Neuroscience and Biobehavioral Reviews 40 (2014) 20–34

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Inflammation and the developing brain: Consequences for hippocampal neurogenesis and behavior

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ARTICLE INFO

Article history:
Received 8 August 2013
Received in revised form 12 January 2014
Accepted 13 January 2014

Keywords:
Inflammation
Hippocampus
Neurogenesis
Development
memory
Cognition
Mood
Neurodevelopmental disorders

ABSTRACT

While the detrimental impact of inflammation on adult hippocampal neurogenesis and associated behaviors has recently gained credence, the effects of inflammation on the developing brain is an area of research which is quickly gaining momentum, and a growing number of research articles on this topic have been published in recent years. Indeed, we now know that pro-inflammatory mediators negatively influence both hippocampal neurogenesis and neuronal cytoarchitecture during brain development. Here we present a comprehensive review of the current literature on inflammation-induced changes in hippocampal neurogenesis during early life and the consequent behavioral deficits which may ensue in later life. We also offer insights into the cellular and molecular mechanisms underlying the hippocampal-dependant behavioral changes observed in neurodevelopmental disorders, particularly in those where cognitive dysfunction plays a major role. We further consider whether early-life inflammation-induced changes in hippocampal neurogenesis may contribute to the onset of mood and cognitive deficits in later life.

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Contents

1. Introduction

There is current consensus that the detrimental impact of inflammatory insults on the immature brain and its long term consequences on cognition and emotion in later life positions neuroinflammation as a significant risk factor for neurodevelopmental, neurodegenerative and psychiatric disorders (Hagberg et al., 2012). The hippocampus, which has a central role in learning and memory, is particularly vulnerable to inflammatory insult due to its high density of receptors for inflammatory mediators. Recent progress in understanding the role of inflammation in hippocampal neurogenesis (the birth of new neurons) has bolstered

Abbreviations: BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CA, Cornu ammonis; DG, dentate gyrus; E, embryonic day; EC, entorhinal cortex; *E. coli*, *Escherichia coli*; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; GSK-3β, glycogen synthase kinase 3β; GCL, granular cell layer; IFNγ, interferon-γ; IL-1, interleukin-1; IL-6, interleukin-6; IL-1ra, Interleukin-1 receptor antagonist; IL-1R1, Interleukin-1 type-1 receptor; LPS, lipopolysaccharide; LTP, long-term potentiation; MIA, maternal immune activation; MAM, ethylazoxymethanol acetate; NFκB, nuclear factor-kappaB; NPC, neural precursor cell; NSPC, neural stem/progenitor cell; poly(I:C), polyinosinic-polycytidylic acid; P, postnatal day; SGZ, subgranular zone; TNF-α, tumour necrosis factor-α.

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0149-7634/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neubiorev.2014.01.004

this line of investigation. Neurogenesis occurs during development and it is now widely accepted that it also occurs throughout adulthood, in two distinct regions of the brain; the subventricular zone and the dentate gyrus (DG) of the hippocampus (Altman and Das, 1965; Eriksson et al., 1998; Gage, 2000; Gould et al., 1999; Spalding et al., 2013). It is a multistep processes involving the proliferation, differentiation and migration of undifferentiated neural stem/progenitor cells (NSPCs), resulting in a post-mitotic, integrated, and fully functional neurons (Gage, 2000; Kempermann et al., 2004a). While adult neurogenesis is an individualized process, with neurons of different developmental stages all present simultaneously (Kempermann, 2011; Kempermann et al., 2004a) and requires a permissive microenvironment, neurogenesis in the developing brain occurs as a highly orchestrated temporally defined event. Despite these differences however, it has been proposed that the intrinsic mechanisms of embryonic and adult hippocampal NSPCs remain the same throughout development and adulthood (Pleasure et al., 2000). The detrimental impact of inflammation on adult hippocampal neurogenesis and associated behaviors has recently gained credence (Kohman and Rhodes, 2012; Yirmiya and Goshen, 2011). Likewise, we now know that pro-inflammatory cytokines negatively influence the development of hippocampal neurons during the embryonic period (Green et al., 2012; Keohane et al., 2010). However, exploration of the short- and long-term behavioral and cognitive consequences of an inflammatory insult during the embryonic or perinatal period, which may be mediated by hippocampal neurogenesis, is still in its infancy. Indeed, cognitive and emotional deficits associated with psychiatric and neurodevelopmental disorders such as schizophrenia, autism and cerebral palsy currently represents a major healthcare problem. Given the momentum at which evidence is accumulating on the adverse effects of inflammation on brain development (Hagberg et al., 2012), this review will examine current evidence of the consequences of early life exposure to inflammation on hippocampal neurogenesis both in early life and in adulthood. It will also offer insights into the cellular and molecular mechanisms underlying the hippocampal-dependant behavioral changes observed in neurodevelopmental disorders, particularly in those where cognitive dysfunction plays a major role. We further consider whether inflammation-induced changes in hippocampal neurogenesis during early life may contribute to behavioral deficits later in life.

2. The hippocampus

2.1. Hippocampal structure and function

The hippocampus derives its name from the Latin for sea horse '*hippocampus*'; it is folded into the medial temporal lobe with a distinctive curved shape. It is a bilateral limbic structure, and is phylogenetically one of the oldest parts of the central nervous system (CNS) (Crossman and Neary, 2006). As a whole it is known as the hippocampal formation and consists of the hippocampus proper (the Cornu ammonis, (CA1-3)), the DG, the subiculum, the presubiculum, parasubiculum and the entorhinal cortex (EC) (Amaral and Lavenex, 2007). It plays an integral role in declarative memory, spatial memory, learning, emotion and synaptic plasticity. Indeed structural changes to the hippocampus have been suggested to play a role in the pathophysiology of both neurodegenerative and psychiatric disorders (Frisoni et al., 2008; Videbech and Ravnkilde, 2004). The hippocampus has also been identified as a site of adult neurogenesis, as it contains undifferentiated proliferating NSPCs which give rise to new neurons throughout adulthood (Altman and Das, 1965; Eriksson et al., 1998; Gage, 2000; Gould et al., 1999; Spalding et al., 2013).

The first suggestion that the hippocampus had a major role in memory came in the mid 1950s when the medial temporal lobe of Patient H.M was removed bilaterally for intractable epilepsy. The result was severe anterograde and partial retrograde amnesia, leaving H.M. unable to form new memories (Scoville and Milner, 1957). Since then, research using experimental animals and humans has shown that the hippocampus is crucial for both the formation and recall of declarative memories as well as, for spatial memory and navigation (Eichenbaum and Cohen, 2004; Lavenex and Lavenex, 2013; Squire et al., 2004). Declarative memory consists of memories that can be consciously recalled such as knowledge or facts, and can further be subdivided into episodic and semantic memories, which are those concerned with specific events and the knowledge of words, respectively (McClelland et al., 1995). Spatial memory is concerned with the encoding and retrieval of spatial information (O'Keefe and Nadel, 1978). The hippocampus, along with the overlapping cerebral cortex is also associated with long-term storage of large quantities of information. Thus it plays an important role in the consolidation of information from short-term memory to long-term memory. During the past few decades a great deal of research has been carried out to identify the mechanisms underlying memory consolidation, storage and retrieval (Kampa et al., 2011). For example, the DG, traditionally considered the information gateway to the hippocampus, is thought to consolidate memories by reducing cross-talk between neurons and hence reducing interference between overlapping spatial or contextual information, so that it is usable by CA3 (Sahay et al., 2011). The CA3, a region involved in the organization of information in a sequential order (Lee et al., 2005), connects with the CA1 region which is involved in obtaining, storing and the retrieval of memories. The theory put forward by Cajal in 1913 that activity-dependent synaptic plasticity at appropriate neuronal synapses during memory formation is necessary for consequent storage of information, is now widely accepted (Cajal, 1913). Based on this, the phenomenon of long-term potentiation (LTP) (a longlasting increase in synaptic responsiveness induced by a brief train of intense synaptic activation) was modeled in rabbit hippocampus by Bliss and Lomo (1973) and is believed to be a biological substrate underlying at least some forms of memory. This theory has been consolidated by numerous studies (Bliss and Collingridge, 1993; Bliss and Lomo, 1973; Lynch, 2004; Morris et al., 1986).

Due to Kluver and Bucy's finding that removal of the temporal lobe from monkeys caused emotional disturbance in these animals (Kluver and Bucy, 1937), and to its position in the limbic system, the hippocampus has long been hypothesized as having a role in emotion. Since then, studies have shown that hippocampal lesions impair the proper functioning of the hypothalamic-pituitary-adrenal axis and the associated stress response (Buchanan et al., 2009; Sapolsky et al., 1984), and have thus demonstrated an integral role for the hippocampus in the brains' response to psychosocial stress. The dual role of the hippocampus in both cognition and emotion has been postulated to be anatomically segregated into the dorsal and ventral sub-regions of the hippocampus (Moser and Moser, 1998). This concept has now gained credence due to experimental studies showing that lesions to the dorsal or ventral areas of the hippocampus exert differential effects on behavior (Fanselow and Dong, 2010; Jarrard et al., 2011). Specifically, the ventral hippocampus has been shown to preferentially regulate emotion and anxiety whereas the dorsal hippocampus is primarily involved in spatial learning and memory (Bannerman et al., 2004; Kjelstrup et al., 2002; McHugh et al., 2011). Interestingly, recent evidence has emerged that treatment for stress-related psychiatric disorders, including antidepressants and lithium, selectively increase neurogenesis in the ventral but not dorsal

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