Mechanisms of Hippocampal Aging and the Potential for Rejuvenation

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Abstract

The past two decades have seen remarkable progress in our understanding of the multifactorial drivers of hippocampal aging and cognitive decline. Recent findings have also raised the possibility of functional rejuvenation in the aged hippocampus. In this review, we aim to synthesize the mechanisms that drive hippocampal aging and evaluate critically the potential for rejuvenation. We discuss the functional changes in synaptic plasticity and regenerative potential of the aged hippocampus, followed by mechanisms of microglia aging, and assess the cross talk between these proaging processes. We then examine proyouth interventions that demonstrate significant promise in reversing age-related impairments in the hippocampus and, finally, attempt to look ahead toward novel therapeutics for brain aging.

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INTRODUCTION

With age, the brain progressively loses its ability to physically and functionally adapt to new stimuli. This decline in plasticity manifests as striking impairments in various cognitive abilities and increases vulnerability to neurodegenerative disorders. Until recently, age-related cognitive decline was considered an inevitable aspect of human life; recent investigations into the cellular and systemic drivers of brain aging, however, strongly suggest otherwise. Brain aging is, in fact, a mutable process, raising the tantalizing possibility that age-related cognitive impairments might be slowed or even reversed. Although aging disrupts functionality in many areas of the brain, the hippocampus, situated in the medial temporal lobe, is particularly susceptible to age-related decline in cognitive abilities normally ascribed to this area, including spatial and episodic learning and memory (**Figure 1**). In this review, we focus on the intricacies of hippocampal aging, although many of the synaptic, cellular, and systemic changes described—and potential interventions for reversing such changes—may also apply to other brain regions ravaged by aging, such as the prefrontal cortex.

AGING AND FUNCTIONAL DECLINE: SYNAPTIC PLASTICITY AND HIPPOCAMPAL-DEPENDENT COGNITIVE FUNCTION

DG: dentate gyrus

The hippocampus is a complex structure composed of functionally distinct subregions: the dentate gyrus (DG), CA1, CA2, CA3, and subiculum (**Figure 1**). Information processing in the hippocampus occurs through a mostly unidirectional circuit, the trisynaptic pathway, whereby projections

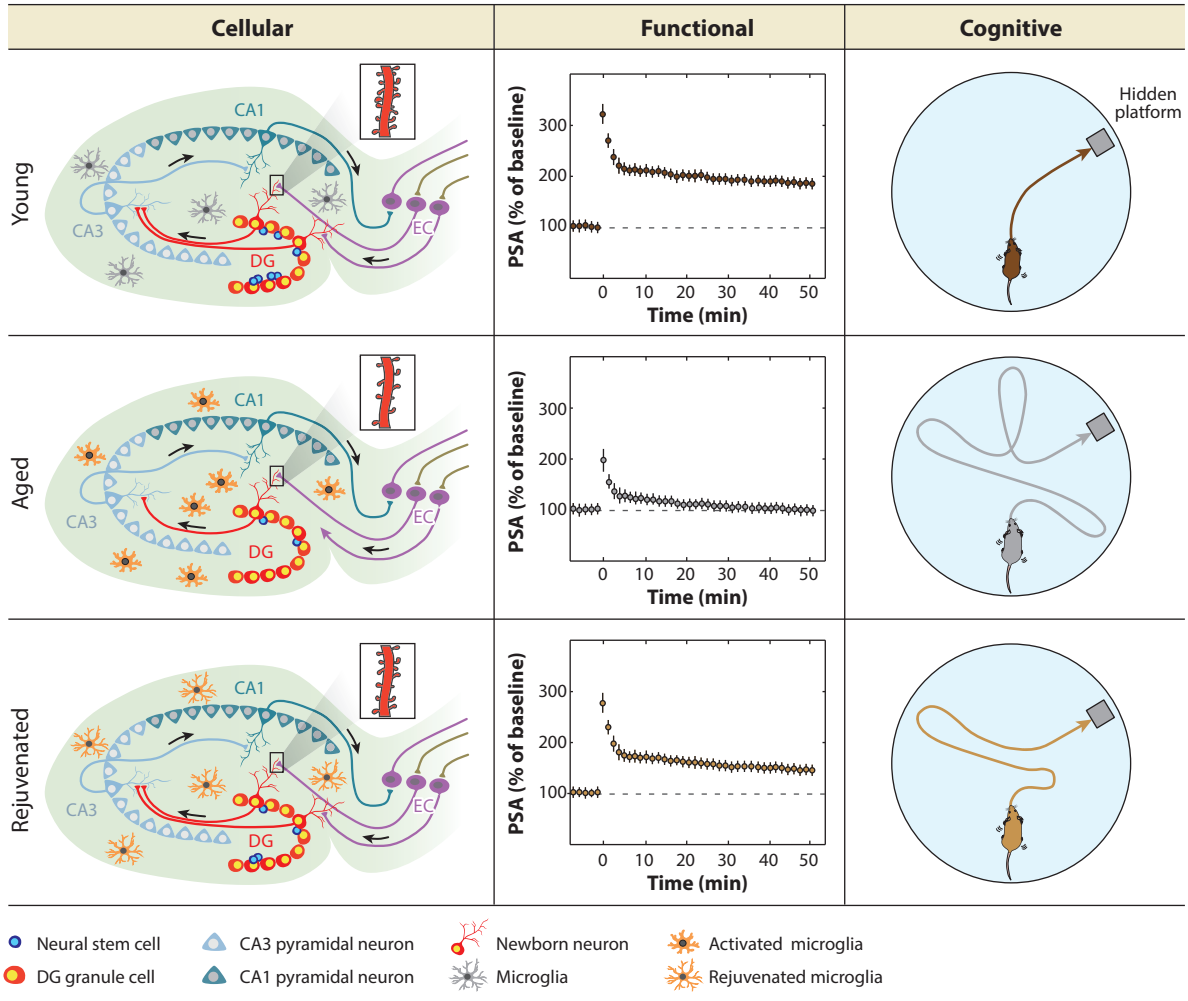

Figure 1

Hallmarks of hippocampal aging and rejuvenation. Cellular, functional, and cognitive processes are altered during aging and rejuvenation in the adult hippocampus. Changes in synaptic spines, adult neurogenesis, and microglia activation result in impaired synaptic plasticity, shown here as the age-dependent decline in long-term potentiation amplitude, which in turn impedes performance in spatial learning and memory tasks. Abbreviations: DG, dentate gyrus; EC, entorhinal cortex; PSA, population spike amplitude.

from the entorhinal cortex (EC) connect to the DG via the perforant path, which in turn gives rise to mossy fibers that terminate within both the DG and CA3. Fibers projecting from CA3, termed Schaffer collaterals, innervate CA1, and finally CA1 outputs to the subiculum and the EC (Eichenbaum 2004). Granule cells and pyramidal cells are the primary excitatory neurons within the DG, CA1, and CA3, respectively, and their activity levels are regulated tightly by a heterogeneous population of inhibitory neurons. Within the DG, the subgranular zone (SGZ) is a major neurogenic region populated by neural progenitor cells (NPCs) (Kempermann 2015). Both mature hippocampal neurons and NPCs interact extensively with glia cells, microglia (resident macrophages), and the neurovasculature, resulting in a bidirectional regulation of cellular

SGZ: subgranular zone

NPC: neural progenitor cell

functionality. Synaptic plasticity, the activity-dependent changes in the strength of synaptic connections between neurons, is thought to underlie hippocampal-dependent spatial and episodic learning and memory (Volianskis et al. 2015). With age, intracellular and intercellular changes within the hippocampus contribute to a gradual loss of synaptic plasticity that acts as a major driver of age-related functional and cognitive decline (**Figure 1**).

Age-Related Neuronal Changes

Modern advances in postmortem tissue analysis and in vivo imaging have converged to establish aging does not elicit significant neuronal death in the hippocampus of humans, nonhuman primates, or rodent models. Rather, investigations into hippocampal aging have expanded to include characterizations of molecular and cellular processes in order to elucidate how they collectively drive the aging process at the neuronal level.

Molecular changes. Transcriptional analysis of the aging hippocampus using RNA sequencing has revealed a specific age-associated gene expression signature, with deregulation of coding genes, noncoding RNAs, and aberrant RNA splicing (Stilling & Fischer 2011). Exon usage analysis has also revealed an age-dependent enrichment in aberrant splicing of neuronal genes associated with morphology, synapse formation, synaptic transmission, and synaptic plasticity (Stilling & Fischer 2011). At the chromatin level, histone tail modification by histone deacetylases (HDACs) has been linked to brain aging and hippocampal cognitive decline (Dos Santos Sant' Anna et al. 2013, Peleg et al. 2010, Stilling & Fischer 2011). Expression of HDAC2 in particular increases with age in neuronal regions of the hippocampus and negatively regulates plasticity-related gene expression (Chouliaras et al. 2013, Guan et al. 2009). A recent cognitive study of impaired versus unimpaired aged rats further indicated the landscape of hippocampal histone modifications is dependent on age, cognitive capacity, and hippocampal subregion (Castellano et al. 2012). At the genomic level, experience-dependent changes in methylation levels have been identified as necessary for synaptic plasticity and hippocampal-dependent learning and memory (Levenson et al. 2006, Miller & Sweatt 2007). Expression of DNA methyltransferase *Dnmt3a2* decreases with age in the hippocampus, and mimicking this age-related decline by RNA interference impairs hippocampal-dependent cognition in adult mice (Oliveira et al. 2012). Collectively, these findings point to age-related changes in transcriptional and epigenetic regulation as potential drivers of hippocampal aging, although future investigations are needed to provide in-depth mechanistic insight.

Cellular changes. Many cellular processes underlying neuronal homeostasis have been investigated increasingly in the aging hippocampus, including glucose metabolism, oxidative stress, and autophagy. The functional capacity of a healthy neuron relies heavily on available adenosine triphosphate (ATP) levels, sourced from cellular glycolysis as well as localized mitochondrial production. Reports have shown that resting cellular glucose and ATP levels do not differ in the young and aged brain, but under metabolic demand an age-dependent disruption in metabolism occurs (Kantarci et al. 2010, Tack et al. 1989). Additional reports indicate neuronal glucose uptake is impaired in the aging hippocampus, and the abundance of enzymes associated with glycolysis and gluconeogenesis declines with age (Ding et al. 2013, Freeman et al. 2009). Increased mitochondrial dysfunction has also been characterized in the aging brain, leading to decreased capacity for ATP production and increased production of reactive oxygen species (ROS) (Navarro et al. 2008, Weinreb et al. 2007). Although ROS have been identified as signaling molecules that promote synaptic plasticity, accumulation of ROS with age is believed to cause oxidative stress, which instead can impair synaptic plasticity (Hu et al. 2006). More recently, researchers proposed a link between

aging-impaired mitochondrial activity and synaptic function of complex neuronal networks in the hippocampus (Lu et al. 2012). Nuanced cross talk between oxidative stress and autophagy has been emerging from the literature, and deterioration of neuronal autophagy has been identified as a hallmark of brain aging, implicated in neuropathology (Filomeni et al. 2015, Lee et al. 2012, Ling & Salvaterra 2011, Lipinski et al. 2010). Roles for neuronal autophagy in mediating synaptic plasticity and hippocampal cognitive decline have also been suggested (Dong et al. 2015, Shehata et al. 2012). Taken together, these findings represent several interconnected mechanisms of hippocampal aging, highlighting the complexity of the aging process at the intracellular level.

LTP: long-term potentiation

Age-Related Synaptic Dysfunction

Long-term potentiation (LTP) and long-term depression (LTD), the persistent strengthening and weakening of synaptic connections, are both necessary for proper memory regulation. Electrophysiological stimulation of the hippocampal circuitry reveals an age-dependent decrease in excitatory postsynaptic potential, as well as reduced induction of LTP and increased facilitation of LTD, indicating overall impairments in excitatory synaptic function consistent with observed cognitive decline (Deupree et al. 1993, Norris et al. 1996, Rosenzweig et al. 1997).

Initiation of hippocampal LTP depends on increased surface localization of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluR1 via site-specific phosphorylation and is sustained by long-term *N*-methyl-D-aspartate (NMDA) receptor expression (Lee et al. 2003, Niewoehner et al. 2007). Analysis of hippocampal CA1 tissue revealed a significant decrease in GluR1 surface expression and site-specific phosphorylation in learning-impaired aged rats, linking GluR1 dynamics with age-related cognitive impairments (Yang et al. 2015). A significant decrease in NMDA receptor subunit GluN1 has been characterized in aging rat hippocampal CA2 and CA3 regions as well (Liu et al. 2008). Shotgun proteomics studies have also identified broad, age-dependent changes in the hippocampal synaptoproteome, the landscape of proteins localized to pre- and postsynaptic regions. Analysis of male hybrid aged rats revealed reductions in proteins that regulate presynaptic vesicle dynamics, such as synapsin-1, syndapin-1, and clathrin, as well as the postsynaptic structural proteins internexin, actin, and tubulin isoforms (VanGuilder et al. 2010). Additional analyses from this study revealed age-dependent reductions in synaptophysin, postsynaptic density 95, and soluble NSF attachment protein receptor (SNARE) family protein expression. An independent proteomics study of the female rat hippocampal synaptoproteome revealed contradictory age-dependent increases in actin and SNARE family protein levels, suggesting the possibility of species- or sex-dependent variation in synaptoproteome aging (Sato et al. 2005). Nevertheless, these findings point collectively to significant alterations at the level of presynaptic vesicle release and recycling, as well as in synaptic structural dynamics. Indeed, a third proteomics study has further corroborated age-dependent dysregulation of neuronal cytoskeleton markers, in addition to a curious upregulation of extracellular matrix (ECM) markers with age in the hippocampus (Végh et al. 2014). Although researchers have established recently that ECM properties influence synaptic structure and stability in adulthood directly (Levy et al. 2014), these proteomics data suggest a novel role for ECM stiffness in regulating hippocampal synaptic dynamics with aging.

Evaluation of synaptic structure has expanded in recent years from classically static measurements of density and size to measurements of real-time dynamic remodeling. Not surprisingly, snapshots of synaptic structure in fixed tissue have amassed somewhat controversial results; researchers have observed reductions in synaptic spine number in the aging mouse hippocampus, but the evidence remains contentious in rat or human hippocampal tissue (Flood & Coleman 1990, Geinisman et al. 1986, Markham et al. 2005, Nicholson et al. 2004). A longitudinal study using

two-photon imaging of live cortical neurons revealed a surprising age-dependent increase in the stability of newly formed spines and axonal boutons but a decrease in long-term retention of these structures (Mostany et al. 2013). The authors propose this unbiased stabilization of short-lived synaptic structures may be forming inefficient neuronal networks that contribute to age-related cognitive impairments. It remains to be determined, however, exactly how hippocampal spine dynamics are altered with age and how changes in cytoskeletal structure or ECM composition may play a role in mediating impairments in hippocampal plasticity, learning, and memory.

Age-Related Cognitive Impairments

Although severe forms of cognitive dysfunction such as dementia commonly arise owing to age-related neurodegenerative disorders, such as Alzheimer's disease, some healthy aging individuals experience significant impairments in higher-order cognitive functions, including hippocampal-dependent spatial and episodic learning and memory (Hedden & Gabrieli 2004, Hertzog et al. 2003, Oberauer et al. 2003). Impairments in hippocampal-dependent cognitive functions mimicking human aging have also been reported in animal models, including rodents and nonhuman primates. For example, the rodent has been an extensively tested model system employed for investigating mammalian hippocampal aging because of its adequately sophisticated hippocampus and modest two-year lifespan. Rodent model organisms display significant age-dependent impairments in spatial learning and memory via the Morris and radial arm water mazes (de Fiebre et al. 2006, Villeda et al. 2014) and Barnes maze (Bach et al. 1999), as well as declines in episodic memory via the contextual fear conditioning paradigm (Moyer & Brown 2006, Villeda et al. 2014). Testing on elderly humans in a virtual reality–based Morris water maze revealed cognitive impairments in spatial learning and memory, compared to young adult controls, that mimic those observed in rodents (Driscoll et al. 2003).

The use of model organisms has been an invaluable approach to begin investigating cellular and molecular mechanisms underlying hippocampal aging and cognitive decline. Although numerous neuronal factors that change with age have been identified, few have been demonstrated as functional mediators of cognition within the context of hippocampal aging, highlighting the urgency for identifying functional molecular mediators of age-related cognitive decline (Oliveira et al. 2012, Pavlopoulos et al. 2013, Villeda et al. 2014). To date, mouse models have led to the discovery of epigenetic mediators of age-related hippocampal cognitive decline, such as *Dnmt3a2* and *RbAP48*. Loss of these factors in young hippocampi promoted cognitive impairments, and restoration in aged hippocampi ameliorated cognitive impairments, supporting the notion that brain aging is mediated in part by molecular alterations (Oliveira et al. 2012, Pavlopoulos et al. 2013). Additionally, investigators have also developed genetic mouse models of senescence-accelerated aging, such as SAMP8, that display premature impairments in hippocampal cognition (Yanai & Endo 2016). This area of research represents a burgeoning field that will benefit greatly from in-depth molecular analysis at the transcriptional and epigenetic levels to gain proper mechanistic insight into the drivers of cognitive decline in the aging hippocampus.

AGING AND REGENERATIVE DECLINE: ADULT STEM CELLS AND HIPPOCAMPAL NEUROGENESIS

In the adult brain, new neurons are generated continuously from localized pools of NPCs and progress through several stages of maturation, ultimately becoming functional, mature, new neurons that integrate into existing neural circuits. Within the hippocampus, adult neurogenesis occurs in the SGZ of the DG, where neural stem cells (NSCs) reside in close proximity to the

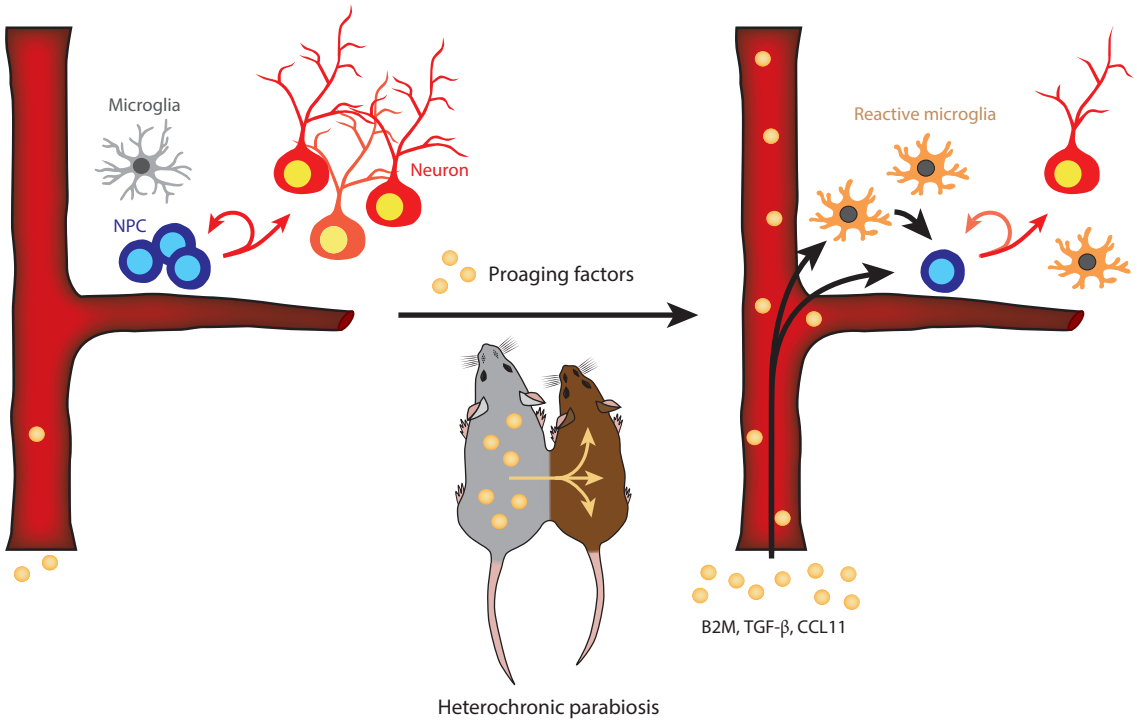

Figure 2

Age-related changes in the hippocampal neurogenic niche. This schematic highlights three major components affected by aging, adult neurogenesis, microglia activation, and the systemic environment. Blood-borne proaging factors (depicted by heterochronic parabiosis, or the surgical conjoining of the circulatory system of an aged animal to that of a young one) activate microglia and perturb proliferation of NPCs, resulting in decreased neurogenesis. Abbreviations: B2M, β2-microglobulin; CCL11, C-C motif chemokine 11; NPC, neural progenitor cell; TGF-β, transforming growth factor-β.

neurovasculature (Fuentealba et al. 2012) (**Figure 2**). Despite initial controversy, human neurogenesis in the DG is now generally accepted and revealed to be quite substantial. Indeed, about one-third of granule cells slowly turn over in adult humans, a number that declines precipitously with age (Spalding et al. 2013). How impaired neurogenesis in the DG contributes to age-dependent hippocampal cognitive decline is subject to intense scientific scrutiny. Nevertheless, the decrease in neurogenesis over the course of a life is often (although not always) associated with a decline in hippocampal-dependent cognition (Drapeau et al. 2003, Merrill et al. 2003, Seib et al. 2013), suggesting age-related neurogenesis impairments may contribute to hippocampal functional loss.

Age-Related Decline in Adult Neurogenesis

The process of neurogenesis is well documented through the use of a variety of molecular markers, allowing careful dissection of the effects of age on each stage of neurogenesis. Glial fibrillary acidic protein– and nestin-positive NSCs are subdivided into two populations: quiescent radial glia–like (RGL) cells and actively dividing horizontal cells that generate neurons and glia. Dividing NSCs give rise to T-box brain protein 2 (Tbr2)-positive, lineage-restricted NPCs that eventually become doublecortin (Dcx)-positive immature neurons, which migrate into the granule cell layer

NSC: neural stem cell

and, following a wave of apoptosis, differentiate into NeuN-positive mature neurons (Christian et al. 2014).

In mice, aging is associated with a decreased number of NSCs (Encinas et al. 2011), a reduced number of transiently proliferating cells (Ben Abdallah et al. 2010), and a decrease in total cell proliferation (Kuipers et al. 2015, Seki & Arai 1995) (**Figure 2**). Notably, the decline in NSCs is not uniform across populations, with a dramatic loss of nestin-positive cells but relative preservation of Sox1-positive progenitor cells (Kuipers et al. 2015). Currently, it is unclear whether quiescent RGL cells also experience age-related depletion. However, the fact that certain stimuli—such as environmental enrichment (Kempermann et al. 2002) and exercise (van Praag 2005) (**Figure 1**)—can increase neurogenesis in aged rodents suggests there is a population of quiescent cells capable of producing NPCs actively even in old age. With regards to proliferation, in adult mice between one and nine months of age, Ki67-positive transiently amplifying cells decline exponentially (Ben Abdallah et al. 2010), with a concomitant decrease in Tbr2- or Dcx-positive neuroblasts and immature neurons (Gebara et al. 2013). By 12 months old, the number of proliferating Dcx-positive cells declines by almost 90% compared to young adults (Kuipers et al. 2015). Although the migration and maturation of immature neurons are delayed with age (Heine et al. 2004), the changes are minimal, as is the rate of apoptosis (Rao et al. 2006). Thus, the age-related decline in neurogenesis is attributed mainly to decreased proliferation.

Drivers of Age-Associated Changes in Neurogenesis

Intrinsic changes. Despite a relative shortage of detailed data, several cell-intrinsic changes have been proposed to contribute to the decline in neurogenesis with age. Lineage tracing suggests that NPCs undergo a division-coupled conversion into terminally differentiated astrocytes, leading to an age-related exhaustion of the NPC pool (Encinas et al. 2011). The mechanisms of this conversion are unknown. Epigenetic mechanisms, such as DNA methylation, DNA hydroxymethylation, and chromatin remodeling, are crucial regulators of NPC self-renewal and differentiation (Yao et al. 2016) and thereby present an additional way to impact neurogenesis during the aging process. For example, ten-eleven translocation methylcytosine dioxygenase 1 (TET 1) protein, which converts 5-methylation to 5-hydroxymethylation (5hmC), has been shown to regulate neurogenesis-related genes in the hippocampus and impair spatial learning and memory (Zhang et al. 2013). Given that 5hmC levels may change with age in the hippocampus (Chen et al. 2012, Szulwach et al. 2011), future studies should investigate the role of TET proteins in age-related neurogenesis decline. Finally, stem cell telomerase activity, mitochondrial dynamics, and metabolism have been implicated in the regulation of NPCs (Jaskelioff et al. 2011, Khacho et al. 2016), but their effects on hippocampal NPCs in the context of aging remain to be studied.

The neurogenic niche. Neurogenesis is supported by a specific microenvironment, the neurogenic niche, comprising NPCs, astrocytes, microglia, neurovasculature, and the ECM (Kempermann 2015). Within the niche, direct cell-to-cell contact, paracrine and systemic signaling of growth factors, and immune factors regulate neurogenesis. Aging alters niche properties, which may precede the decline in neurogenesis (**Figure 2**).

Aging results in a progressive loss of Wnt-3 expression levels in hippocampal astrocytes with a concomitant decrease in the NSC marker NeuroD1 (Okamoto et al. 2011), implicating the Wnt signaling pathway in the decrease of neurogenesis. This may be due in part to decreased expression of Wnt-regulated survivin in the DG, which leads to increased NPC quiescence in aged animals (Miranda et al. 2012). Consistently, the Wnt inhibitor Dickkopf 1 increases with age, and its NPC-specific deletion promotes neurogenesis in the DG of aged animals and rescues performance in a hippocampal-dependent spatial task (Seib et al. 2013).

Neurotrophic and growth factors are additional cell-extrinsic regulators of neurogenesis (**Figure 2**). The levels of these factors—for example, brain-derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF-2), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor—and their receptors decrease early in the aging process, which may be due to decreased local production by aging hippocampal astrocytes (Shetty et al. 2005) and lower overall systemic levels. Activating FGF signaling via gain-of-function overexpression of the constitutively active *Fgf3r* is sufficient to rescue the age-related neurogenesis decline in aged mice (Kang & Hebert 2015), as is the exogenous application of IGF-1 (Lichtenwalner et al. 2001). In contrast, chronically increased levels of glucocorticoids (GRs) in aged animals decrease neurogenesis (Heine et al. 2004). Acute inhibition of GR receptors increases neurogenesis in aged rats (Mayer et al. 2006), and chronically blocking GR signaling via adrenalectomy rescues age-dependent neurogenesis decline (Cameron & McKay 1999). Finally, age-induced microglia activation and proinflammatory factors impact neurogenesis negatively, and blocking their signaling increases neurogenesis in aged rodents. Together, these studies point to niche and systemic factors as crucial regulators of neurogenesis and illustrate the importance of neuro-immune cross talk.

The neurovasculature is a critical nexus connecting the neurogenic niche with the systemic environment, and its age-related changes have been proposed to impact neurogenesis (**Figure 2**). Aging results in decreased blood perfusion specifically in the DG (Pereira et al. 2007) within the hippocampus and loss of blood–brain barrier integrity in the DG and CA1 (Montagne et al. 2015), suggesting that the neurogenic niche is particularly sensitive to vascular changes with age.

The systemic milieu. Heterochronic parabiosis, in which the circulatory systems of an aged and young animal are conjoined, indicates an old systemic milieu elicits a striking aging effect on neurogenesis and hippocampal-dependent cognition (Villeda et al. 2011) (**Figure 1**). The major histocompatibility complex class I (MHC class I) component β2-microglobulin (B2M) and cytokines TGF-β1 and C-C motif chemokine 11 (CCL11) have so far been identified as blood-borne proaging factors (Smith et al. 2015, Villeda et al. 2011, Yousef et al. 2015). The levels of these factors elevate in the plasma and hippocampus with age, and inhibiting their signaling via blocking antibodies, genetic depletion, or pharmaceutical agents rescues the decline in neurogenesis and hippocampal-dependent memory. Of note, reduced cell surface levels of MHC class I can mitigate the negative effects of B2M (Smith et al. 2015). Although MHC class I and B2M were traditionally thought not to be expressed in neurons, pioneering work has implicated these classical immune factors in synapse elimination and synaptic plasticity in the developing and adult brain (Datwani et al. 2009, Huh et al. 2000, Lee et al. 2014, McConnell et al. 2009, Shatz 2009). The specific roles of immune factors in hippocampal aging are being investigated readily and constitute an increasingly rewarding field. Interestingly, the negative effects of proaging factors on hippocampal function can be rescued by manipulating immune signaling at the choroid plexus (CP), a monolayer of epithelial cells that forms the blood–cerebrospinal fluid barrier (Baruch et al. 2013, 2014). Age-related changes in the relative expression of IL-4 and IFN-γ results in increased CCL11 levels in the CP, and rebalancing cytokine expression promotes neurogenesis and plasticity-related gene expression in the hippocampus and partially restores spatial learning deficits in aged mice (Baruch et al. 2013). These studies raise the exciting prospect that decreasing circulating proaging factors may provide a tenable approach for reversing age-related hippocampal deficits.

BDNF: brain-derived neurotrophic factor

IGF-1: insulin-like growth factor-1

MHC class I: major histocompatibility complex class I

B2M: β2-microglobulin

Functional Impact of Age-Related Neurogenesis Decline

The functions of newborn neurons in the DG remain a contentious area of research but are thought to include short- and long-term contributions to hippocampal plasticity. Newborn neurons are

highly excitable, and their acute activation and recruitment may support spatial learning tasks and pattern separation—that is, the disambiguation of similar stimuli (Aimone et al. 2011). Notably, newborn neurons in aged mice are functionally indistinguishable to those in young animals (Morgenstern et al. 2008), suggesting that they retain their impact on neurogenesis-dependent cognition. In aged rodents, performance in spatial and pattern separation tasks is improved by indirect manipulations that promote neurogenesis, such as exercise and enrichment (Wu et al. 2015), although nontargeted benefits cannot be ruled out. More specifically, chemically or genetically ablating neurogenesis in young animals (mimicking an aged state) impairs spatial discrimination of similar (but not dissimilar) contexts (Niibori et al. 2012). In contrast, increasing neurogenesis in young mice, by genetically disrupting the apoptosis of newborn neurons, improves pattern separation (Sahay et al. 2011); whether similar results occur in aged mice remains to be seen. Notably, researchers increasingly appreciate that running-induced neurogenesis promotes forgetting of established contextual memories (Akers et al. 2014, Kodali et al. 2016), and that dorsal and ventral newborn neurons have distinct cognitive and emotive functions (Bannerman et al. 2004). Thus, the impact of neurogenesis on hippocampal-dependent function in the aged brain is far from clear.

A more lasting contribution of neurogenesis is to cognitive reserve—the ability of the hippocampus to recruit compensatory mechanisms in the case of age-related functional loss (Kempermann 2015). Neurogenesis represents an alternative mechanism of neuronal plasticity that acts in parallel to synaptic plasticity to increase the resiliency of hippocampal functions against age-related deterioration. Indeed, the degree of neurogenesis in young adulthood is thought to predict the risk of developing age-related memory disorders (Gemma et al. 2010). The sustained increase in neurogenesis in the aged DG in response to long-term enrichment suggests that neurogenesis may contribute to hippocampal plasticity even in old age (Kempermann et al. 2002), a hypothesis that needs to be examined directly.

AGING AND NEUROINFLAMMATION: MICROGLIA AND IMPLICATIONS FOR HIPPOCAMPAL FUNCTION

Age-Related Microglia Changes: Morphology to Activation

In the young brain, microglia display a ramified morphology and are distributed evenly across the parenchyma. With age, microglia undergo extensive morphological changes, displaying an amoeboid morphology typically associated with activation by proinflammatory signals (**Figure 1**). This is characterized by larger cell bodies; smaller, thicker, and less circular dendritic arbors; and altered dynamics of their processes compared to young microglia (Sierra et al. 2007). In the hippocampus, aging also increases the total number and density of microglia, although the significance of this increase is unclear (Long et al. 1998, Mouton et al. 2002). In aged humans, microglia demonstrate significant heterogeneity (Grabert et al. 2016), displaying an activated or dysmorphic phenotype characterized by extensive structural deterioration, including cytoplasmic beading, spheroid formation, and the presence of deramified, atrophic, fragmented, or unusually tortuous processes. The incidence of dystrophic phenotypes increases in older individuals, leading to the hypothesis that dystrophy reflects microglial cells undergoing cellular senescence (Lopes et al. 2008, Streit 2006).

MHC class II: major histocompatibility complex class II

Age-related morphological changes in microglia are also accompanied by increased expression of activation surface markers, including MHC class II and CD11b, as well as proinflammatory cytokines, such as IL-1β, tumor necrosis factor-α (TNF-α), IL-6, and IL-18 (Barrientos et al. 2015). Large-scale transcriptome analysis studies of young and aged microglia have found widespread

upregulation of proinflammatory genes related to the complement system, Toll-like receptor signaling, and inflammasomes. In contrast, factors known to inhibit microglia activation, including CX3CL1-CX3CR1 and CD200-CD200R signaling, are downregulated in aged microglia (Cribbs et al. 2012, Lukiw 2004). Interestingly, CX3CR1 and CD200 knockout mice exhibit a hypersensitive proinflammatory response reminiscent of aged microglia. Multiple in vivo aging models employing inflammatory stimuli or stressors have also demonstrated that aged animals sustain a larger and more prolonged activation than young animals, a phenomenon termed priming that results in higher levels of neuroinflammation, tissue damage, and cognitive deficits (Udeochu et al. 2016). Altogether, this age-related morphological shift toward an activated phenotype in microglia is ideally situated to disrupt the complex cross talk normally occurring between microglia and the other hippocampal cell types, including neurons and adult NPCs (**Figure 1**).

Age-Related Functional Implications: Synaptic Plasticity, Neurogenesis, and Cognition

As resident immune phagocytes of the brain, microglia interact rapidly with their microenvironment to maintain homeostasis, carrying out roles such as pathogen recognition and phagocytic clearance. Recent work has unexpectedly unveiled microglia as pivotal regulators of synaptic and cellular plasticity, positing microglia as potential mediators of age-related functional decline in the aging brain.

Synaptic plasticity. Microglia fine-tune neuronal activity and sculpt synaptic networks in the adult hippocampus, suggesting that these cells are prominent modulators of synaptic plasticity. Genetic deletion of CX3CR1 in young mice, which mimics the loss of CX3CR1 signaling with aging, results in elevated microglia activation and significant impairments in LTP (Rogers et al. 2011). Similarly, CD200 knockout mice, which mimic the decline of CD200 with aging, show increased TNF-α levels and reduced LTP (Costello et al. 2011). Conversely, inhibition of microglia activation during aging by minocycline treatment partially restores age-related LTP deficits and attenuates IL-1β and IL-18 levels (Griffin et al. 2006). Restoring CD200 to mimic youthful levels by intrahippocampal infusion also dampens microglia activation and rescues age-related LTP deficits in aged rats (Cox et al. 2012). Together, these findings suggest increased proinflammatory cytokine levels associated with microglia activation in the aged hippocampus may negatively regulate neuronal activity.

Investigators have proposed recently that synaptic degeneration associated with aging and Alzheimer's disease is regulated by microglia through increased complement signaling with age (Shi et al. 2015). In aged mice, genetic deletion of the complement molecule C3 protects from age-dependent loss of synapses in CA3, increasing the density of dendritic spines and improving hippocampal-dependent memory (Shi et al. 2015). Similarly, aged mice with a genetic deletion of the complement molecule C1q exhibit greater synaptic density, enhanced synaptic plasticity, and improved spatial learning and memory (Stephan et al. 2013). More recently, C1q was found to be necessary for oligomeric amyloid-β–induced synapse loss, and it impaired LTP in a preplaque mouse model of Alzheimer's disease by triggering microglia-mediated synaptic pruning (Hong et al. 2016). In addition to complement factors, MHC class I deficiency results in significant dendritic atrophy with decreased stubby spines in the hippocampus of aged mice (Lazarczyk et al. 2016). Thus, the age-dependent increase in complement and other immune-related factors may drive the aberrant activation of microglia-dependent pruning pathways, resulting in synapse loss with age.

Adult neurogenesis. The discovery that microglia regulate neurogenesis raises the intriguing possibility that the age-dependent decline in neurogenesis may be in part due to the proinflammatory state of aged microglia (**Figure 2**). Indeed, neuroinflammation is a known negative regulator of adult hippocampal neurogenesis (Ekdahl et al. 2003, Monje et al. 2003). In the context of exercise, global depletion of all microglia subpopulations from young or aged hippocampal tissue mitigates enhancements in neurogenesis, suggesting microglia exert a net positive effect on regenerative capacity (Vukovic et al. 2012, Ziv et al. 2006). In contrast, specific depletion of the colony stimulating factor 1 receptor/MHC class II–positive microglia subpopulation enhances neurosphere formation, suggesting an inhibitory role for this subpopulation in regulating NPC proliferation (Vukovic et al. 2012). Moreover, depletion of microglia in hippocampal tissue from aged but not young mice results in increased neurosphere formation, suggesting that the inhibitory effects of microglia on neurogenesis are age dependent (Vukovic et al. 2012). Whether this age-dependent suppression of NPC activity can be directly attributed to microglia-mediated age-related neuroinflammation remains to be examined. In addition to modulating neuroinflammation, microglia impact neurogenesis directly via CX3CL1-CX3CR1 signaling. Interestingly, recapitulating a youthful environment by pharmacologically increasing CX3CL1 in aged rats results in a reduction in microglia activation and a concomitant increase in NPC proliferation (Bachstetter et al. 2011). Microglia are also implicated at later stages of neurogenesis, clearing apoptotic newborn neurons via phagocytosis; however, this process is refractory to age (Sierra et al. 2010). These findings point to differential regulation by aging microglia on the different stages of neurogenesis, although the mechanisms by which microglia regulate neuronal differentiation and maturation during aging are unknown.

Cognition. The role of microglia in regulating neuroinflammation and synaptic circuits naturally leads to the question of whether they contribute to age-related cognitive decline. Multiple lines of evidence suggest microglia activation is a precursor to synaptic and cognitive deficits in the hippocampus. Microglia-specific genetic deletion of CX3CR1 results in microglia activation; proinflammatory cytokine signaling; and deficits in LTP, neurogenesis, and hippocampal-dependent learning and memory (Parkhurst et al. 2013). In aged mice, deletion of *Sirtuin 1* in microglia and other macrophages also increases proinflammatory cytokine production and leads to impaired spatial learning and memory (Cho et al. 2015). Interestingly, reducing expression of microglial-associated inflammatory markers in the aged hippocampus to youthful levels by treating aged mice with the anti-inflammatory agent luteolin improves spatial memory (Jang et al. 2010). Inhibition of leukotriene signaling with the antiasthma drug montelukast also reduces microglia activation, increases NPC proliferation, and improves spatial learning and memory in aged rats (Marschallinger et al. 2015). Aging also elevates complement signaling in microglia, which has been implicated in cognitive dysfunction in the adult hippocampus (Shi et al. 2015, Stephan et al. 2013, Vasek et al. 2016). For example, viral activation of microglia drives cognitive impairments in hippocampal-dependent spatial memory in a C1q-dependent manner (Vasek et al. 2016), whereas mice lacking C3 are protected against age-related hippocampal cognitive decline (Shi et al. 2015). Although growing evidence points to a microglia-specific role in driving age-related cognitive impairments, mechanistic insight bridging microglia dysfunction with cognitive decline remains to be elucidated.

AGING AND PROYOUTH INTERVENTIONS: POTENTIAL FOR HIPPOCAMPAL REJUVENATION

One of the most exciting recent findings is that hippocampal aging is a mutable process, raising the possibility of restoring age-related regenerative, synaptic, and cognitive functions (**Figure 1**).

Notably, a growing body of work suggests that manipulating the aged systemic milieu is a tenable strategy for brain rejuvenation. Here we review two promising interventions, exercise and systemic exposure to young blood, that illustrate the validity of this holistic approach. Nonetheless, given the complexity of the aging process, ultimately we envision a multifaceted approach that targets proaging processes at the intracellular, intercellular, and systemic level to combat age-related functional decline.

Exercise: Synaptic Plasticity, Neurogenesis, Neuroinflammation, and Cognition

Substantial evidence suggests that exercise is beneficial for preserving hippocampal function with age (**Figure 1**). In aged rodents, long-term voluntary running results in better acquisition and retention of hippocampus-dependent memory, including Morris water maze performance (Kumar et al. 2012, van Praag 2005), inhibitory avoidance (Speisman et al. 2013), object recognition (Kumar et al. 2012), and contextual fear conditioning (Gibbons et al. 2014). In elderly humans, cardiovascular fitness correlates with faster and more accurate spatial short-term memory (Maass et al. 2015), less hippocampal atrophy (Erickson et al. 2011), and increased synchrony in hippocampal resting-state networks (Voss et al. 2010). The extent of improvement is variable, likely owing to individual differences in neurovascular plasticity and cognitive reserve (Duzel et al. 2016).

Exercise-induced cognitive improvements are mediated by changes in synaptic plasticity, neurogenesis and neuroinflammation. Transcriptionally, running reverses the aging-associated downregulation of genes related to cell growth and attenuates expression of genes involved in immune function (Kohman et al. 2011). In aged rodents, running reverses age-related LTP impairments in the DG (O'Callaghan et al. 2009) and increases the proliferation and survival of newborn neurons (Speisman et al. 2013, van Praag 2005). Importantly, running-enhanced neurogenesis correlates with increased performance in fine pattern separation, a task normally attributed to neurogenesis (Wu et al. 2015). In middle-aged to aged rodents, running lowers the number of proliferating Iba1-positive macrophages and reduces MHC class II/CD68-positive activated microglia in females (but not males) (Gebara et al. 2013), with a concurrent increase in CX3CL1 expression (Vukovic et al. 2012), suggesting a shift toward a less inflammatory microglia phenotype. Indeed, old mice with access to a running wheel display decreased IL-1β levels, increased BDNF, and improved memory performance (Speisman et al. 2013). Running also increases hippocampal perfusion in elderly humans (Burdette et al. 2010) but not aged mice (van Praag 2005) and improves neurovascular health in CA1 of aged mice (Soto et al. 2015). Notably, running does not increase neurogenesis, improve pattern separation, or alter the expression of proinflammatory cytokines in very old to geriatric mice (Creer et al. 2010, Lezi et al. 2014), suggesting that the positive effects of running decline with extreme aging.

An increasingly popular line of research is to identify systemic factors that stimulate the cognitive benefits of exercise. Such factors are powerful points of entry for developing exercise mimetics with similar memory-enhancing effects in the aged hippocampus (Guerrieri & van Praag 2015). Cleavage and secretion of the muscle protein fibronectin type III domain-containing protein 5 (FNDC5) following exercise-induced activation of peroxisome proliferator-activated receptor gamma coactivator 1-α (also known as PGC-1α) upregulates *bdnf* in the hippocampus, which is recapitulated by overexpressing FNDC5 in the liver of sedentary mice (Sanchis-Gomar et al. 2015, Wrann et al. 2013). The ketone body β-hydroxybutyrate (BHB), released by the liver after exercise, stimulates *bdnf* promoters in the hippocampus by inhibiting HDAC2 and HDAC3. Ventricular delivery of BHB increases BDNF expression and synaptic plasticity in hippocampal slices (Sleiman et al. 2016), and oral supplementation of BHB increases word recall in memory-impaired humans (Reger et al. 2004). Cathepsin B (CTSB), a myokine released by muscles after exercise,

increases BDNF expression, neurogenesis, and memory performance. These central effects were blocked in CTSB knockout mice subjected to running (Moon et al. 2016). Whether artificially increasing systemic levels of any one or a combination of these factors can recapitulate the central effects of exercise in normally aged animals is under intense investigation.

GDF11: growth differentiation factor 11

Young Blood: Synaptic Plasticity, Neurogenesis, and Cognition

Heterochronic parabiosis studies provide some of the strongest evidence that systemic factors modulate brain rejuvenation (Bouchard & Villeda 2014). In the aged hippocampus, exposure to young blood by heterochronic parabiosis increased the number of BrdU- and Sox2-positive NPCs and Dcx-positive neuroblasts in the DG (Villeda et al. 2011). Heterochronic parabiosis also rescued age-related decline in LTP, increased the number of dendritic spines, and promoted neuronal activity in the aged hippocampus demonstrated by increased *c-fos* expression and CREB phosphorylation (Villeda et al. 2014). Moreover, repeated intravenous administration of young plasma to aged animals reversed impairments in hippocampal-dependent cognition (Villeda et al. 2014). These studies point to the existence of circulating factors that regulate hippocampal rejuvenation (**Figure 1**).

The hunt for proyouth factors to date has been more controversial, so far yielding one candidate: growth differentiation factor 11 (GDF11). Initially, GDF11 levels were shown to decrease with age, and recombinant GDF11 was found to recapitulate partially the youth-promoting effects of young blood on neurogenesis in the subventricular zone (Katsimpardi et al. 2014) and on myogenesis in the periphery (Sinha et al. 2014). However, later studies contradicted several earlier key findings, including the age-related decrease in GDF11 levels and its proyouth effects on muscle function (Egerman et al. 2015), prompting the need to gain mechanistic insight into the potential rejuvenating effects of the factor. Notably, the proyouth effects of GDF11 on the regenerative capacity of the aged brain have not been contested (Katsimpardi et al. 2014).

Although the validity of pursuing proyouth factors as a goal has been called into question (Conboy et al. 2015), we believe that identification of these factors is a tenable approach to translating the exciting findings from parabiosis and young plasma administration into clinical use. Currently, three clinical trials examining the safety and effects of young or cord plasma on Alzheimer's disease (**http://clinicaltrials.gov** identifier NCT02256306), frailty (NCT02418013), and expression of age-related biomarkers (NCT02803554) are under way, although caveats have been noted in the last trial (Kaiser 2014). Notwithstanding, several key considerations pertinent to young blood antiaging interventions need to be addressed. For instance, the effects of young plasma on neurogenesis, synaptic plasticity, neuroinflammation, neurovascular perfusion, and other age-related hippocampal processes are unknown. For functional rejuvenation, aged animals were subject to an aggressive dosing schedule that was sufficient to overcome the inhibitory elements in the aged milieu. Whether a similar schedule is possible in humans is unresolved. If not, it may be necessary to simultaneously inhibit proaging factors to achieve cognitive improvements. Future studies should also address at what levels proyouth candidates become effective and whether it is possible to reach those levels in humans. Long-term effects and side effects of young plasma should be considered. It remains unclear how long-lasting the beneficial effects of young plasma administration are, but given the continuous production of proaging factors in the elderly, chronic young plasma administration will likely be necessary. Although significant side effects have not been observed in animal studies, given the regenerative effects of proyouth factors, possible runaway regeneration—that is, cancer—should not be discounted. Rather than utilizing young plasma as a therapeutic, it may be more prudent to administer a combination of proyouth factors (or proaging factor neutralizers), of which the mechanisms and side effects are well understood.

CONCLUSION

The past two decades have seen rapid progress in our understanding of the mechanisms that drive hippocampal aging. Advancements in large-scale proteomics and in vivo imaging have enabled an unprecedented, comprehensive look at age-dependent synaptic, structural, and cellular dysfunction in the hippocampus. Delineation of neurogenic processes and exploration of their behavioral functions in aged animals have positioned impaired neurogenesis as a potential driver of age-related cognitive decline, although contradicting data necessitate further evaluation. A growing appreciation of neuroimmune cross talk in regulating synaptic plasticity and neurogenesis in the adult hippocampus further highlights the need for future studies in the context of aging. The exciting finding that hippocampal aging is amenable to proyouth interventions also calls for additional interrogation into the promises and limitations underlying such rejuvenating approaches. Elucidating basic mechanisms of hippocampal aging and rejuvenation will provide groundwork for developing clinically viable interventions in the elderly that may counteract brain aging and vulnerability to age-related neurodegenerative disorders.

SUMMARY POINTS

1. The aged hippocampal neuron displays aberrant regulation of transcriptional, epigenetic, and homeostatic cellular processes.
2. Altered expression of synaptic plasticity–related molecules in the aged hippocampus leads to deficiencies in neuronal signaling.
3. Age-related hippocampal functional deficits include impairments in spatial and episodic learning and memory tasks.
4. Multiple cellular, niche, and systemic mechanisms drive age-related decline in neurogenesis that often parallels hippocampal cognitive deficits.
5. Aging increases microglia activation and neuroinflammation, which may contribute to impaired hippocampal plasticity and function.
6. Exercise improves hippocampal-dependent spatial memory in aged animals by enhancing synaptic and cellular plasticity.
7. Heterochronic parabiosis and young blood administration point to the existence of circulating factors that regulate hippocampal rejuvenation.
8. Manipulating proyouth or proaging systemic factors may be a clinically viable approach toward antiaging therapeutics.

FUTURE ISSUES

1. The molecular mediators linking aberrant transcriptional and epigenetic changes to hippocampal aging and functional decline need to be elucidated.
2. The functions of newborn neurons in the context of aging require more investigation. The possibility of improving hippocampal-mediated cognition in aged animals using methods that promote neurogenesis specifically and the mechanisms behind those methods should be addressed.

3. The secreted factors and surface molecules mediating neuron-microglia interactions in aged animals and their downstream intracellular signaling pathways should be elucidated.
4. The molecular and cellular mechanisms bridging age-related microglia dysfunction with cognitive decline need further research.
5. The necessity, sufficiency, and mechanisms of exercise-induced systemic factors in improving hippocampal cognition in aged animals should be investigated.
6. Additional proaging and proyouth blood factors and their mechanisms need to be identified.
7. The promises and limitations of rejuvenating therapies for human use should be delineated carefully.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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