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Neuroinflammation negatively affects adult hippocampal neurogenesis and cognition: can exercise compensate?

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ABSTRACT

Adult hippocampal neurogenesis is believed to be integral for certain forms of learning and memory. Dysregulation of hippocampal neurogenesis has been shown to be an important mechanism underlying the cognitive impairment associated with normal aging, as well as the cognitive deficits evident in preclinical models of Alzheimer's disease and other neurodegenerative diseases. Neuroinflammation is a significant pathological feature of these conditions; it contributes to the observed cognitive decline, and recent evidence demonstrates that it also negatively affects hippocampal neurogenesis. Conversely, during the past twenty years, it has been robustly shown that exercise is a potent inducer of hippocampal neurogenesis, and it is believed that the positive beneficial effect of exercise on cognitive function is likely due to its pro-neurogenic effects. However, the interplay between exercise- and neuroinflammatory-induced changes in hippocampal neurogenesis and associated cognitive function has only recently begun to receive attention. Here we review the current literature on exercise-induced effects on hippocampal neurogenesis, cognitive function and neuroinflammation, and consider exercise as a potential pro-neurogenic and anti-inflammatory intervention for cognition.

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1. Introduction

Neurogenesis, the process of generating new neurons from multipotent stem cells occurs during embryonic development and it is now widely accepted that it also occurs in the adult mammalian hippocampus. Neurogenesis in the adult brain is primarily restricted to two major sites; the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ) lining the lateral ventricles. In the hippocampus, multipotent undifferentiated neural stem cells (NSCs) generated in the SGZ give rise to neural progenitor cells (NPCs) which proliferate and migrate into the granule cell layer (GCL) of the DG and then differentiate into neurons, astroglia or oligodendrocytes. Granule cell neurons then project into the CA3 region of the hippocampus where they become fully functional neurons that are integrated into the brain circuitry (Gage, 2000; Kempermann et al., 2004). It is now estimated that 700 new neurons are generated in the hippocampus of humans every day (Spalding et al., 2013) suggesting

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a functional role for hippocampal neurogenesis in humans. The hippocampus is the site of the brain involved in learning and memory recent years, studies where neurogenesis was ablated in the hippocampus of rodents have demonstrated diminished cognitive performance in tasks relying on hippocampal-dependent memory such as the Morris water maze (MWM), contextual fear conditioning, spatial and object recognition and pattern separation (Clelland et al., 2009; Jessberger et al., 2009; Saxe et al., 2006; Snyder et al., 2005). While some discrepancies remain in the literature, for the most part pattern separation, a DG-dependant specific cognitive process in which two similar contexts need to be distinguished, has been proposed to be reliant on hippocampal neurogenesis (Deng et al., 2010). Moreover, synaptic plasticity has been shown to be enhanced in newly generated cells in the hippocampus (Schmidt-Hieber et al., 2004), and it has also been demonstrated that these new cells have increased potential for long term potentiation (LTP) (Snyder et al., 2001).

It has also become apparent that there is clinical relevance associated with adult hippocampal neurogenesis and cognition. Cognitive decline can occur with age as well as in a number of neuropsychiatric and neurodegenerative conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and depression. It is now becoming apparent at least from studies using animal models, that hippocampal neurogenesis can also be affected in these conditions. For example, evidence emerged in the 1990's that adult hippocampal neurogenesis in rodents is subject to an age-related decline (Kuhn et al., 1996). Although it was assumed that a similar scenario may occur in humans, recent data has suggested that the age-related decline in humans may not be so pronounced (Spalding et al., 2013). The experimental approaches that generated the data in these two studies (immunohistochemical analysis in animal hippocampus and ^{14}C DNA from *post-mortem* human hippocampus) are very different however due to the limitations of measuring adult neurogenesis in humans. Thus until advances in clinical neuroimaging technologies are made the dynamics of neurogenesis over the longer term for example, it will be difficult to determine whether findings in animal studies translate to humans and thus are of clinical significance. Similarly, *post-mortem* studies of AD been associated with both impaired (Crews et al., 2010) and increased (Jin et al., 2004; Perry et al., 2012) hippocampal neurogenesis transgenic mouse models of the disease also show differing effects, probably due to the huge variability in the current models available (reviewed in (Lazarov and Marr, 2010; Marlatt and Lucassen, 2010)). Alterations in adult hippocampal neurogenesis have also been observed in PD and HD (reviewed by (Winner and Winkler, 2015)), however limited *post-mortem* studies have been carried out to date. Interestingly, there is a high incidence of depression in patients suffering from these neurodegenerative conditions, and evidence has revealed that the number of proliferating cells in the human DG has been shown to be increased in patients treated with antidepressants (Boldrini et al., 2012). While it is as yet unclear whether a reduction in hippocampal neurogenesis occurs in depressed individuals, it has been shown that when hippocampal neurogenesis was ablated in rats, the behavioural responses to chronic antidepressant treatment were blocked (Santarelli et al., 2003) suggesting a causative role for neurogenesis in the efficacy of antidepressants. Chronic neuroinflammation is a common pathological feature in normal aging as well as in these neurodegenerative conditions and has been shown to negatively affect hippocampal neurogenesis and cognitive processes across the lifespan (Green and Nolan, 2014; Kohman and Rhodes, 2013; Yirmiya and Goshen, 2011). Conversely, positive modulators of adult hippocampal neurogenesis and associated cognitive function include environmental enrichment, learning, and exercise (Bekinschtein et al., 2011; Gould et al., 1999; Kempermann et al., 1997; Voss et al., 2013).

Until relatively recently the beneficial effects of exercise have been primarily associated with maintaining a healthy heart rate and blood pressure as well as a healthy body weight. Indeed, regular exercise is recommended to lower the risk of the development of cardiovascular problems such as heart attack, high cholesterol, high blood pressure and stroke (Stults-Kolehmainen, 2013). However, beyond the potential for exercise to reduce the risk of stroke occurring, there are other positive effects of exercise on brain health. One significant line of research that has emerged over the last couple of decades is that exercise increases neurogenesis in the adult hippocampus (van Praag et al., 1999b), at least in rodents. Exercise has been shown to not only increase adult hippocampal neurogenesis (Clark et al., 2011; Kronenberg et al., 2006; van Praag et al., 1999b), but also to improve the cognitive abilities of rodents housed with access to running wheels (Rhodes et al., 2003; van Praag et al., 1999a; van Praag et al., 2005). Furthermore, although it is not currently possible to routinely measure hippocampal neurogenesis in living humans, a growing number of studies have demonstrated that exercise training improves performance in cognitive tests and is also associated with increased hippocampal volume in humans (Erickson et al., 2011; Pereira et al., 2007). Regarding the detrimental effects of chronic neuroinflammation on neurogenesis and cognition, it is as yet unknown whether exercise could act as a potential anti-inflammatory agent in this respect. Here we review current evidence from the literature that demonstrates the detrimental effects of pro-inflammatory cytokines on hippocampal neurogenesis and cognition. We further discuss the potential ability of the pro-neurogenic properties of exercise to reduce neuroinflammation as a mechanism to induce its beneficial effect on cognitive function.

2. Neuroinflammation and hippocampal neurogenesis

The innate immune system initiates a rapid and non-specific inflammatory response to pathogenic infection and injury, while the adaptive immune system responds in a slower but specific manner and provides lasting immunity to facilitate recovery from injury or infection. B and T cells, which can infiltrate the CNS from the periphery, are the cellular mediators of the adaptive immune response while in the CNS itself, microglial cells are the primary mediators of the innate neuroinflammatory response. Microglia are responsible for the maintenance of brain homeostasis under normal conditions quiescent microglia (also known as ramified or resting microglia) display small cell bodies and multiple extending processes, with which they probe the environment for signals of injury, trauma or other disruption of homeostasis. Under disturbed or pathological conditions, microglia undergo morphological and functional alterations and become activated. These activated or amoeboid microglia are phagocytic and display enlarged cell somas with one or less extending process, and release a host of either pro [interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), nitric oxide synthase-2 (NOS-2), cyclooxygenase-2 (COX2) and chemokine ligand-2 (CCL2)] or anti-inflammatory [interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-13 (IL-13), transforming growth factor-β (TGF-β) and Arginase-1] mediators. Other cells such as astrocytes, infiltrating macrophages and endothelial cells can also produce these mediators, but levels vary depending on stimulating conditions, cellular location and exposure to previous stimuli (Kettenmann et al., 2011). Microglial activation has previously been reported to have mainly detrimental effects on neurons, especially in conditions of chronic activation. However, numerous studies have now demonstrated that microglia are involved in regeneration and neuroprotection (Czeh et al., 2011). Recent research on the nature of such opposing roles of microglia has focused on their polarisation in response