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Invited Review

Chronic peripheral inflammation, hippocampal neurogenesis, and behavior

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ABSTRACT

Adult hippocampal neurogenesis is involved in memory and learning, and disrupted neurogenesis is implicated in cognitive impairment and mood disorders, including anxiety and depression. Some long-term peripheral illnesses and metabolic disorders, as well as normal aging, create a state of chronic peripheral inflammation. These conditions are associated with behavioral disturbances linked to disrupted adult hippocampal neurogenesis, such as cognitive impairment, deficits in learning and memory, and depression and anxiety. Pro-inflammatory cytokines released in the periphery are involved in peripheral immune system-to-brain communication by activating resident microglia in the brain. Activated microglia reduce neurogenesis by suppressing neuronal stem cell proliferation, increasing apoptosis of neuronal progenitor cells, and decreasing survival of newly developing neurons and their integration into existing neuronal circuits. In this review, we summarize evolving evidence that the state of chronic peripheral inflammation reduces adult hippocampal neurogenesis, which, in turn, produces the behavioral disturbances observed in chronic inflammatory disorders. As there are no data available on neurogenesis in humans with chronic peripheral inflammatory disease, we focus on animal models and, in parallel, consider the evidence of cognitive disturbance and mood disorders in human patients.

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1. Introduction

Pathologic conditions as varied as arthritis, diabetes mellitus, obesity, systemic lupus erythematosus (SLE), and inflammatory bowel disease (IBD) create a state of chronic peripheral inflammation. They do so either by directly producing inflammation or by triggering pathological metabolic states, which in turn contribute to inflammatory processes. Inflammatory responses are not limited to the periphery; systemic inflammation also affects the central nervous system. These same conditions are associated with behavioral disturbances, such as cognitive impairment, deficits in learning and memory, and depression. Despite the important impact on the quality of life, very few studies have focused on the central mechanisms underlying these behavioral problems in chronic inflammatory states. Adult hippocampal neurogenesis is an important form of neuroplasticity, and data from animal models suggest that chronic peripheral inflammation disrupts hippocampal neurogenesis. Therefore, impaired neurogenesis as a consequence of chronic inflammation might underlie some of the behavioral manifestations of these disorders in humans. This review provides an overview of data that suggest links between chronic peripheral illness, adult hippocampal neurogenesis, and behavior.

Although many illnesses involve chronic inflammation (e.g. liver disease, cardiovascular disease and some forms of cancer), this review will focus on those conditions where sufficient data are available from animal models of chronic inflammation and behavioral correlates in humans. The authors regret that they cannot cite many original papers and some reviews due to space limitations.

2. Adult neurogenesis

For many years, the production of new neurons in mammalian brain had been considered to be restricted to early development. With the discovery and implementation of new methodologies, it is now clear that neurogenesis occurs in adult animals, including humans (Abrous et al., 2005; Eriksson et al., 1998; Zhao et al., 2008). Although neurogenesis can occur in multiple sites throughout the adult brain, however, under physiological conditions in rodents, neuronal progenitor cells (NPC) produce neurons mainly in two specific regions: in the subventricular zone (SVZ) and in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus (Jessberger and Gage, 2014; Spalding et al., 2013). In humans, the existence of adult neurogenesis was discovered using bromodeoxyuridine labeling subsequently analyzed in postmortem tissue (Eriksson et al., 1998), and later confirmed using a carbon dating technique based on elevated C^{14} in the atmosphere as a consequence of atomic bomb testing (Spalding et al., 2013). In addition to the SGZ and SVZ, striatum was also identified as a neurogenic niche (Ernst and Frisen, 2015).

Neural progenitor cells are distributed along the SGZ, the boundary between the granule cell layer (GCL) and the hilus. Within neurogenic regions, multipotent stem cells divide asymmetrically, producing one stem cell and one daughter progenitor cell that can differentiate into a neuron or an astrocyte. In the hippocampus in rodents, approximately 60% of newborn cells fail to terminally differentiate and do not survive (van Praag et al., 1999). Neurons that do survive migrate short distance into the granular cell layer of the dentate gyrus, and become integrated into existing neuronal circuitry. Cell bodies stay at the GCL, dendrites project through the molecular cell layer, and axons project toward the hilus and CA3, while receiving input from the entorhinal cortex. The granular cell layer can change in volume by up to 20% due to changes in the rate of neurogenesis (Kohman and Rhodes, 2013).

There are a number of key differences in adult hippocampal neurogenesis between rodents and humans (Jessberger and Gage, 2014; Spalding et al., 2013). For example, in rodents, neuroblasts migrate from the SVZ to the olfactory bulbs; in humans, neuroblasts and new neurons from the SVZ migrate to the striatum, where they become striatal interneurons (Ernst et al., 2014; Ernst and Frisen, 2015). Also, whereas the extent of adult hippocampal neurogenesis declines with age, the rate of decline is smaller in humans then in rodents. Furthermore, over time, the exchange of hippocampal neurons is greater in humans compared to that seen in rodents, and the total number of dentate gyrus neurons increases in rodents whereas it decreases in humans during adult life. In mice, it takes several weeks for the newly developed neuron to mature (Kempermann et al., 2003); however, it takes 6 months in macaque monkeys (Kohler et al., 2011), and presumably it might take even longer in humans.

Proliferation, maturation, and survival of newborn neurons as well as their eventual incorporation into the hippocampal neuronal network are determined by multiple factors. Adult hippocampal neurogenesis is stimulated by environmental enrichment and exercise (Kempermann et al., 2003; van Praag et al., 1999), and neurogenesis is suppressed by acute and chronic inflammation (Ben-Hur et al., 2003; Borsini et al., 2015; Monje et al., 2003; Zonis et al., 2013, 2015). The microenvironment in the neurogenic niche is important, and is mediated by a range of critical factors, including the oxygen supply, nutrition, hormones, and trophic factors, but also, to a large extent, by the cellular and humoral activity of the immune system (Kohman and Rhodes, 2013; Yirmiya and Goshen, 2011).

The hypothalamic–pituitary–adrenal (HPA) axis plays an important role in hippocampal neurogenesis. Short-term mild stress and a modest rise in circulating glucocorticoids might increase neurogenesis (Schoenfeld and Gould, 2013), reflecting adaptive responses to a changing environment. By contrast, severe or chronic stress suppresses neurogenesis (Cameron and Glover, 2015; Egeland et al., 2015). In turn, neurogenesis also appears to be involved in responses to stressors (Cameron and Glover, 2015). Thus, suppression of hippocampal neurogenesis leads to activation of the HPA axis (Schloesser et al., 2009). In mice with disrupted neurogenesis, glucocorticoid levels are slower to recover after moderate stress, and are less suppressed by dexamethasone. The small subset of neurons identified in the dentate gyrus appeared to be critical for hippocampal negative control of the HPA axis (Snyder et al., 2011).

3. Adult neurogenesis and behavior

In this review we will describe the changes attributed to the SGZ of hippocampus.

The role of neurogenesis in hippocampal function and behavior continues to be a subject of intense debate. Neurogenesis cannot be imaged or otherwise measured in living human subjects; therefore, most information on the behavioral consequences of normal and abnormal neurogenesis has been obtained from studies in laboratory animals.

A strong case can be made for the involvement of adult hippocampal neurogenesis in memory and learning (Deng et al., 2010; Saxe et al., 2006; Winocur et al., 2006; Zhao et al., 2008). New granule cell neurons have higher levels of excitability and plasticity and are thought to play an important role in forming memories (Ge et al., 2007), spatial learning (Deng et al., 2010), pattern separation (Sahay et al., 2011), cognitive flexibility, and the association between old and new memories (Jessberger and Gage, 2014; Kohman and Rhodes, 2013). In general, disrupting neurogenesis interferes with spatial and contextual memory retrieval. However, not all studies have found an association