Abbreviations: AMPA, 3-hydroxy-5-methyl-4-isoxazolepropoionic acid; APOE, apolipoprotein E; BDNF, brain-derived neurotrophic factor; BrdU, 5-bromo-2′-deoxyuridine; CA, *Cornu Ammonis*; CAMKII, Ca^{2+}/calmodulin-dependent protein kinase III; CORT, corticosterone; CREB, cyclic-AMP response element-binding protein; DCX, doublecortin; DG, dentate gyrus; EAAC1, excitatory amino-acid carrier-1; ER, estrogen receptor; ERK, extracellular-signal-regulated kinase; GABA, γ-aminobutyric acid; FGF2, fibroblast growth factor 2; Flk-1, fetal liver kinase-1; GABA, glial fibrillary acidic protein; GFAP, long-term potentiation; GLP-1, glucagon-like peptide-1; HPA, hypothalamus–pituitary–adrenal; IGF-1, insulin growth factor 1; IGF-2, insulin-like growth factor 2; IL1β, interleukin-1β; IRS1, insulin receptor substrate 1; LT, lactate threshold; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; NeuN, neuronal nuclei; NeuroD, neurogenic differentiation protein; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; NRSF, neuron restrictive silencer factor; NSCs, neural stem cells; PCNA, proliferating cell nuclear antigen; PKB, protein kinase B; PSD95, post-synaptic density 95; RE1, repressor element-1; REST, RE1-silencing transcription factor; RMS, rostral migratory stream; SGZ, subgranular zone; sHSP, small heat shock proteins; SNAP-25, synaptosomal-associated protein 25; SVZ, subventricular zone; TNF, tumour necrosis factor; TrkB, tropomyosin receptor kinase B; VEGF, vascular endothelial growth factor..

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retain the capacity to generate new neurons into adulthood (Altman and Das, 1965; Eriksson et al., 1998). As such, this brain region has been the focus of intense research regarding the relationship between adult neurogenesis, neuronal plasticity, and cognitive function. Indeed, numerous studies have investigated how modulating hippocampal neurogenic function can affect cognitive performance (Bruel-Jungerman et al., 2007; Gould et al., 1999a; Jessberger et al., 2009; Kee et al., 2007; Shors et al., 2001b; Winocur et al., 2006; Yau et al., 2011). In this review, we will present an overview of the various intrinsic and extrinsic factors known to modulate hippocampal structural plasticity, giving special attention to hormones and physical exercise.

2. The hippocampus, learning and memory

The hippocampus is a bilateral structure found in the medial temporal lobes in the mammalian brain and is an integral part of the limbic system. The major hippocampal regions include the dentate gyrus (DG), the *Cornu Ammonis* (CA) 1 and the CA3.

It is generally accepted that the hippocampus is associated with declarative memory (i.e., conscious or explicit memories of facts and events), spatio-temporal contextualization of these memories, and also spatial learning and memory (Anderson et al., 2007). Impairments in these forms of memories and in learning processes have been continuously observed in several animal models of hippocampal disturbance (Lassalle et al., 2000; Morris et al., 1982; Morris, 1981; Yartsev and Ulanovsky, 2013). In addition, such deficits are also observed in patients with damage to the hippocampus and/or other areas of the medial temporal lobes as a consequence of either direct lesions or progressive pathologies such as Alzheimer's disease (Corkin, 2002; Perl, 2010; Scoville and Milner, 1957).

The identification of place cells (which become activated when an individual is placed in a specific location in a particular environment) in the hippocampus of different species has provided further evidence that this structure, in collaboration with other brain regions, plays a relevant role in the spatio-temporal organization of events (Burgess et al., 2002; O'Keefe and Dostrovsky, 1971).

Particularly, the DG sub-region has been reported to exhibit a crucial role in distinguishing similar patterns or events, a function known as pattern separation (Clelland et al., 2009; Creer et al., 2010; Sahay et al., 2011a). The CA3 sub-region is thought to be involved in recalling previously stored information in response to incomplete stimulus, a process known as pattern completion (Kesner, 2007). In addition, the temporal organization of events or spatial patterns has been related with the CA1 sub-region (Kesner et al., 2004). Moreover, a recent study has demonstrated that ocean cells from the entorhinal cortex play a major role in spatio-temporal contextualization of memories before they even reach the hippocampal formation (Kitamura et al., 2015).

3. Structural plasticity in the dentate gyrus

3.1. Adult hippocampal neurogenesis

Under physiological conditions, neurogenesis (a form of structural plasticity) occurs in two germinal regions of the adult mammalian brain: the subventricular zone (SVZ) of the lateral ventricles, and the subgranular zone (SGZ) of the hippocampal DG (Lie et al., 2004).

In the hippocampal DG, adult neurogenesis is topologically limited. New DG granule cells are generated from a resident population of neural stem cells (NSCs) located in the SGZ. Although there is still some debate around the features and classification of these neural progenitors, it is currently accepted that a population of glial fibrillary acidic protein (GFAP)-positive/Nestin-positive radial glia-like cells and Sox2-positive non-radial cells constitute the putative NSCs (Zhao et al., 2008). These multipotent adult neural stem cells divide asymmetrically to either self-renew and maintain the NSCs population or give rise to intermediate progenitors. These progenitors in the DG of the hippocampus proliferate, differentiate and migrate 20–25 μm away from the SGZ into the granule cell layer (GCL), where they eventually mature and integrate into the pre-existing neuronal circuitry, displaying similar features to those of DG neurons that were generated during embryonic development (van Praag et al., 2002; Zhao et al., 2008). The dendrites of the newborn granule cells project to the molecular layer of the DG, where they receive inputs from the entorhinal cortex, and their axons extend through the hilus of the DG towards the CA3 region, integrating the mossy fibres (Kempermann et al., 2004a, 2004b).

Notably, about 9000 new granule cells are produced daily in the DG of young rats (Cameron and Mckay, 2001). Of these new granule cells, approximately 50% survive and at least 80% of these differentiate into neurons (Cameron et al., 1993; Dayer et al., 2003).

Adult neurogenesis has been studied mainly in rodents, but similar observations have been reported in other animals such as birds (Goldman and Nottebohm, 1983), monkeys (Kornack and Rakic, 1999), and humans (Eriksson et al., 1998; Knoth et al., 2010; Spalding et al., 2013). Indeed, Spalding et al. (2013) observed that about 700 newborn neurons are generated each day in the hippocampus of adult human brains (Spalding et al., 2013). However, although neurogenesis occurs into adulthood, this form of structural plasticity does decline progressively with age (Amrein et al., 2011; Ben Abdallah et al., 2010; Gil-Mohapel et al., 2013; Gould et al., 1999b; Kempermann et al., 1998; Knoth et al., 2010; Kuhn et al., 1996; Ngwenya et al., 2015; Olariu et al., 2007). Of note, some studies suggest that this age-induced decline in hippocampal neurogenesis is greater in rodents than in primates (including humans), which show a less severe decrease in hippocampal neurogenic function (Ngwenya et al., 2015; Spalding et al., 2013). Nevertheless, this age-dependent decrease in hippocampal neurogenesis may contribute, at least in part, to the cognitive impairments commonly associated with the normal ageing process (Knoth et al., 2010; Kuhn et al., 1996; Rao et al., 2006). In addition, not all neurons produced in the adult brain survive and reach full maturity. Indeed, a large proportion of newborn neurons (approximately 50%) degenerate within a few weeks after being generated (Cameron et al., 1993; Dayer et al., 2003; Gould et al., 2001, 1999a). Importantly, the survival of adult-generated DG neurons is highly dependent on the ability of these cells to react to experience, suggesting that overproduction of granule cells prepares the DG for environmental conditions that might benefit from the incorporation of more new neurons. In the absence of stimulus, such as in laboratory controlled settings, these neurons are not necessary and are therefore eliminated (Leuner and Gould, 2010).

3.2. Morphology and physiology of newborn dentate granule neurons

Several studies have characterized the anatomical and physiological properties of newly generated granule cells in the adult DG. Experiments using retroviral labelling with green fluorescent protein to specifically mark newborn neurons have shown that these cells display the typical morphological features of dentate granule neurons (Espósito et al., 2005; van Praag et al., 2002). Further morphological characterization has determined that during the first and second weeks after their birth, newborn immature neurons start expanding dendritic processes towards the molecular layer and axon fibres towards the CA3 sub-region. At this stage, spineless dendrites that have reached the inner molecular layer start receiving functional excitatory GABAergic inputs. Subse-