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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.

Keywords

chronic peripheral inflammation; activated microglia; hippocampus; neurogenesis; behavior

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

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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 than 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; Zonis et al., 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 between memory and adult hippocampal neurogenesis. For example, genetic ablation of neurogenesis was not found to affect performance in the Morris water maze (Bergami et al., 2008) as well as on other tests of memory and learning (Groves et al., 2013). The reason(s) for these discrepancies is not clear.

Many studies have focused on involvement of neurogenesis in depression, but the findings are difficult to put into a cohesive framework. Some studies found that altered or decreased neurogenesis is associated with depression-like behavior (Wang et al., 2015), but others have not found this relationship (Petrik et al., 2012). This discrepancy might result from the inherent limitations in modeling human clinical depression in animals. Nevertheless, there is good evidence that neurogenesis might be involved in the mechanism of action of antidepressant drugs, as the chronic administration of different classes of antidepressants increases hippocampal neurogenesis (Duman, 2004; Malberg and Duman, 2003; Pechnick et al., 2011). One of the mechanisms of antidepressant action is suppressing the cyclin-dependent kinase inhibitor p21^{Cip1} (p21). p21 arrests cell proliferation and is expressed in NPC and in early developing neurons. We have shown that antidepressants stimulate neurogenesis by inhibiting p21, thus releasing cell-cycle arrest and stimulating proliferation of progenitors of neuronal lineage (Pechnick et al., 2011; Pechnick et al., 2008).

4. Peripheral Immune System-to-Brain Communication

Many inflammatory conditions are associated with both altered neurogenesis and behavior abnormalities as outlined below. Several mechanisms alert the brain to inflammation in the periphery. Locally produced pro-inflammatory cytokines activate primary afferent pathways, such as the vagus nerve, and circulating pro-inflammatory cytokines access the brain via the circumventricular organs and saturable transport systems (Dantzer et al., 2008b). Pro-inflammatory cytokines disrupt the blood-brain barrier, allowing activated lymphocytes and cytokines to circulate between the peripheral immune system and the brain (Morris et al., 2015). Engagement of this peripheral immune system-to-brain communication ultimately leads to activation of astrocytes in the central nervous system (CNS), which contribute to the local immune response by releasing pro-inflammatory cytokines (Ransohoff and Brown, 2012). Inflammation also causes cytokine production by neurons.

Resting resident microglia, the brain's counterpart to macrophages, support neurogenesis. When activated by peripheral and central inflammatory signaling, microglia release multiple pro-inflammatory molecules, including cytokines, chemokines, reactive oxygen species, and nitric oxide, resulting in neuroinflammation. Whether inflammation is peripheral or central (e.g., Parkinson's disease, multiple sclerosis, Alzheimer's disease or encephalitis), the common outcome is activation of microglia. Even when activated, microglia can still support neurogenesis depending on the microenvironment, the cytokine profile, levels of cytokine

production (Ekdahl et al., 2009), or modulation of neuronal synapses (Chen and Trapp, 2015); however, most of the time, activated microglia suppresses hippocampal neurogenesis. In this way, activated microglia might contribute to the behavioral manifestations of chronic inflammatory disorders. As adult hippocampal neurogenesis occurs within an angiogenic niche (Palmer et al., 2000), in addition to microglia, endothelial cells can be activated and produce multiple cytokines that can affect neurogenesis.

5. Acute Inflammation and Neurogenesis

A great deal of work has been devoted to dissecting the role of cytokines in the direct and indirect regulation of neurogenesis (Borsini et al., 2015; Goshen and Yirmiya, 2009; Kohman and Rhodes, 2013). NPC constitutively express receptors for pro-inflammatory cytokines (Green et al., 2012). Despite some controversies and discrepancies arising from the use of different experimental models, most *in vitro* experiments have shown that pro-inflammatory cytokines suppress NPC proliferation. For example, we showed in *in vitro* experiments that interleukin (IL)-6 markedly induces expression of p21 in hippocampus-derived murine NPC, which in turn, arrests proliferation of progenitors of neuronal lineage, while astroglial cells continued to proliferate (Zonis et al., 2013). This could be one of the mechanisms underlying cytokine-induced decreases in the expression of the early neuronal marker doublecortin (DCX), suggesting preferential differentiation into astrocytes rather than into neurons. High levels of cytokines induce apoptosis of newborn neurons (Ben-Hur et al., 2003; Iosif et al., 2006; Monje et al., 2003) and also trigger oxidative stress that directly damages developing neurons. As an example of an indirect mechanism, pro-inflammatory cytokines released in the periphery activate the HPA axis, and high levels of glucocorticoids strongly suppress NPC proliferation (Cameron and Glover, 2015). Interestingly, patients receiving glucocorticoid treatment for inflammatory conditions have been found to exhibit memory deficits (Wolkowitz et al., 1997), further suggesting a link between inflammation and HPA-axis-mediated NPC suppression.

In contrast to experiments with single cytokine exposure, multiple cytokines, chemokines, prostaglandins, and other inflammatory molecules and hormones act cooperatively in the course of acute or chronic peripheral inflammation. Peripheral administration of lipopolysaccharide (LPS), an experimental method commonly used to stimulate the innate inflammatory response, promotes release of the pro-inflammatory cytokines from peripheral immune cells that serve as critical mediators of the communication between the periphery and the CNS. Acute administration of LPS disrupts NPC proliferation (Kohman and Rhodes, 2013; Zonis et al., 2013), decreases differentiation into neurons, and reduces survival of neuroblasts (Ekdahl et al., 2003; Monje et al., 2003). Experiments with intraventricular LPS injections (Borsini et al., 2015; Ekdahl et al., 2009; Kohman and Rhodes, 2013) and *in vitro* studies (Borsini et al., 2015) show that, during an innate immune response, cytokines and activated microglia are, to a large extent, responsible for the decrease in neurogenesis.

It should be noted that, even though acute inflammation occurs within a limited time frame, the disruptive effects on neurogenesis can last longer because of the time required for the newly developed neurons to mature and integrate into the neuronal circuitry of the granule cell layer. Acute inflammation can lead to immediate changes in behavior, the so-called

“sickness behavior,” (Dantzer et al., 2008b), but it is unlikely that this is related to changes in neurogenesis because of the short latency (hours). By contrast, delayed disruptions in spatial memory and the depression-like behavior and anxiety seen with acute administration of LPS in rodents likely results from the long-lasting effects of LPS-induced inflammation on neurogenesis (Valero et al., 2014). Indeed, some patients with acute sepsis exhibit hippocampal atrophy (Semmler et al., 2013) and long-term cognitive impairment such as memory alteration, lack of attention, concentration, and/or global loss of cognitive function (Iwashyna et al., 2010; Semmler et al., 2013; Streck et al., 2008), and 30% of patients who survive critical acute illness develop depression (Dantzer et al., 2008a).

6. Chronic Peripheral Inflammation and Neurogenesis

Relatively few *in vivo* experimental models of chronic peripheral inflammatory diseases have been studied with regard to neurogenesis, and almost all have examined neurogenesis in the SGZ of the dentate gyrus of the hippocampus. Currently available data showing the consequences of chronic inflammatory states on hippocampal neurogenesis are summarized below. Because neurogenesis has been linked to memory and learning, depression, and stress regulations, a discussion of the effects of chronic inflammatory conditions on neurogenesis will focus on these specific domains.

6.1 Chronic intestinal inflammation

IBD, which comprises Crohn’s disease and ulcerative colitis, is a chronic inflammatory condition with a relapsing course. In addition to the peripheral immune system-to-brain communication, there is also a gut-brain axis, with the vagus nerve serving as a major two-way communicator (Bravo et al., 2011; Kennedy et al., 2014). Experimental models of IBD show a clear connection between intestinal inflammation and changes in brain function. For example, electrophysiological recordings of hippocampal slices from animals with chronic intestinal inflammation show enhanced excitability, likely due to increased tumor necrosis factor (TNF)- α signaling and microglial activation within the brain (Riazi et al., 2008).

Recently, we characterized the effects of chronic intestinal inflammation on hippocampal neurogenesis using a mouse model of IBD (Zonis et al., 2015). Repeated administration of cycles of dextran sodium sulfate in the drinking water produces colonic epithelial cell lesions; acute intestinal inflammation is seen 7–14 days after start of treatment, and chronic intestinal inflammation develops later. This pattern of acute disease exacerbation followed by remission similarly occurs in humans with IBD (Strober et al., 2002). During the acute phase of colitis, plasma levels of IL-6 are increased, accompanied by activation of resident hippocampal microglia, as well as increased levels of IL-1 β , TNF- α , and p21 in the hippocampus. As p21 is expressed in NPC and in early neuroblasts (Pechnick et al., 2011), it is plausible to consider that cytokine-induced p21 expression might be responsible for the decreased neurogenesis, given that nestin and brain lipid binding protein, both markers of NPC, as well as DCX, an early neuronal marker, are all decreased (Zonis et al., 2015). In mice, approximately 3 weeks are required for the new neurons to mature (Kempermann et al., 2003). Although the chronic phase of inflammation was not associated with microglial activation, the effects of microglia activation on day 7 were still apparent 3 weeks later (i.e.,

on day 29), as evidenced by the decreased number of DCX-positive early neurons. At the same time, glial fibrillary acidic protein (GFAP), a marker of astroglia, was increased, indicating continuing astrocyte activation.

It is difficult to extrapolate a reduction in neurogenesis to behavioral abnormalities because there are no data available on behavior in experimental animals with chronic intestinal inflammation. However, in patients with IBD, a high degree of comorbidity exists between functional gastrointestinal and neuropsychiatric disorders (Kennedy et al., 2014). Patients with IBD have a 2-fold increase in the rates of anxiety and depression, and these symptoms are more severe during periods of active disease (Graff et al., 2009). In addition, some patients show cognitive impairment (Kennedy et al., 2014). For example, IBD patients show deficits in affective memory recall, verbal IQ, and reduced prepulse inhibition, a form of information processing that is critical for normal cognitive functioning. Moreover, proton magnetic resonance spectroscopy has shown changes in brain structure (Chen et al., 2011) as well as evidence for abnormal hippocampal glutamatergic neurotransmission in IBD patients (Niddam et al., 2011).

6.2. Diabetes mellitus

Type 1 diabetes (TD1) is thought to arise from dysregulated B-lymphocytes triggering the generation of pancreatic β -cell autoantibodies (Atkinson, 2012). Activated innate immunity and an acute-phase inflammatory response, including raised concentrations of circulating IL-6, TNF- α , and IL-1 β , are implicated in the pathogenesis of type 2 diabetes (TD2) (Donath and Shoelson, 2011; Moulton et al., 2015). Although TD1 and TD2 have different pathogeneses, both diseases are characterized by activation of innate immunity (Bach et al., 2004). Observed sustained increases in circulating cytokines can produce microglia activation, with a subsequent reduction in neurogenesis. However, metabolic dysregulation, including brain glucose metabolism, hyperglycemia, hyperinsulinemia, and hypercholesterolemia, are also observed in these models, all of which can affect neurogenesis (Anderson et al., 2002; Rafalski and Brunet, 2011). This may make it difficult to parse the specific effects of inflammation.

Of the three animal models of TD2, db/db mice and Zucker rats exhibit decreased NPC proliferation and survival; Goto-Kakizaki rats demonstrate an increase in NPC proliferation, but survival is either decreased or unchanged (Ho et al., 2013). Importantly, treatment with the anti-inflammatory drug indomethacin blocks decreases in neurogenesis in the streptozocin-induced model of TD1. This finding supports the view that inflammation and activated microglia are responsible for neurogenesis suppression in diabetes mellitus. Studies in both TD1 and TD2 rodent models found decreased dendritic branching of the neurons (i.e., decreased plasticity) and decreased hippocampal long-term potentiation, a cellular mechanism thought to underlie some forms of learning and memory (Bliss and Collingridge, 1993). In animal models of diabetes, reduced neurogenesis is associated with learning and memory deficits and depression-like behavior. Both the reduced hippocampal neurogenesis and the behavioral manifestations can be reversed by insulin treatment (Ho et al., 2013), further supporting the mechanistic links between diabetes, abnormal neurogenesis, and behavior (Stranahan, 2015).

In both TD1 and TD2 patients, magnetic resonance imaging studies show evidence of hippocampal atrophy (Ho et al., 2013), and patients show an increased risk for developing dementia and cognitive impairment (Koekkoek et al., 2014; Reagan, 2012). Although TD2 tends to be a disease of older individuals, and, as discussed in Section 6.4, aging can also affect cognitive function, cognitive impairment also occurs in TD1, which develops earlier in life (Tonoli et al., 2014), suggesting an independent association.

Activation of the immune system and increased levels of pro-inflammatory cytokines in diabetic patients and in animal models might directly suppress hippocampal neurogenesis, but it also can act indirectly by activating the HPA axis and increasing levels of circulating glucocorticoids. Indeed, increased production of glucocorticoids has been found in experimental animals (Ho et al., 2013; Stranahan, 2015) and in diabetic patients (Moulton et al., 2015). There also is a strong link between both types of diabetes and depression (Moulton et al., 2015), and cytokine-induced activation of the HPA axis has been proposed as a common mechanism underlying these two conditions (Moulton et al., 2015).

6.3 Obesity

Obesity is the driver of metabolic syndrome and a well-recognized risk factor for developing TD2. Many obese individuals also are prediabetic or have TD2, thus confounding experimental and clinical studies of obesity and cognition.

Obesity and overnutrition are associated with chronic low-grade inflammation in peripheral tissues as well as increased secretion of cytokines by adipose tissue (Cai, 2013; Wisse, 2004). Mice given a high-fat diet exhibit obesity and physiological signs of TD2, including increased insulin and glucocorticoid secretion (Ho et al., 2013). Importantly, these mice also have increased expression of pro-inflammatory cytokines in the hippocampus (Boitard et al., 2014), likely leading to decreased NPC proliferation. This decrease in hippocampal neurogenesis in high-fat-diet mice may also be due to increased lipid peroxidation and decreased levels of brain-derived neurotrophic factor (Molteni et al., 2002), a critical mediator of neuronal survival and plasticity.

Studies of cognition in obese animals show impaired learning and performance. In a variable-interval delayed alternation test of learning and memory, there were no between-group differences in learning the alternation rule or at short intervals, but, compared with non-obese rats, obese rats were impaired at longer intervals, where performance is hippocampus-dependent (Winocur et al., 2005). Other studies have shown impaired performance in spatial learning, long-term memory tasks, and contextual fear conditioning (Castanon et al., 2015), and some animal models of obesity show depression-like behavior in the forced swim and tail suspension tests. Interestingly, in some studies, the depression-like behavior only occurred under stressful conditions or when the animals were challenged with LPS (Castanon et al., 2015), lending further support to a link between inflammation, stress, and behavior changes.

In humans, obesity has been associated with depression (Martin-Rodriguez et al., 2015) as well as cognitive impairment, including deficits in complex attention, verbal and visual memory, and decision making (Martin and Davidson, 2014; Prickett et al., 2015).

It has also been suggested that impairment in attentional processes as well as working and episodic memory in obese individuals might contribute to loss of control over food intake (Martin and Davidson, 2014). However, studies linking obesity and cognitive impairment should be interpreted cautiously, as methodological limitations and numerous potential confounding factors have been noted (Prickett et al., 2015).

6.4 Aging

A hallmark of aging is dysregulation of both adaptive and innate immune responses in the periphery and in the brain. With age, there is a reduction in T-cells, including CD4+T cells; an increased number of innate immune cells, including monocytes, neutrophils and natural killer cells; and increased levels of circulating pro-inflammatory cytokines and C-reactive protein. Together, this creates a state of chronic, low-grade inflammation or “inflammaging” (Franceschi et al., 2007). In addition, the permeability of the blood-brain barrier increases, especially in the hippocampus (Montagne et al., 2015), which may allow peripheral inflammatory mediators to directly enter the CNS and activate microglia. In turn, this can produce reactive oxygen species and/or pro-inflammatory cytokines that inhibit neurogenesis. Indeed, protein levels of cytokines are increased in the brain of aged animals. Furthermore, IL-6, TNF- α , and IL-1 β production increase with age in response to LPS stimulation, indicating that aging microglia are more responsive to inflammatory stimuli (Xie et al., 2003), and the production of these pro-inflammatory cytokines can both decrease proliferation and increase apoptosis (Iosif et al., 2006; Zonis et al., 2013). The proliferative activity of NPC is greatly reduced in the hippocampus of aged animals and maturation of new neurons is delayed, as assessed by a reduction in the number of dendritic nodes and the expression of NeuN, a marker for mature neurons. Similar age-related reductions in neurogenesis and cell proliferation have been found in non-human primates (Lee et al., 2012).

Chemokines might also be involved in aging-related decreases in neurogenesis. The chemokine fractalkine, or CX3CL1, is a neuroimmune regulator that inhibits microglia activity and cytokine release under inflammatory conditions. Fractalkine is reduced in the hippocampus of aged animals, leading to increased microglia activation and decreased neurogenesis (Bachstetter et al., 2011). By contrast, other chemokines, including CCL11, are increased in the aging mouse and human blood as well as in cerebrospinal fluid (CSF), and they suppress proliferation of NPC (Villeda et al., 2011). Other factors may also play a role, such as the age-related increased levels of glucocorticoids caused by increases in circulating cytokines observed in animal models and humans (Lee et al., 2012; Stein-Behrens and Sapolsky, 1992).

Age-related cognitive impairment and the link between aging and depression seem to be associated with a number of factors that affect hippocampal neurogenesis. For example, an association has been found between aging-related cognitive decline in healthy older adults and elevated plasma levels of IL-6 (Kennedy et al., 2014), and individuals with hyperactivity of the HPA axis frequently show depression (Cameron and Glover, 2015) as well as a decline in hippocampal-mediated episodic memory performance (Lupien et al., 1994).

Aging-related depression has been linked to increased activation of the immune system and associated inflammation (Singhal et al., 2014).

6.5. SLE

Evidence for a link between inflammation and cognitive changes in SLE is seen in studies of two mouse models: MRL/lpr mutant and B-cell activating factor of the TNF family (BAFF) transgenic mice. MRL/lpr mice, which develop a systemic autoimmune disease similar to SLE in humans, show a decrease in the size of the dentate gyrus by five months of age. Although increased cell proliferation is seen in the SGZ, survival of newly developing neurons is markedly decreased. When cell survival and neuronal differentiation are taken into account, it is estimated that net neurogenesis is decreased approximately 3-fold compared to normal controls. In addition, there is decreased proliferation in the dorsal part of the rostral migratory stream, but a paradoxical increase in proliferation in the paraventricular nucleus (PVN) of the hypothalamus. (Stanojcic et al., 2009). Such increases in proliferation might reflect an attempt to compensate for the decrease in neuronal survival. Activation of the PVN could cause up-regulation of the HPA axis found in MRL/lpr mice (Lechner et al., 1996), which also can reduce neurogenesis. The MRL/lpr mice show anxiety-like behavior and cognitive deficits, including poor spatial learning revealed through the Morris water maze and the spontaneous alternation test (Ballok, 2007). The cognitive deficits as well as depressionlike behavior are seen at the onset of autoimmunity.

B-cell activating factor of the TNF family (BAFF) is essential for the maturation and survival of peripheral B cells, and BAFF transgenic mice develop autoantibodies and an autoimmune syndrome reminiscent of autoimmune disease, including SLE, Sjögren's syndrome, and rheumatoid arthritis (Crupi et al., 2010). These animals exhibit brain inflammation as reflected by increases in total levels of IgG and in CD68 antigen, a marker of the macrophage lineage. Although levels of cytokines in the hippocampus have not been examined, it is likely that microglia are activated in these mice. In the hippocampus, GFAP expression is increased, whereas the number of developing neurons is reduced and the dendritic morphology of these cells is altered, indicating decreased plasticity of the newly developing neurons. Indeed, these changes have been associated with anxiety-like behavior and impaired long-term potentiation (Crupi et al., 2010). In humans, SLE is frequently accompanied by neurologic and psychiatric complications, neuronal degeneration, damage to the blood-brain barrier, and brain atrophy (Stanojcic et al., 2009), and cognitive impairment and depression are common (Meszaros et al., 2012).

7. Conclusions

We have discussed pathologic conditions that involve inflammatory responses in both the periphery and the central nervous system. To confirm causative relations between chronic systemic inflammation, neurogenesis, and behavior, several important questions need to be addressed and methodological limitations have to be considered.

Although there are substantial data showing a link between chronic inflammation and decreases in adult hippocampal neurogenesis, few preclinical studies have examined the relationships among adult neurogenesis, chronic inflammation, and hippocampal-dependent

behaviors. Future studies should focus on experimental models of systemic inflammatory illnesses in which neurogenesis is conditionally ablated or increased by drugs or other experimental manipulations (e.g., exercise).

It is important to note that the response to chronic peripheral inflammation is profoundly affected by activation of the HPA axis and the release of endogenous glucocorticoids. It remains challenging to dissect the effects of inflammation per se from the complex multifaceted responses to these pathological conditions. Furthermore, many chronic inflammatory conditions are treated with high doses of glucocorticoids, which suppress hippocampal neurogenesis. Although this approach might improve the inflammatory state, it may actually worsen the behavioral disturbances.

Illnesses involving chronic inflammation are associated with cognitive impairment, deficits in learning and memory, and depression in humans. Although the effects of these diseases on adult hippocampal neurogenesis have not yet been characterized, it is plausible to hypothesize that inflammation-induced disruption of neurogenesis might underlie these behavioral disturbances, especially when inflammation persists for an extended period of time (Figure). Many of these chronic disorders follow a course with varying periods of relapse and remission. If inflammation-induced disruption of neurogenesis underlies the behavioral problems, then the magnitude of inflammation and degree of behavioral disturbance should follow a similar time course. In IBD patients, depression is more severe during periods of active disease (Graff et al., 2009), but there is little information on the relationship between the intensity of the inflammatory state and extent of behavioral disturbance. A major limitation to testing this hypothesis is that neurogenesis cannot be imaged or otherwise measured in living human subjects. A method to visualize and quantitate hippocampal neurogenesis in patients suffering from chronic inflammatory conditions would provide a major breakthrough in this area of research.

A question of critical importance is whether treating the chronic inflammatory state reduces the cognitive impairment, deficits in learning and memory, or depression. Interestingly, many antidepressant drugs have anti-inflammatory effects (Hannestad et al., 2011). Anti-inflammatory drugs have been found to have some efficacy in the treatment of depression (Fond et al., 2014; Na et al., 2014); however, most of these studies were carried out in patients that did not have chronic inflammatory conditions. In one study examining the efficacy of the TNF- α antagonist etanercept in treatment of psoriasis, participants exhibited significant improvement in depressive symptoms, an effect independent of improvement of disease severity (Tyring et al., 2006). To our knowledge, no clinical studies have been carried out to determine whether treating the inflammatory state alleviates cognitive impairment and deficits in memory and learning, and absence of these data represents a fundamental gap in our knowledge base. A number of classes of drugs and other procedures (e.g., exercise) can stimulate hippocampal neurogenesis, but to our knowledge, neither preclinical nor clinical studies have been carried out to determine whether they reduce the behavioral sequelae of chronic inflammatory conditions.

Much work remains to be done, but it is possible that a deeper understanding of the interplay between different aspects of inflammation and adult hippocampal neurogenesis may help to

develop future strategies to treat and/or prevent the behavioral disturbances that occur in patients with chronic inflammatory disorders.

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Highlights

- Chronic systemic illnesses, metabolic disorders, and aging create a state of chronic peripheral inflammation
- Pro-inflammatory cytokines produced in the periphery communicate with the brain and activate resident microglia
- Activated microglia locally release pro-inflammatory cytokines that disrupt hippocampal neurogenesis
- Disruption of hippocampal neurogenesis might underlie the cognitive impairment, learning deficits, and mood disorders observed in patients with chronic inflammatory conditions and might also contribute to behavioral disturbances that occur in aging patients

Figure.

Proposed pathways showing the converging effects of chronic peripheral inflammatory disease on neurogenesis and behavior. The SGZ of hippocampus. Inflammation in the periphery is communicated to the brain via humoral and neural pathways. Resident microglia are activated and release pro-inflammatory cytokines that disrupt hippocampal neurogenesis. Peripheral cytokines activate the HPA axis and increased circulating glucocorticoids also suppress neurogenesis. Reduced neurogenesis might underlie some of

the neurobehavioral changes associated with chronic inflammatory conditions. Pink, DCX-positive cells in the SGZ. Blue, DNA specific dye DAPI for nuclei staining.

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