The neurogenic niche in Alzheimer's disease

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ABSTRACT

Adult hippocampal neurogenesis is the process of generation and functional incorporation of new neurons, formed by adult neural stem cells in the dentate gyrus. Adult hippocampal neurogenesis is highly dependent upon the integration of dynamic external stimuli and is instrumental in the formation of new spatial memories. Adult hippocampal neurogenesis is therefore uniquely sensitive to the summation of neuronal circuit and neuroimmune environments that comprise the neurogenic niche, and has powerful implications in diseases of aging and neurological disorders. This sensitivity underlies the neurogenic niche alterations commonly observed in Alzheimer's disease, the most common form of dementia. This review summarizes Alzheimer's disease associated changes in neuronal network activity, neuroinflammatory processes, and adult neural stem cell fate choice that ultimately result in neurogenic niche dysfunction and impaired adult hippocampal neurogenesis. A more comprehensive understanding of the complex changes mediating neurogenic niche disturbances in Alzheimer's disease will aid development of future therapies targeting adult neurogenesis.

1. Introduction

Alzheimer's Disease (AD) is an age-related form of dementia associated with cognitive deficits, mood disorders, and neuropathological features including beta-amyloid plaques and tau neurofibrillary tangles [1]. AD pathology is associated with synaptic dysfunction, neuroinflammation and neuronal loss. Adult hippocampal neurogenesis (AHN) is the process of proliferation, differentiation, integration, and maturation of neural stem cells into newborn neurons in the hippocampus, a region closely associated with spatial memory and learning. AHN is disrupted in both AD mouse models and human patients and may therefore serve as the "canary in the coal mine" of the aging brain, as deficits in AHN often precede AD symptoms. Harnessing the neurogenic capacity of the brain represents a promising therapy, however; despite this potential, regulation of AHN in vivo remains a poorly defined process due to the myriad sources of neural circuit inputs and neuroimmune determinants within the neurogenic niche. This review integrates recent developments in the understanding of AD-associated dysfunction of AHN in the neurogenic niche and highlights promising avenues for further study.

1.1. Adult neurogenesis in rodents and humans

In rodents, adult neurogenesis occurs in both the hippocampus and the sub-ventricular zone (SVZ). Adult neurogenesis in the hippocampus contributes to spatial learning and memory, whereas neurogenesis in the SVZ contributes to olfaction [2]. Recent studies on AHN in humans emphasize the importance of proper methodology and stringent protocols when testing for various markers of AHN [3,4], however these investigations have not extended to SVZ neurogenesis in humans. This review will therefore focus on the neurogenic niche within the hippocampus, where the process of AHN supports spatial learning and memory, but is susceptible to dysfunction in AD [5,6].

1.2. AHN at the crossroads of amyloid and tau pathology

AD is a protein aggregation disorder, wherein the accumulation of two proteins, beta-amyloid (Aβ) and microtubule-associated protein-tau (abbreviated MAPT, but hereafter referred to as tau) form plaques and tangles, respectively. The accumulation of these proteins is associated with neuronal loss and symptoms including memory loss, mood disorders, seizures, and cognitive dysfunction [7]. Aβ accumulation precedes tau deposition, the latter of which is most tightly correlated to neuronal loss and cognitive impairment [8]. The two disease-associated proteins

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accumulate in separate compartments over decades in early AD stages; Aβ deposition originates in the outer cortical layers and then moves inward, while tau originates in the brainstem and spreads trans-synaptically to the entorhinal cortex, hippocampus, and finally the outer cortical layers [9]. Aβ and tau likely meet in the hippocampus during prodromal stages of AD, when hippocampal activity is elevated [10]. The E4 allele of apolipoprotein E (APOE4) is a major genetic risk factor for AD, and is associated with higher prevalence of hippocampal pathology [11]. Genetic knockout of APOE stimulates differentiation of NSCs into astrocytes [12]. Irrespective of genetic background, the synergistic effects of Aβ and tau accumulation in the hippocampus have profound consequences for the process of AHN, which is highly sensitive to external stimuli. AD pathophysiology induces cell-autonomous changes, neuroinflammation, gliosis and network dysfunction that fundamentally alter the neurogenic niche (summarized in Fig. 1).

1.3. The unique properties of the neurogenic niche

The neurogenic niche lines the inner layer of the dentate gyrus (DG), a bilateral midbrain structure within the hippocampus that supports the generation, maturation, and integration of neurons in the adult mammalian brain. Transplantation of adult spinal cord stem cells into other hippocampal regions generates only astrocytes or oligodendrocytes, whereas transplantation into the dentate gyrus produces newborn neurons [13]. Newborn neurons in the DG integrate into the granule cell layer, a tightly organized band of glutamatergic granule cells (GCs) that contribute to learning, memory, and pattern separation. Mature GCs extend their dendrites to the molecular layer, where they synapse with a host of neural circuits that project to the DG. GC axons project to mossy cells in the Cornu Ammonis-3 (CA3) of the contralateral hippocampus (Fig. 1). The hilus, encased by the granule cell layer, contains an assortment of interneuron subtypes, glutamatergic mossy cells, and glial cells that also shape DG activity and neurogenic niche conditions. The sub-granular zone (SGZ) exists between the hilus and granule cell layer and is home to adult neural stem cells (NSCs), a transcriptionally unique cell type that maintains regenerative capacity throughout the lifetime of the organism. NSCs are multipotent, capable of self-renewal, and

delineated into radial and non-radial cells, the former of which represent the primary class of NSCs found in the adult hippocampus. Radial glia-like cells (RGLs, classified as Type-1 cells) express markers such as glial fibrillary acidic protein (GFAP), Sry-related HMG box transcription factor (Sox2), and intermediate filament protein (Nestin).

NSCs can undergo asymmetric division to self-renew and return to quiescence after producing one neural progenitor progenitor cell (NPC) that subsequently matures into either a granule cell or an astrocyte (Fig. 1). The commitment to either glial or neuronal fates is determined by a variety of factors including genetic regulation, neural circuit activity, inflammation, glial influence, and neurotrophic factor availability, all of which are known to be disrupted in AD (Fig. 1). NSCs project an apical process that reaches the inner molecular layer to sense environmental stimuli that control fate decisions [14]. While NSCs can symmetrically self-renew under normal conditions, canonically this occurs infrequently, thus leaving NSCs vulnerable to depletion in response to neurological dysfunction. Alterations in adult neurogenesis can, in turn, adversely affect brain activity and hippocampal-dependent functions [15]. In humans, AHN declines throughout normal aging and this decay rate accelerates in AD due to multiple levels of dysfunction in the neurogenic niche and within NSCs themselves [16]. While loss of AHN in common in mouse models of AD, it is not ubiquitous [17]. These discrepancies are likely due in part to the variety of AD transgenes and circuit alterations unique to each mouse model. A more comprehensive picture of neurogenic niche alterations is critical to understanding the complexities underlying AHN trajectories in human AD patients and model systems.

2. Cell-autonomous dysfunction in neural stem cells

Despite the hospitable environment within the neurogenic niche, NSCs are vulnerable to direct cell-autonomous deficits induced by AD etiology (Fig. 1). For example, reversible lysosomal impairment specifically in aNSCs restrains them in a quiescent state [18]. Somatic mutations in amyloid processing, allele variants, epigenetic dysregulation and tau post-translational modifications may also directly influence aNSC maintenance, proliferation, survival, and eventual integration into
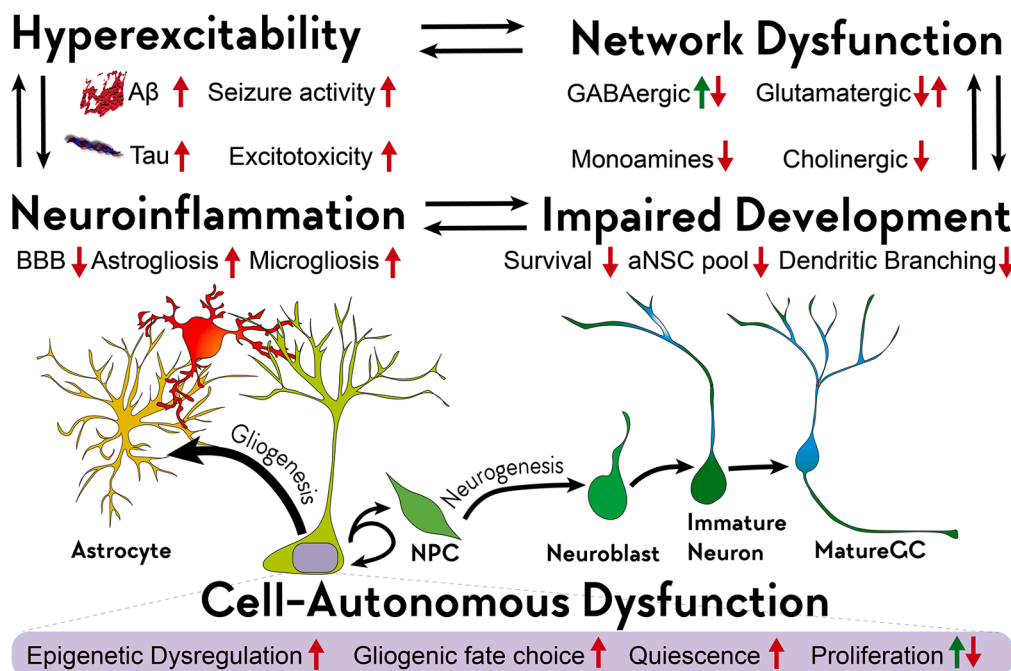

Fig. 1. Diagram summarizing major alterations in the neurogenic niche associated with AD progression. Amyloid and tau accumulation spread from one brain region to another, both induced by and potentiating neuronal **Hyperexcitability**. These alterations reciprocally induce **Neuroinflammation** and **Network Dysfunction** within the neurogenic niche. This resultant dysregulation ultimately contributes to **Impaired Development** of adult-born granule cells in AD. *Red arrows indicate alterations associated with AD that are deleterious to AHN and green arrows indicate changes that promote or stabilize AHN associated with AD in human patients and/or mouse models. Directionality indicates upregulation (up) or down-regulation/loss (down) of a process or protein.*

hippocampal circuitry as adult-born granule cells.

2.1. Epigenetic dysregulation of AHN

Aberrant epigenetic modifications may signal or contribute to the dysfunction of aNSCs in AD [19]. DNA methylation, a key epigenetic mark associated with gene repression, steadily declines with age in early Braak stage AD patients and results in increased β-secretase (BACE1) expression, ultimately resulting in upregulation of Aβ [20]. Similarly, histone acetylation is also commonly disrupted in AD models and patients [21], and certain members of histone deacetylase (HDAC) family have been investigated as therapeutic targets in AD [22]. Emergent evidence also highlights microRNAs (miRNAs), single-stranded non-coding RNAs, as key epigenetic regulators in both adult neurogenesis and AD pathophysiology [23]. Recently, miR-132 reduction was identified in the AD neurogenic niche, the replacement of which rescued neurogenic and memory deficits in an AD mouse model, thus underscoring the vast potential for miRNAs in future studies of targeted therapies [24].

2.2. Amyloid and AHN

Beta-amyloid (Aβ) is derived by the cleavage of amyloid precursor protein (APP), a membrane-bound cellular signaling protein. Depending on the cleavage site, amyloid processing elicits effects ranging from cell proliferation and growth to immunoprotection, synaptic dysfunction, and neurotoxicity [25]. Mutations or altered expression in the genes for β-secretases (BACE1 and BACE2), APP, presenilin-1, (PS1), and presenilin-2 (PS-2), cause overproduction and premature accumulation of extracellular Aβ. Down syndrome patients harbor an extra copy of APP on chromosome 21, resulting in AD-like neuropathological deficits [26], and familial AD patients with PS1 mutations exhibit accelerated neurogenesis that hastens hippocampal aging [27]. APP overexpression has also been shown to alter expression patterns of chloride channels which mediate polarization of developing neuroblasts to GABAergic input, as will be addressed in detail later [28].

In the APP/PS1 mouse model, soluble Aβ impairs aNSC proliferation and Aβ oligomers stimulate microglial proliferation [29], inducing an early increase in proliferation at middle age eventually depletes the aNSC pool [30]. Additionally, Aβ oligomers were shown to induce dysfunction in NSCs directly in-vitro via the glycogen synthase kinase-3β-mediated signaling pathway [31]. Interestingly, human patients with high AD pathology, but no evident cognitive impairment harbor an increased number of NSCs [32]. In-vitro studies indicate that exosomes from NSCs, but not mature neurons may confer resistance to Aβ oligomers [33], indicating possible neuroprotective potential of aNSCs.

Other enzyme-dependent byproducts of APP cleavage include soluble APP-α and β (sAPPα and sAPPβ), which are released into the extracellular space, and amyloid intra-cellular domain (AICD). Although AICD is seldom a research focus, early studies implicate it as a transcription factor of numerous genes regulating proliferation, differentiation, or survival [34]. sAPPα and sAPPβ, which are sAPPα 1–16C-terminal amino acids, bind to extracellular receptors to induce a variety of responses including axonal outgrowth, neuronal differentiation, and microglial activation [35].

2.3. Tau and AHN

Tau is primarily expressed in neurons, with low expression in astrocytes and oligodendrocytes [36]. The central repeat domain region of tau binds microtubules, while the N-terminus binds to the plasma membrane of the cell [37]. RNA splicing regulates tau isoform expression throughout development, switching from three-repeat domain (3R) tau to 4-repeat domain (4R) throughout postnatal maturation into adulthood [38]. Other microtubule-stabilizing proteins such as double-cortin (DCX) are highly expressed in immature neuroblasts and may

compensate for lower mature tau isoform expression in developing neurons. Tau-knockout studies demonstrate that tau is not required for neuronal survival but is necessary for proper migration and integration of adult-born neurons [39]. Tau accumulation in AD is roughly 50% 3R and 50% 4R tau, however most murine tauopathy models predominantly express the 2N4R isoform of human tau, highlighting the need for use of the 6hTau mouse line, a tau-humanized mouse model to dissect the effect of all tau isoforms on AHN within the context of AD [40].

Tau binding affinity to microtubules is dependent upon the tau isoform expressed, as well as the presence of various post-translational modifications (PTMs), including ubiquitination, SUMOylation, acetylation, and phosphorylation. Tau PTMs are also developmentally mediated by various kinases, phosphatases, acetyltransferases, deacetylases and ubiquitin ligases responsive to external stimuli. Subsequently, the interaction between tau and tubulin is more dynamic than that of other microtubule-associated proteins (MAPs), particularly MAP2 and MAP4 [41]. DCX is enriched in developing neuroblasts and co-localizes with phosphorylated tau at the PHF-1 (S396/S404), AT8 (T202, S205), and 12E8 (S262) epitopes, commonly used as markers for pathological tau in late-stage AD [42].

3. Network dysfunction in the neurogenic niche

The dentate gyrus is a nexus for a variety of inputs throughout the brain, and as such is innately sensitive to broad network alterations. Highly dependent on external stimuli, aNSCs extend their processes, commonly termed bushy heads, to the molecular layer, where they receive both direct and indirect input from a variety of incoming circuits. The summation of these inputs regulates aNSC fate choice into either quiescence, proliferation, or differentiation [14]. Synaptic integration of these inputs is also highly reliant on extracellular matrix architecture, which is commonly disturbed in AD [43]. Disruption of monoamine networks is also associated with a host of neurological and mood disorders with which AD shares considerable co-morbidity. Major depressive disorder (MDD) and AD patients share common abnormalities in AHN, neuroinflammation and neurotransmission and reciprocally increase risk for each other [44]. Research focused on AHN in the context of the neurogenic niche will continue to illuminate mechanisms that explain the overlapping risk between AD, MDD, and other mood disorders.

Critically, sex differences manifest in a variety conditions pertinent to AHN; females are more likely to develop AD [45] in both human patients and mouse models, and recent work in rodents has highlighted fundamental differences in maturation and survival of adult born neurons between males and females [46]. Females also diverge from males in both incidence of and response to treatment in MDD, broadly implicating sex differences in the context of AHN, network dysfunction, and neurotrophin signalling [47].

3.1. Glutamatergic signaling

Glutamate is the brains primary excitatory neurotransmitter and binds ionotropic α-amino-3-hydroxy-5-methyl-4-isoazazoleproptionic acid receptors, (AMPARs) and N-methyl-D-aspartate receptors (NMDARs) to mediate long-term potentiation (LTP). Administration of memantine, a commonly prescribed NMDAR agonist, protects against excitotoxicity and expands the NSC pool in wild-type mice [48]. Changes in LTP are common in but may not be unique to AD, as BDNF-mediated LTP is impaired with normal aging [49].

Aberrant excitatory conditions are widespread within AD pathophysiology [50], and can profoundly affect the neurogenic niche and newborn granule cell morphology [51]. Glutamate release can be increased by metabolic and oxidative stress, as well as stressful environments [52], and subsequently causes synaptic and dendritic atrophy in a tau-dependent manner [42]. Direct injection of glutamate to the DG induces hyperexcitability and glutamate excitotoxicity that impairs

spatial memory, promotes gliosis and reduces proliferation [53]. APP-induced seizure activity also causes cellular metabolic stress, excitotoxicity, and depletion of the aNSC pool that coincides with impairment of spatial discrimination [54].

Glutamate also binds to metabotropic glutamate receptors (mGluRs), a class of the G-protein coupled receptor family. Activation of mGluRs has differential effects depending on the localization of such receptors. In the post-synapse, group I mGluRs may potentiate NMDAR activity, thereby increasing the risk of excitotoxicity [55]. Blockade of mGluR5 in vivo has been shown to rescue early hyperexcitability found in the 3xTg-AD model, an equivalent therapy in efficacy to hAPP/Aβ immunization [56]. Extrasynaptic glutamate is regulated by presynaptic release and active glutamate uptake, but astrocytic uptake of glutamate is impaired in mouse models of tauopathy [57].

The first glutamatergic synaptic inputs onto newborn GCs are formed by mossy cells (MCs) that project from the ipsilateral CA3 to the molecular layer and the hilus [58]. MCs exert dynamic control of NSC quiescence via direct glutamatergic signaling and indirect (via hilar interneurons) GABAergic signaling, and selective ablation of MCs induces transient activation of NSCs that results in pool depletion [59].

The entorhinal cortex (EC) provides another major glutamatergic input to hippocampal NSCs via molecular layer projections. The EC is vulnerable to tau toxicity and are commonly affected in both prodromal and late-stage AD [60]. Deep brain stimulation of the EC provokes adult neurogenesis and facilitates spatial memory formation without fundamentally altering neuronal survival or fate choice [61]. Interestingly, lesioning of the EC temporarily supports progenitor survival, although this process is not sustained [62].

3.2. Gabaergic signaling

γ-amino-butyric-acid (GABA), is the brains primary inhibitory neurotransmitter and regulates neuronal excitability via both phasic and tonic inhibition. The primary source of GABA within neurons is derived from extracellular glutamate via glutamic acid decarboxylase, whereas the conversion of GABA back into glutamate is catalyzed by GABA transaminase [63]. GABA binds both ionic and metabotropic receptor subtypes, the former of which induce chloride influx and the latter of which opens inwardly rectifying potassium channels via G-protein activation.

Ionotropic GABAergic synapses form before glutamatergic synapses during development [64], but are dependent on the intracellular chloride gradient to either depolarize or hyperpolarize the target cells. The potassium-chloride gradient is maintained in neurons via two developmentally regulated transporters: Na^+ K^+-Cl^- cotransporter 1 (NKCC1) and K^+-Cl^- cotransporter 2 (KCC2). Expression of NKCC1, which facilitates neuronal depolarization in response to $GABA_A$ receptor activation, shifts to KCC2, which facilitates hyperpolarization during the process of neuronal development and maturation. GABA itself contributes to this developmental shift by upregulating KCC2 expression [65]. This transition normally coincides with formation of glutamatergic synapses and spine development on newborn neurons, but this process is commonly disrupted in neurological disorders, including AD [28].

Developing neurons with delayed or reduced expression of KCC2 would be more readily excitable as they will be depolarized by both glutamatergic and GABAergic neurotransmission, which could fundamentally alter the development of newborn neurons.

In humanized APP transgenic mice, adult-born granule cells show increased dendritic length, spine density and aberrant morphology, which can be rescued by inhibiting $GABA_A$ receptors, further indicating an excitatory nature of GABAergic transmission in this context [66]. Treatment with bumetanide, a highly specific NKCC1 antagonist, also rescues excitatory $GABA_A$ signaling in a mouse model of Down syndrome that also overexpresses APP [26].

4. Interneuron dysfunction

GABA is released by over 20 subtypes of interneurons that are integral to proper brain function in the context of both AD and adult neurogenesis [67]. The precise role of interneurons in AD pathophysiology is not fully understood, however both denervation and compensatory outgrowth of interneuron populations have been observed in various mouse models of AD [68]. The APOE4 allele has also been shown to impair AHN by inducing interneuron dysfunction in APOE knock-in mice [69]. These deficits are rescued by treatment with phenobarbital, a $GABA_A$ receptor potentiator, and recapitulated in APOE3 knock-in mice by treatment with picrotoxin, a GABA receptor antagonist [12]. In the 3xtg-AD mouse model, accumulation of phosphorylated tau in DG interneurons is associated with neurogenic dysfunction that can are each rescued by the $GABA_A$ receptor agonist THIP [70].

Parvalbumin (PV) interneurons are a key hippocampal interneuron subtype, where they are required for spatial working memory [71]. A landmark study showed that gamma frequency (40 Hz) entrainment of PV interneurons regulates microglial activity and amyloid levels in 5xFAD mice [72]. DG PV interneurons maintain quiescence of neural stem cells via γ2-containing $GABA_A$ receptors, while simultaneously promoting survival of their newborn progeny [73]. PV interneurons form immature synapses onto newborn precursor cells, but do not synapse on neural stem cells, suggesting that direct PV regulation of NSCs occurs through GABA spillover from PV-granule cell synapses [74]. Dysfunction and/or loss of hippocampal PV neurons, as observed in some mouse models of AD, is likely to negatively impact the neurogenic niche [75].

4.1. The Septo-hippocampal loop in AHN

The GABAergic septo-hippocampal circuit is vital for learning and memory [76], and is comprised of GABAergic neurons within the medial septum that extend projections through the fornix to the hippocampus and dentate gyrus (DG), where they indirectly control NSC quiescence through hilar and DG interneurons [74]. Unfortunately, like many forebrain populations, this critical circuit degenerates in several AD models, including the J20 amyloid model, the TauPS2APP triple transgenic model, and the VLW model of tauopathy [77]. Septal GABAergic dysfunction and/or degeneration of this population in AD could contribute to dysregulation of AHN via indirect signaling along the hilar interneuron or forebrain cholinergic axes.

4.2. Neuropeptides: NPY, CCK, SST

Many interneuron subtypes are defined by co-release of GABA and various neuropeptides, which elicit a variety of synaptic and cellular effects. An interneuron population commonly implicated in AD pathology are Neuropeptide-Y (NPY^+) neurons. While NPY neurons are almost exclusively GABAergic, NPY itself exerts weak excitatory activity at the Y1 receptor, and strong inhibitory activity when it binds the Y2 receptor, capable of suppressing glutamate release and N-type presynaptic calcium currents in hippocampal slices [78]. NPY projections are expanded in the DG and hippocampus of hAPP overexpressing- J20 mice that express abundant Aβ1-42 and are prone to seizures [79]. Such compensatory responses are not reflected in humanized APP mice with lower Aβ1-42 production [79], but can be triggered during recovery from kainic-acid induced seizures [80].

NPY releasing neurons can also co-release somatostatin peptide (SST). Like NPY, SST neurons are capable of providing compensatory inhibition within the hippocampus via perisynaptic contacts [79], and their observed loss in some APP mouse models [81] may underlie selective vulnerability in the aging brain. Conversely, the compensatory outgrowth of somatostatin neurons in one APP model may be due to the ability of the SST neuropeptide to upregulate neprilysin activity, which subsquently degrades both Aβ 1–42 and Aβ 1–40 [82]. SST neurons are

also capable of inducing both GABA$_A$ and GABA$_B$ mediated inhibition, and their activity is regulated by brain states implicated in learning and memory and rewarded behaviour [83]. SST is significantly down-regulated in both brain and CSF from AD patients, and both GABA and SST are dramatically reduced in the CSF of APOE4 allele carriers [84].

Cholecystokinin (CCK), best known for digestive responses, is released in the gut following food ingestion. Despite these putative gut-brain links, CCK is also the most abundant neuropeptide in the brain, where it is released by hilar interneurons and acts directly on both CCK-A and CCK-B receptors (CCKARs and CCKBRs). It was recently demonstrated that CCK supports neurogenesis via glial intermediaries in the DG, and that CCK knockdown induces a proinflammatory state and concomitant gliosis [85]. CCK has also been shown to modulate neurotrophin expression in the hippocampus and septum of rats [86], and may have a fundamental role in AD progression within the hippocampus [87].

4.3. Acetylcholine

Cholinergic projections from the diagonal band of Broca directly innervate immature neurons and support their development, however these projections degenerate in mouse models of AD [88]. Selective loss of forebrain cholinergic neurons mimics many AD symptoms, including reduced proliferation of NPCs [89,90]. Basal forebrain atrophy also correlates with amyloid burden and accelerated disease progression in AD and MCI patients [91]. Conversely, administration of acetylcholinesterase inhibitors, which are commonly used to treat AD, induces Ca^{2+} influx in NSCs, stimulating and boosting survival of NSC and NPC proliferation [92,93]. It has also been noted that acetylcholinesterase inhibitors may operate indirectly through muscarinic activation of septal GABAergic interneurons [94], described in detail later.

4.4. Serotonin

Serotonergic dysfunction is highly implicated in mood disorders and cognitive dysfunction in AD, and serotonergic fiber loss has been commonly observed in AD [95]. Unfortunately, elucidation of serotonergic control of AHN has been highly inconsistent, as serotonin (5-HT) can either inhibit or excite neurons based on the subtype of 5-HT receptor engaged. A broad census of studies suggests that increased 5-HT promotes proliferation, survival, and differentiation of NPCs, and that decreased 5-HT has the opposite effect, but importantly, not all results support this conclusion [96]. A number of studies have demonstrated increased neurogenesis after administration of compounds specific for the 5-HT1, 4, 6, 7 receptor subtypes [97], and serotonergic modulation represents a promising therapeutic strategy for AD [98]. These effects are promising for future clinical studies; while rarely discussed, mood disturbances are common symptoms of AD and robustly affect patient and caregiver quality of life.

4.5. Norepinephrine

Norepinephrine (NE), also known as noradrenaline, directly activates multipotent hippocampal precursors via β$_3$-adrenergic receptors [99]. Noradrenergic fibers from the locus coeruleus (LC) heavily innervate the DG under normal conditions, where they release NE during novel situations, i.e., enriched environments known to stimulate AHN. Unfortunately, noradrenergic transmission decreases precipitously in AD, as tau pathology originates in the LC and brainstem [100]. Depletion of NE from the neurogenic niche may therefore preclude aNSCs from properly responding to profound external stimuli.

4.6. Reelin and Cajal-Retzuis neurons

Reelin acts on the Disabled 1 (Dab1) receptor to regulate neuritogenesis and granule cell migration in AHN [101], but also serves crucial roles in synaptic regulation. Reelin is primarily produced by Cajal-Retzuis cells, an understudied subtype that, despite sharing common markers with interneurons (that may also express reelin), are functionally distinct excitatory neurons [102]. Reelin potentiates NMDAR to promote LTP, however; ApoE and reelin share the Apoer2 receptor, which is reduced in APOE4 neurons, thus inhibiting reelin signalling [103]. Reelin signaling is also dysregulated in AD [104] and accumulates in focal inclusions termed "reelin plaques" within the rodent hippocampal molecular layer throughout normal aging [105].

4.7. Neurotrophin signaling in Alzheimer's disease

Neurotrophins are peptide hormones instrumental in regulating neuronal development, survival, and maintenance. Recent studies highlight neurotrophins as both biomarkers and potential therapeutic agents for AD; brain-derived neurotrophic factor (BDNF), and the unprocessed form pro-BDNF are commonly decreased in AD patients [106], and BDNF polymorphisms are associated with AD vulnerability [107]. Conversely, higher BDNF expression can confer resilience to cognitive decline throughout aging and in the context of AD pathology [108]. BDNF replacement using adeno-associated viral (AAV) vectors rescues BDNF levels, neuronal loss, and behavioral deficits without altering tau phosphorylation in a common tauopathy mouse model [109]. BDNF supplementation also protects against Aβ-induced neurotoxicity in vitro and in vivo in rats [110], but when conditionally delivered from astrocytes, rescues synaptic plasticity and cognitive deficits without directly affecting neurogenesis [111].

Nerve growth factor (NGF) signaling is commonly dysregulated in AD; NGF levels rise in conjunction with NGF tyrosine kinase receptor (TRKA) downregulation, which may ultimately result in apoptotic signaling of NGF through the p75 neurotrophin receptor [112]. Similarly, NGF supplementation boosts newborn neuron survival in young adult, but not aged rats [113].

5. Neuronal infection, neuroinflammation, and AHN

A recent model of AD etiology suggests that disease progression is initiated or modified by infectious particles including bacteria, fungi, or virons such as herpesvirus or cytomegalovirus [114]. Although rare, viruses such as (Zika virus) are known to directly infect neural stem cells and disrupting Notch signalling [115]. If AD is indeed triggered by microbial infection, then viral infection of aNSCs may play a critical role in disease progression.

Studies in the 5xFAD model suggest that Aβ serves an immunoprotective function; aggregation on infectious particles labels them for destruction by microglia, the brain's resident immune cells [116]. Nonetheless, it appears that Aβ accumulation in response to infection ultimately leads to Aβ deposition [117], which, in turn, results in activation of microglia, resulting in the release of pro-inflammatory cytokines and synaptic pruning [118].

5.1. Microglia

Microglia are recruited by active synapses, where they make physical contacts with both synapses and astrocytes to either remove or protect synapses, depending on local stimuli [119]. While microglial synaptic pruning is necessary for normal brain development, activation by both Aβ and tau deposition induces aberrant glial activation and exacerbates phagocytic phenotypes [120]. Microglia release pro-inflammatory cytokines as well as neuroprotective and trophic factors, but phagocytosis of apoptotic cells fundamentally alters the microglial secretome, subsequently limiting neurogenesis both in vitro and in vivo [121].

Neuroinflammation and gliosis are associated with NSC pool depletion, and reduced survival of neural progenitor cells (NPCs) and immature neurons [122]. Neuroinflammation also alters the excitation/inhibition balance in the hippocampus; in the presence of LPS, microglia

secrete interleukin-1 beta (IL-1β), suppressing the postsynaptic action of GABA via activation of neuronal PKC, and reducing presynaptic GABA release via activation of toll-like receptor 4 (TLR4) [123] in the spinal dorsal horn. Hippocampal progenitors express IL-1β receptors, which mediate the effects of chronic stress by suppressing AHN [124]. Microglia have also been shown to selectively engulf inhibitory synapses while simultaneously secreting BDNF after LPS administration, resulting in an increase in excitatory neurotransmission throughout the brain [125].

5.2. Astrocytes

aNSCs can assume either neuronal (neurogenic) or astrocytic (gliogenic) fates, and increasingly trend towards the latter throughout aging [126]. Astrocytes make perisynaptic contacts on newborn neurons and support neurogenesis via both membrane-bound and extracellular factors [127], yet can also negatively regulate adult neurogenesis via notch signalling [128]. Under normal conditions, astrocytes act as neurotransmitter sinks and converters at the synaptic cleft, where they uptake glutamate and GABA, processing them into glutamine to supply back to neurons, however this process is impaired in AD [129]. Astrocytes release D-serine to support synaptic integration and dendritic development of adult-born neurons in vivo [130], however abnormally high D-serine production is associated with neurotoxicity [131].

Amyloid accumulation impairs astrocytic uptake of glutamate [132], further exacerbating hyperexcitability in the neurogenic niche. Conversely, in the 5xFAD Aβ model, reactive astrocytes contain high levels of GABA due to compensatory activation GAD67 that enhances tonic inhibition in the dentate gyrus and suppresses both LTP and memory formation, suggesting that astrocytes may also provide inhibition within the hippocampus [50]. Astrocytic reactivity may also be utilized to conditionally deliver BDNF to the hippocampus, rescuing dendritic spine density and morphology and partially recovering cognitive deficits in 5xFAD mice [133]. Astrocytes can also bidirectionally modulate neuroinflammation in the neurogenic niche; while A2 reactive astrocytes release neuroprotective factors, A1 neurotoxic astrocytes release deleterious cytokines or and phagocytize synapses when induced by neuroinflammatory stimuli or throughout the course of natural aging [134]. Astrocyte-derived proinflammatory cytokines such as interleukin-1 (IL-1), nitric oxide, and interleukin-6 (IL-6) can also drive NSC differentiation [135].

In addition to acting as synaptic modulators, astrocytes are also the primary synthesizers of glycogen, which is broken down into lactate and shuttled to neurons for use as energy substrate [136]. Both astrocytic glucose and Aβ uptake are dependent upon insulin-like growth factor-1 receptor signaling, which declines within natural aging [137]. Astrocytes can also donate healthy mitochondria to and uptake damaged mitochondria from mature neurons under stress conditions [138]. Finally, astrocytes are crucial intermediaries between the bloodstream and the brain. In response to neuronal activity, astrocytes release vasoactive factors to regulate blood perfusion to the brain, a process commonly impaired in the presence of Aβ [139].

5.3. Vascular dysfunction in the neurogenic niche

The DG is extensively permeated by blood vessels, where the high metabolic requirements of adult neurogenesis demand nutrients, trophic factors and structural support, but can also negatively regulate neurogenesis via plasma-borne molecules including corticosterone or chemokines [140]. AHN is acutely sensitive to peripheral influence; age-dependent alterations in plasma-borne factors reduced AHN as demonstrated by parabiosis experiments in rodents [141]. Maintenance of the blood–brain barrier (BBB) is critical to maintaining homeostasis in the brain, however the integrity of the BBB degrades throughout normal aging and AD progression [142]. Amyloid mouse models of AD demonstrate profound dysfunction of gliovascular pairing required for normal BBB function, which may underlie the reduced cerebral blood

flow common in AD patients, such that definition of a subclass of AD is sometimes referred to as "vascular dementia" [139]. Vascular amyloid accumulation results in a condition called cerebral amyloid angiopathy, found in at least 25% of AD cases, and highly associated with loss of potassium channels (Kir4.1) and water channels AQP4 in AD patient and mouse model brains [143]. Despite these associations, new evidence suggests that cerebral capillary damage and BBB breakdown in the hippocampus do not require Aβ or tau accumulation, and may therefore represent an early biomarker for human cognitive dysfunction [144]. Early alterations in cerebral vasculature or BBB integrity in prodromal stages of AD are likely to alter the microenvironment of the neurogenic niche via microglial activation [145] and/or infiltration of T-cells, which can suppress AHN [146].

6. Conclusions

In light of recent discoveries, we posit that the process of AHN is a key hub within the vicious cycle of neurological dysregulation. Following conventional theories of AD etiology, this cycle likely originates with inflammatory injury or insult in the aging brain that contributes to hyperexcitability and network dysfunction within the neurogenic niche. Reduced proliferation, survival, and/or increased gliogenesis by aNSCs may then in turn exacerbate each facet of AD progression. Detection of AHN deficits may therefore herald the onset of cognitive dysfunction and AD progression, and therapies that support neurogenic activities may protect the aging brain from further cognitive impairment. AHN therefore remains a process of interest for both biomarker studies and prospective therapies in the context of AD and natural aging. The complexity of neurogenic niche alterations in AD are major barriers to therapeutic development, but are not insurmountable via cell-type specific targeting of small molecules or biologics. More broadly, further study of the unique regenerative properties of the dentate neurogenic niche and eventual failure of such systems in late-stage AD will illuminate key neural and molecular pathways for prospective therapies of a wide variety of age-related disorders and neurodegenerative diseases.

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