

## REVIEW

# Hippocampal neurogenesis and pro-neurogenic therapies for Alzheimer's disease

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**Abstract**

Adult hippocampal neurogenesis (AHN) facilitates hippocampal circuits plasticity and regulates hippocampus-dependent cognition and emotion. However, AHN malfunction has been widely reported in both human and animal models of Alzheimer's disease (AD), the most common form of dementia in the elderly. Pro-neurogenic therapies including rescuing innate AHN, cell engraftment and glia-neuron reprogramming hold great potential for compensating the neuronal loss and rewiring the degenerated neuronal network in AD, but there are still great challenges to be overcome. This review covers recent advances in unraveling the involvement of AHN in AD and highlights the prospect of emerging pro-neurogenic remedies.

**KEYWORDS**

Alzheimer's disease, cognitive deficit, hippocampus, neurogenesis, pro-neurogenic therapy

## 1 | INTRODUCTION

Adult hippocampal neurogenesis (AHN) in the hippocampal dentate gyrus (DG) subset enables the neuronal network to encode new information flexibly and update stored content in due time.<sup>1</sup> Though the number of adult-born neurons declines with age, there is increasing evidence of an indispensable role for limited AHN in hippocampus-dependent learning, memory and emotional regulation.<sup>2</sup>

Alzheimer's disease (AD) is the most common cause of dementia in people over age 65. It is characterized by progressive neurodegeneration in the brain, with no treatment to date for halting disease progression. A sea of money has been invested in the development of anti-AD drugs. Two major drug targets include the extracellular amyloid-beta (A $\beta$ ) protein and intraneuronal hyperphosphorylated

tau. Besides considering the anti-neurodegenerative potential of AHN and other pro-neurogenic treatments, neuroscientists are also trying to develop new drugs to directly facilitate neurogenesis in the AD brain.<sup>3</sup>

However, introducing neurogenesis is challenging in AD. The pool of active hippocampal neural stem cells (NSCs) is prone to being progressively depleted due to sustained homeostatic abnormality within the neurogenic niche under AD and accelerated aging.<sup>4</sup> Innate AHN is dysregulated under AD and the underlying mechanisms remain largely unknown,<sup>5</sup> which hinders the development of pro-AHN drugs.

Simultaneously, emerging techniques such as cell transplantation and glia-neuron reprogramming also shed new light on the pro-neurogenic treatment of AD.<sup>3</sup> These strategies may help overcome

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the quantitative and spatiotemporal restriction of innate AHN, but their efficiency and safety still remain controversial.

Here, we review progress in unveiling the involvement of AHN in AD, discuss the controversies around the change of AHN in AD patients and animals, and highlight the prospect of emerging pro-neurogenic therapies for AD.

## 2 | AHN IN HUMANS

While the overwhelming majority of neurons in human brain differentiate during embryogenesis, scattered adult neurogenesis has been widely revealed in some mammals in recent decades as well—predominantly in the hippocampal subgranular cell zone (SGZ), subventricular zone (SVZ)<sup>2</sup> and occasionally in the amygdala,<sup>6</sup> stratum,<sup>7,8</sup> etc. In particular, neurogenesis in the hippocampal subset, namely AHN, shows high correlation with cognition and dementia in animal studies. Thus, in this review the focus is on neurogenesis in the hippocampus.

Neurogenesis is derived from the proliferation of NSCs and the subsequent neuronal differentiation of intermediate progenitor cells (IPCs). Broadly speaking, the biological process of neurogenesis also involves the migration, dendritic maturation and synaptic integration of newborn neurons. Different biomarkers can be used to identify different phases during the neurogenesis (Figure 1), among which is the expression of doublecortin (DCX). Though DCX is in fact not universal across species,<sup>9</sup> instable post-mortem<sup>10</sup> and nonexclusive to new neurons,<sup>11</sup> it is widely recognized as a gold standard for the evaluation of neurogenesis.

### 2.1 | Controversies over the existence of AHN in humans

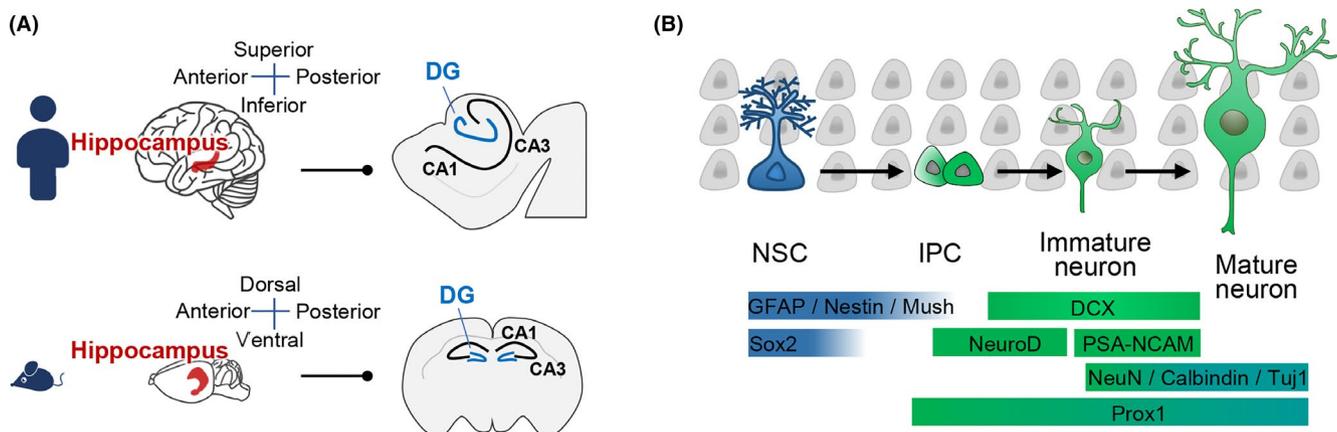
In recent decades, there has been heated debate about whether AHN also exists in human.

In 1998, researchers from Sweden and America first reported the existence of AHN in autopsies from cancer patients ( $n = 5$ , 57–72 years of age) who had received one intravenous infusion of bromodeoxyuridine (BrdU), a thymidine analog which can incorporate into the DNA of dividing cells—for diagnostic purposes before death. Based on the co-labeling of BrdU-positive cells with NeuN, a marker of mature neurons, they thought these newborn cells in the hippocampus were neurons.<sup>12</sup>

However, a subsequent study reported that AHN labeled by DCX and beta III tubulin was detectable only in infants ( $n = 10$ ), and proliferating cells in the hippocampus of older humans ( $n = 13$ , 3–23 years of age) were considered to be microglia since Ki67-immunoreactive cells could be stained by the ionized calcium-binding adaptor molecule-1 (Iba1) antibody.<sup>13</sup> This finding that AHN tends to disappear in adult humans is generally consistent with a new study published in 2018 which reported that the number of newborn hippocampal neurons declined sharply before 1 year of age, with only a few isolated young neurons observed by 7–13 years of age, and no AHN detected in neurobiologically healthy adults and patients with epilepsy ( $n = 17$ , 18–77 years of age).<sup>14,15</sup> Consistent with these reports, it has been revealed that despite NSCs and IPCs being continuously observed in the human hippocampus, their neurogenic potential is seemingly negligible since the age-associated expression of the Ki67 (cell proliferation) and DCX (neuronal differentiation) is unrelated.<sup>16,17</sup>

However, the controversy has been reignited by the most recent studies, which detected consistent biomarkers for AHN, as previously, but used either enhanced immunostaining protocols<sup>18</sup> or autaptic samples with shorter post-mortem delays (PMD), which have been demonstrated to impair brain antigenicity.<sup>10</sup> These studies demonstrated that the AHN was preserved both in neurobiologically healthy individuals and those diagnosed with neurodegenerative diseases including AD at about 90 years old.<sup>19–23</sup>

Considering the studies to date, we cannot reach a conclusion yet on whether AHN is preserved or not in humans until more direct and solid evidence is revealed. Nevertheless, given the majority of findings and the most recently published evidence, some neuroscientists



**FIGURE 1** Adult hippocampus neurogenesis. (A) Illustration of the anterior-posterior (ventral-dorsal) axis of hippocampus. (B) Different biomarkers of AHN during different stages

argue that it is currently unreasonable to abandon the idea that AHN exists in human and could potentially make important contributions to hippocampus-dependent functions.<sup>9</sup>

## 2.2 | Challenges in detecting human AHN

It is quite challenging to unveil AHN in humans. Most studies to date have used immunostaining and/or immunoblotting to detect the expression of neurogenesis marker proteins to determine the existence of AHN. However, the specificity, reliability and stability of these methods remain debatable.

A specific biomarker for AHN in human is lacking. Though DCX has been widely used as a gold standard for detecting neurogenesis, its expression is actually not universal across species<sup>9</sup> and not exclusive to newborn neurons.<sup>11</sup> Consideration of whether the DCX-stained cell shares typical morphological characteristics with immature neurons or not may help in reaching a more reliable conclusion before more a selective biomarker is found. However, DCX-staining is instable post-mortem and different PMDs might result in different immunostaining morphologies.<sup>10</sup>

Dual antigen retrieval also seemed helpful in revealing more extensive AHN,<sup>18</sup> but opponents have insisted that it could provide misleading results by changing cell morphology and impairing immunostaining specificity.<sup>11</sup> Along with immunostaining, RNA-sequencing and scope can provide parallel evidence. However, different studies have reached inconsistent conclusions. Evidence for the existence of human AHN is presented by studies showing the expression of several genes related to neurogenesis including DCX,<sup>23</sup> bone morphogenetic protein-6 (BMP6)<sup>24</sup> and AST4<sup>25</sup> in adult human hippocampus, but another group reported that though DCX mRNA and protein could be clearly detected in some hippocampal cells, those cells were not dentate granule cells, i.e. the cell-type predicted to be generated in AHN.<sup>26</sup>

Post-mortem cellular breakdown greatly hinders the measurement of AHN in autopsy, while bioptic hippocampal samples obtained from patients with, for example, epilepsy and glioma can hardly provide evidence about the existence of AHN in healthy individuals. As an alternative, researchers have been working for decades on viewing neurogenesis *in vivo* in human brains using techniques such as magnetic resonance imaging/spectroscopy (MRI/MRS),<sup>27,28</sup> <sup>14</sup>C-dating<sup>29</sup> and positron emission tomography (PET),<sup>30</sup> but to date there is no algorithm or tracer that can selectively identify neurogenesis. Combinative use of fluorescent labeling with two-photon live imaging has furnished us with a comprehensive view of neurogenesis in animal experiments,<sup>31</sup> but ethical and safety concerns should be addressed before application of this technique to humans.

In addition, most if not all studies to date have used autoptic brain samples from individuals who died from/with chronic diseases such as heart failure, cancer, hemorrhage and infection as neurobiologically healthy controls, but they were not in fact healthy. It should be also taken into consideration that each adult human,

unlike experimental animals, generally shows a complicated history of growing, aging, illness and medication. Each of these experiences might result in irreversible changes in AHN at a certain time period.

## 3 | AHN IN AGING

Regardless of controversies over the scale of AHN in adults, it is well-accepted that postnatal hippocampal neurogenesis does drop with age. Given that aging is an indispensable aspect of AD, investigations of the mechanism underlying the age-dependent decline of AHN will provide us with parallel suggestions for unravelling the involvement of AHN in AD.

It has been revealed in post-mortem tissues that mRNA levels of NSC marker genes Nestin and GFAP remain almost unchanged with age, while genes indicating cell proliferation and neurogenesis like Ki67 and DCX both show progressive and significant decreases.<sup>17,22</sup> This suggests that the NSC pool is preserved but its neurogenic potential is somehow impaired during aging.

Ethical restrictions make it quite difficult to collect human brain samples. Given that AHN also shows age-dependent decline in murine models,<sup>32,33</sup> animal studies may reveal some mechanisms shared with humans underlying the aging-induced AHN impairment. It was found in mice that the pool of NSCs falls in juveniles as a result of abundant early-life neurogenesis, but a number of activated NSCs subsequently return to a resting state thanks to the progressively reduced expression of a pro-activation gene achaete-scute homolog 1 (Ascl1). In consequence, the pool of NSCs remains relatively stable in adulthood.<sup>34</sup>

However, at later ages, most NSCs transform from an alpha-type, which maintains the classic type-1 radial morphology and induces neurogenesis, to an omega-type, which shows reactive-like morphological complexity and much lower probability of division.<sup>35</sup> The transformation between different NSC subsets might be driven by a change of intracellular gene expression profile. Indeed, using single-cell RNA sequencing, one study has shown that different NSCs have highly similar yet distinct transcriptional profiles. A subpopulation of NSCs expressing GLI family zinc finger 1 (Gli1) showed long-term self-renewal properties while the Ascl1-expressing NSCs underwent limited proliferative activity before they become exhausted, providing further evidence of the existence of heterogeneous NSC populations within the adult hippocampus.<sup>36</sup>

Animal studies have also suggested important roles of several genes such as Cdk4/cyclinD1,<sup>37</sup> Lamin B1,<sup>32</sup> BMP6,<sup>38</sup> Tet2<sup>39</sup> and  $\beta$ 2-microglobulin<sup>40</sup> in determining the decline of AHN during aging. In addition, systemic factors like the circulatory environment also contribute to changes in AHN. Aged blood can impair hippocampal neurogenesis through upregulation of the expression of vascular cell adhesion molecule 1 (VCAM1) in brain endothelial cells (BECs), which can activate microglia, thus leading to increased neuroinflammatory responses and suppression of AHN.<sup>41</sup> In addition, plasma chemokines like eotaxin and glucocorticoid hormones have also been shown to correlate significantly with neurogenesis in aged

mice.<sup>41,42</sup> Administration of plasma from exercised aged mice, which contains glycosylphosphatidylinositol-specific phospholipase D1 (Gpld1) derived from liver, can transfer the effects of exercise on AHN and cognition to sedentary aged mice.<sup>43</sup>

It should be noted that although newborn hippocampal neurons drop in number during aging and exhibit slow development, these cells also display remarkable potential for neural network plasticity.<sup>44</sup> Therefore, pro-neurogenic administration still has potential to improve hippocampus-dependent cognition in senescent individuals.<sup>4</sup>

## 4 | AHN AND AD

AHN is highly vulnerable to homeostatic abnormality in the neurogenic niche under diseases.<sup>45</sup> Despite the fact that AHN disorders have been widely reported in both AD patients and animals, how AHN is facilitated or suppressed during different AD stages remains inconclusive.<sup>5</sup> It is also unclear whether and to what extent the AHN malfunction contributes to the pathogeny of AD. Notwithstanding, ablation of AHN can exacerbate cognitive deficits in AD,<sup>46</sup> and pro-neurogenic treatments were found to be effective in ameliorating the cognitive impairment in AD.<sup>47,48</sup> Here, we discuss the involvement of AHN in AD in both human and animal studies.

### 4.1 | AHN changes in AD patients

AD is a chronic disease with progressive neurodegeneration caused by multiple pathophysiological factors that may dysregulate AHN at different stages and in different ways. Currently, the reports about how AHN changes during AD progress are inconsistent (Table 1).

It was first reported in 2004 that early-moderate-severe AD patients generally showed higher expression of AHN biomarkers, including the well-recognized DCX and other neurogenesis-related proteins such as the polysialylated neural cell adhesion molecule (PSA-NCAM), NeuroD, Calbindin, etc., compared with neuropathologically normal (but generally younger in age) controls.<sup>49</sup>

However, subsequent studies using comparable immunostaining methods and post-mortem samples observed merely increased expression of Ki67 (marker for cell proliferation) and Nestin, but decreased expression Musashi-1 (marker for stem cells), as well as no significant alteration in DCX and  $\beta$ -III-tubulin (marker for neuronal differentiation/migration), suggesting that though NSCs seem to show higher rates of proliferation to compensate for the attenuation of their pool, they induce no increase in the number of migratory neuroblasts and immature neurons. This kind of compensative proliferation seems to induce only NSC-derived gliosis but not neurogenesis.<sup>10,50</sup>

By contrast, more studies have suggested a predominant decrease in AHN in AD patients. Reduced expression of both DCX

TABLE 1 AHN changes in AD patients

Age (years)	N	PMD (h)	Method	Biomarker changes	Refs.
43–87, CN 52–97, AD	13, CN 45, AD	2.5–38	IF	<ul style="list-style-type: none"> <li>• DCX ↓</li> <li>• DCX<sup>+</sup>PSA-NCAM<sup>+</sup>/DCX<sup>+</sup> ratio ↓</li> <li>• DCX<sup>+</sup>Prox1<sup>+</sup>/DCX<sup>+</sup> ratio ↓</li> <li>• DCX<sup>+</sup>NeuN<sup>+</sup>/DCX<sup>+</sup> ratio ↓</li> <li>• DCX<sup>+</sup><math>\beta</math>III-tubulin<sup>+</sup>/DCX<sup>+</sup> ratio ↓</li> <li>• DCX<sup>+</sup>CB<sup>+</sup>/DCX<sup>+</sup> ratio ↓</li> <li>• No significant change in DCX<sup>+</sup>GFAP<sup>+</sup> /DCX<sup>+</sup> and DCX<sup>+</sup>CR<sup>+</sup>/DCX<sup>+</sup> ratios</li> </ul>	21
79–93, CN 86–95, MCI 85–99, AD	6, CN 6, MCI 6, AD	4.4–43.6	IF	<ul style="list-style-type: none"> <li>• DCX<sup>+</sup>PCNA<sup>+</sup> ↓ in MCI + AD cohort (<math>p = .067</math>)</li> </ul>	20
81.2 ± 7.0, AD 80.9 ± 8.5, ND	13, ND 13, AD	NA	IHC	<ul style="list-style-type: none"> <li>• Nestin ↑, PSA-NCAM ↑</li> <li>• Musashi-1 ↓</li> <li>• No significant change in DCX and <math>\beta</math>III-tubulin</li> </ul>	50
87.0 ± 4.6, ND 80.0–86.1 AD	5, ND 14, AD	8.2–11.8	IF	<ul style="list-style-type: none"> <li>• DCX ↓, Sox2 ↓</li> </ul>	24
63–69, CN 63–69, AD	10, CN 9, AD	3.0–17.0	IHC	<ul style="list-style-type: none"> <li>• No significant change in Ki67</li> <li>• GFAP ↑</li> <li>• DCX-immunoreaction was unstable and too low to draw a conclusion</li> </ul>	10
13–74, CN 68–90, AD	10, CN 14, AD	4–20	WB, IHC	<ul style="list-style-type: none"> <li>• No statistical result but prominent increases were shown in representative images of DCX, PSA-NCAM, NeuroD, TUC4 and calbindin</li> </ul>	49

Abbreviations: AD, Alzheimer's disease; BMP6, Bone morphogenetic protein 6; CB, Calbindin; CN, cognitively normal; CR, Calretinin; DCX, Doublecortin; h, hours; IF, Immunofluorescence; IHC, Immunohistochemistry; MCI, mild cognitive impairment; N, number; ND, non-dementia; NeuN, neuronal nuclei; PCNA, proliferating cell nuclear antigen; PMD, Post-mortem delay; PSA-NCAM, Polysialylated neural cell adhesion molecule; WB, Western blotting.

and Sox2 (a marker for IPCs) was found in an immunofluorescent staining study in severe but not early-stage AD patients compared with nondemented controls.<sup>24</sup> This was consistent with a more recent study using high-quality samples with short post-mortem delay (PMD) and defined background information, in which a significant decrease in the number of DCX/PCNA (proliferating cell nuclear antigen) co-labelled neuroblasts was observed in subjects with both mild cognitive impairment (MCI) and AD.<sup>20</sup> Similarly, AD Braak stage-correlated decreases in DCX<sup>+</sup> cells as well as decreased rates of DCX<sup>+</sup>PSA-NCAM<sup>+</sup>, DCX<sup>+</sup>Prox1<sup>+</sup>, DCX<sup>+</sup>βIII-tubulin<sup>+</sup> and DCX<sup>+</sup>Calbindin<sup>+</sup> cells were also revealed in a larger-scale ( $N = 13/45$  for ctrl/AD) study which applied optimized immunostaining protocols to facilitate the detection of AHN.<sup>21</sup>

The controversy can at least partly be blamed on different staining methodologies. The use of DCX as a gold marker of neurogenesis has long been suspect because it does not selectively express in newborn neurons and is sensitive to post-mortem breakdown.<sup>10,51</sup> Besides, some neuroscientists take the view that dual antigen retrieval should not be applied for the detection of AHN since it can induce nonspecific immunoreactivity,<sup>11</sup> but there is currently no better way to prevent post-mortem protein breakdown and immunogenicity impairment. Different sample quality and resources could also result in different results. PMD is also a big concern in the detection of AHN, but it is too difficult for different studies to collect human samples with the same PMD. In addition, variation in subject characteristics such as race, ethnicity, age, gender, living and working environment, medical history, etc. might also contribute to the inconsistency among different reports, and all these factors might have some influence on the AHN.<sup>52</sup>

## 4.2 | AHN changes in AD animals

Similar to human studies, it remains debatable how AHN changes in AD animals. This review provides a summary of studies measuring AHN in different mouse models with AD-mimic Aβ deposition, tauopathy and aging acceleration (Tables 2 and 3).

The majority of studies using amyloid precursor protein (APP) and/or presenilin-1 (PS1) mutated mice including 5x*FAD*,<sup>53</sup> Tg2576,<sup>54,55</sup> J20,<sup>56</sup> PS-1<sup>57,58</sup> and APP/PS1<sup>59-61</sup> lines have reported decreases in AHN compared with wild-type littermates, while several studies have found increases<sup>62-64</sup> or no change<sup>65</sup> in AHN in similar AD models. Further investigations suggest that the alteration of AHN is dependent on the age of animal. The extent of AHN tends to increase in the presenile stages of amyloid pathology but decrease during senile stages.<sup>66-68</sup> AD animals may also show differences in AHN change with different living experiences<sup>69</sup> as well as in different DG subregions like SGZ and granular cell layer (GCL).<sup>70</sup>

In contrast to Aβ-models, in mice with AD-like tauopathy AHN consistently decreases in different studies (Table 3). The intracellular hyperphosphorylation and accumulation of tau in AD patients can be mimicked by overexpression of wild-type or mutated human tau (hTau) in animals,<sup>71,72</sup> and different patterns of hTau-overexpression

may influence AHN through different mechanisms. For example, hTau accumulation in GABAergic interneurons within the DG subset impairs AHN by facilitating NSC-derived astrogliosis.<sup>47</sup> 3R-hTau overexpression in DG hilar astrocytes leads to AHN deficits by altering mitochondrial dynamics and function,<sup>73</sup> and overexpression of anti-aggregant tau<sup>RDΔKPP</sup> mutant instead of pro-aggregant tau<sup>RDΔK</sup> in mice can enhance AHN by activating the canonical Wnt signaling pathway.<sup>74</sup> In addition, it should be noted that, though phospho-tau accumulation is detrimental to AHN, tau *per se* as a microtubule associated protein plays essential roles in axonal growth and synapse formation.<sup>75</sup> Depletion of tau can hinder the experience-dependent regulation of AHN in conditions such as chronic stress and environmental enrichment.<sup>76,77</sup>

In triple transgenic (3xTg) AD mice which carry triple mutations of APP<sup>swe</sup> (KM670/671NL), PS-1 (M146V) and MAPT (P301L), AHN has consistently been found to be impaired at 2-18 months of age,<sup>47,78-81</sup> while the extent of AHN tends to increase at an early age (with impairment in survival and maturation) but decrease in the elderly,<sup>82</sup> and the transient upregulation of AHN comes at the cost of advanced depletion of the NSC pool<sup>4</sup> in SAM-P8, an AD-like mouse line showing accelerated senescence but carrying undefined gene mutations. These lines might provide us with a closer look at AHN changes in the AD brain compared with monotype transgenic models, while whether and how AHN impairment results from Aβ and/or tau pathology as well as other pathological factors deserves further investigation, since they may exert different influences on AHN.<sup>75,83</sup>

Taking current evidence together, AHN generally shows deficits in late-stage AD while temporary increases may occur at certain phases during the disease progression.

## 4.3 | AHN promotion for AD treatment

Given the critical role of AHN in hippocampus-dependent learning and memory, and the potential of neurogenesis to compensate for neuronal loss and rewiring degenerated neural circuits, researchers are seeking to promote or at least preserve innate AHN in a bid to ameliorate cognitive deficit in AD.

Indeed, enhancing AHN by exercise, which can facilitate NSC proliferation, neuronal differentiation and maturation,<sup>84</sup> or by combinative using of brain-derived neurotrophic factor (BDNF), which can promote the survival and differentiation of newborn neurons,<sup>85</sup> with P7C3 (also known as aminopropyl carbazole), which protects newborn neurons from apoptosis,<sup>86</sup> can both improve cognition in AD mice.<sup>48</sup> Moreover, potentiating GABAergic signaling by 4,5,6,7-tetrahydroisoxazolo [5,4-c]pyridin-3-ol (THIP, also known as gaboxadol) or pentobarbital is also capable of protecting AHN in AD by strengthening GABAergic transmission within the neurogenic niche.<sup>47,87</sup> In contrast, complete ablation of AHN by focal irradiation or Nestin-driven thymidine kinase ( $\delta$ -HSV-TK) expression + ganciclovir (GCV) can exacerbate cognitive deficits in AD.<sup>46,48</sup>

However, it should be noted that the effectiveness of pro-AHN remedies is presumed to be primarily dependent on the functional

TABLE 2 AHN changes in AD animals

Model	Mutation(s)	Age & biomarker changes	Refs.
Tg2576	APP KM670/671NL (Swedish)	<ul style="list-style-type: none"> <li>• 3-month, BrdU-proliferation ↑, survival ↓; BrdU<sup>+</sup> DCX<sup>+</sup> ↓</li> <li>• ROV-dendrite maturation ↓, axon growth ↓</li> <li>• 9-month, BrdU ↓, BrdU<sup>+</sup>NeuN<sup>+</sup> ↓, BrdU<sup>+</sup>NeuN<sup>+</sup>/BrdU<sup>+</sup> ↓</li> </ul>	131 132
PDAPP	APP V717F (Indiana)	<ul style="list-style-type: none"> <li>• 12-month, BrdU-proliferation ↓, survival ↓</li> <li>• DCX-SGZ ↓, oGCL ↑</li> <li>• BrdU<sup>+</sup>/DCX<sup>+</sup>-No change in SGZ, oGCL ↑</li> <li>• No change in NeuN and GFAP</li> </ul>	70
J20	APP KM670/671NL (Swedish) APP V717F (Indiana)	<ul style="list-style-type: none"> <li>• 3-month, BrdU ↑, DCX ↑</li> <li>• 12-month, BrdU ↑</li> <li>• 3-month, BrdU-proliferation ↑, survival ↓; Ki67 ↑, NeuN ↑, PSA-NCAM ↑</li> <li>• 5-month, BrdU-proliferation ↓</li> <li>• &gt;9-month, No change in BrdU and Ki67</li> <li>• 2–3 months, ROV-dendrite maturation ↓</li> </ul>	64 68 56
PS1	PS-1 M146V	<ul style="list-style-type: none"> <li>• 3-month, BrdU ↓, BrdU<sup>+</sup>/NeuN<sup>+</sup> ↓</li> </ul>	57
	PS-1 P117L	<ul style="list-style-type: none"> <li>• ~3-month, BrdU ↓, βIII-tubulin ↓, calbindin ↓</li> </ul>	58
	PS-1 A246E	<ul style="list-style-type: none"> <li>• 12-month, BrdU ↑, No change in BrdU<sup>+</sup>/NeuN<sup>+</sup></li> </ul>	63
APP/PS1	APP KM670/671NL (Swedish) PS-1-dE9	<ul style="list-style-type: none"> <li>• 2-month, BrdU ↓, BrdU<sup>+</sup>/DCX<sup>+</sup> ↓</li> <li>• 6-month, BrdU ↓, BrdU<sup>+</sup>/NeuN<sup>+</sup> ↓, No change in Ki67</li> <li>• 7-day, BrdU ↓, no change in Nestin, DCX<sup>+</sup>Nestin<sup>+</sup>, GFAP<sup>+</sup> Nestin<sup>+</sup>, NeuN and dendrite maturation</li> <li>• 1-month, BrdU ↓, Nestin ↓, dendrite maturation ↓, no change in DCX<sup>+</sup>Nestin<sup>+</sup>, GFAP<sup>+</sup> Nestin<sup>+</sup> and NeuN</li> <li>• 3, 7-month, BrdU ↓, Nestin ↓, DCX<sup>+</sup>Nestin<sup>+</sup> ↓, GFAP<sup>+</sup> Nestin<sup>+</sup> ↓, NeuN ↓, dendrite maturation ↓</li> </ul>	60 61 59
5xFAD	APP KM670/671NL (Swedish)	<ul style="list-style-type: none"> <li>• 2, 3, 4, 7-mnth, DCX ↓</li> </ul>	53
	APP I716V (Florida)	<ul style="list-style-type: none"> <li>• 4-month, DCX ↑, Ki67 ↑</li> </ul>	67
	APP V717I (London)	<ul style="list-style-type: none"> <li>• 8-month, DCX ↓, No change in Ki67</li> </ul>	
	PS1 M146L (A>C)		
	PS1 L286V		
3xTg	APP KM670/671NL (Swedish)	<ul style="list-style-type: none"> <li>• 2, 3-month, no change in HH3</li> <li>• 4, 6, 9, 12-month, HH3 ↓ (prominent in female)</li> <li>• 2-month, Ki67 ↓, DCX ↓, Ki67<sup>+</sup>/DCX<sup>+</sup> ↓, Ki67<sup>+</sup>/GFAP<sup>+</sup> ↓</li> <li>• 11, 18-month, BrdU ↓, Ki67 ↓, DCX ↓</li> <li>• 6-month BrdU ↓, DCX ↓, ROV-dendrite maturation ↓</li> <li>• GFAP-GCL ↓, ML ↑</li> <li>• 6-month BrdU/NeuN ↓, DCX ↓</li> </ul>	81 78,80 47 79
	PS-1 M146V		
	MAPT P301L		
SAM-P8	NA	<ul style="list-style-type: none"> <li>• 3-month, BrdU ↑, DCX ↑, ROV-dendrite maturation ↓</li> <li>• 6-month, BrdU ↓, DCX ↓, ROV-dendrite maturation ↓</li> <li>• 5-month, BrdU-proliferation ↑, survival ↓; DCX ↑, NeuN ↓, BrdU<sup>+</sup>/NeuN<sup>+</sup> ↓, GFAP ↓, BrdU<sup>+</sup>/GFAP<sup>+</sup> ↓</li> <li>• 10-month, BrdU- no change in proliferation, survival ↓; No change in DCX, NeuN ↓, BrdU<sup>+</sup>/NeuN<sup>+</sup>, GFAP ↓, BrdU<sup>+</sup>/GFAP<sup>+</sup> ↓</li> </ul>	4 82

Abbreviations: GCL, granular cell layer; HH3, phosphorylated Histone H3; NA, not available; oGCL, outer granule cell layer; ROV, retrovirus; SGZ, subgranular cell zone.

maturation and synaptic integration of newly-born neurons. Increase merely in the extent of AHN should not necessarily bring any significant benefit to learning and memory. That may be the reason why forcibly preventing the apoptosis of immature neurons with P7C3 + LV-Wnt3 without exercise has shown limited efficiency in ameliorating cognitive deficits in AD.<sup>48</sup>

Other pro-neurogenic drugs like NNI-362<sup>88</sup> and doxycycline,<sup>89</sup> as well as treatments like neurostimulation,<sup>90</sup> running,<sup>84</sup> environmental

enrichment<sup>91</sup> and dietary interventions,<sup>92</sup> have also shown potential for the facilitation of AHN in AD, but the molecular mechanisms underlying most of these interventions still remain largely unknown. Besides, gene therapy—for example, lentivirus-mediated overexpression of Wnt3,<sup>93</sup> an upstream activator of β-catenin pathway—can be also used to promote AHN and treat AD.

Notwithstanding, it should be noted that innate AHN is still limited in scale, and shows neuronal type monotonicity, spatial

**TABLE 3** AHN changes in animals with AD-like tauopathy

Tau pathology	Age / time & Biomarker changes	Refs.
2N4R hTau KI Murine tau KO	• 2-month, BrdU ↑, DCX ↑	133
hTau (3R+4R) KI Murine tau KO	• 2, 6-month, Ki67 ↓, DCX ↓ • 12-month, DCX ↓	71
Intra-DG injection of human Tau42-Cy5	• 2-month + 8 wpi, no significant change in DCX, ROV-dendrite maturation ↓	134
2N4R hTau OE in DG GABAergic interneurons	• 2-month + 4 wpi, BrdU ↓, DCX ↓, NeuroD1 ↓, ROV-dendrite maturation ↓, • 2-month + 6 wpi, NSC-derived astrogliosis ↑	47
1N3R hTau OE in hilar astrocytes	• 3-month + 4 mpi, No significant change in BrdU-proliferation, DCX ↓	73
THY-Tau22/Tg30 (Thy1.2-IN4R hTau (G272V, P301S))	• 6-month, BrdU ↑, DCX ↑ • 12-month, DCX ↓, Ki67 ↓, 3R-tau ↓	72 135
Tg30&tau KO (Thy1.2-IN4R hTau (G272V, P301S), with murine tau KO)	• 12-month, DCX ↑	135
Tau <sup>VLW</sup> (Thy1-2N4R hTau (G272V, P301L, R406W))	• 2-month, DCX ↓, IdU ↓	136
Tau <sup>RDΔK</sup> (OE of hTau four repeat domain, with pro-aggregant ΔK280 mutation)	• 8-day, no significant change in BrdU • 12-dmonth, hippocampal volume ↓	74
Tau <sup>TauRDΔKPP</sup> (Tau <sup>RDΔK</sup> with additional anti-aggregant Ile277Pro and Ile208Pro mutations)	• 8-day, no significant change in DG BrdU, hippocampal volume ↑ • 12-dmonth, hippocampal volume ↑	74

Abbreviations: hTau, human tau; KI, knock-in; KO, knock-out; OE, overexpression; ROV, retrovirus.

restriction and vulnerability to homeostatic abnormality in the brain. In particular, (1) the number of innate radial NSCs drops sharply during aging, (2) only excitatory granular cells are generated during AHN, (3) hippocampal NSCs are restricted within the DG SGZ, and (4) changes in AHN are likely to be driven by pathological factors in AD. All these factors complicate the application of pro-AHN treatments against AD.

Nevertheless, further studies investigating the dysfunction of innate AHN in AD are still needed. Though limited in number, there have been findings indicating the critical role of AHN in hippocampal memory formation and loss, which are the two fundamental concerns in AD and other types of dementia. Moreover, AHN is at least a stable and accessible *in vivo* experimental model for studying how AD-related pathological factors affect the process of neurogenesis. It can be used not only for developing drugs to enhance innate AHN, but also for directing future studies of stem cell-based therapies and genetic glia-neuron conversion.

## 5 | OTHER PRO-NEUROGENIC THERAPIES FOR AD

Given the limitation of innate AHN in rescuing the intensive and extensive neurodegeneration in AD brains, neuroscientists are seeking other ways to induce neurogenesis, such as cell grafting and

glia-neuron reprogramming, whereby the regeneration of specific type of neurons in a spatiotemporally flexible way can be achieved.

### 5.1 | Cell transplantation

Stem cells and neuronal precursors can be used in transplants for AD treatment, and the majority of previous studies have reported positive outcomes of cell therapy in alleviating AD symptoms.<sup>94</sup> For example, a single dose of human NSCs derived from fetal telencephalon ( $5 \times 10^5$  cells/ $5 \mu\text{l}$ , bilateral injection into lateral ventricles) exerted widespread anti-AD effects in 13-month NSE/APPsw transgenic mice, including decreasing A $\beta$ 42 levels, downregulating tau phosphorylation, attenuating gliosis and suppressing neuroinflammation in the brain.<sup>95</sup> Similarly, single or multiple doses of mesenchymal stem cells (MSCs) (i.v.,  $1 \times 10^6$  MSCs/ $200 \mu\text{l}$  for each dose) showed anti-inflammatory effects, promoted A $\beta$  cleavage and decreased phospho-tau level.<sup>96</sup> Repetitive intranasal delivery of human NSCs ( $8 \mu\text{l}$ ,  $1 \times 10^6$  cells,  $4 \mu\text{l}/\text{side}$ ) also exhibited widespread neuroprotective effects against AD.<sup>97</sup>

Moreover, neural crest-derived nasal turbinate stem cells (NTSCs),<sup>98</sup> bone marrow mesenchymal stem cells (BM-MSCs),<sup>99,100</sup> umbilical cord-derived mesenchymal stem cells (hUC-MSCs),<sup>101</sup> human induced pluripotent stem cell (hiPSCs)<sup>102,103</sup> etc. have also shown therapeutic effects in preclinical studies.

However, there are still potential risks in cell therapy. (1) Similar to innate AHN, the donor cell-derived neurogenesis may also be altered by AD pathologic factors. For example, high-level accumulation of phosphorylated tau in GABAergic interneurons can facilitate NSC-derived astrogliosis and suppress neurogenesis in AD.<sup>47</sup> (2) The host brain may exhibit immunological rejection of engrafted cells. (3) Squeezing engrafted cells between existing cells would exert negative effects on each cell type. (4) Grafted cells hold potential for tumorigenicity.

The good news is that clinical trials have already shown the safety and therapeutic effectiveness of stem cell transplantation in neurodegenerative diseases such as Parkinson's disease.<sup>104</sup> Clinical trials in AD patients are also ongoing. A phase-I clinical trial has shown that mild-to-moderate AD patients ( $N = 9$ ) receiving a stereotactic brain injection of human UCB-MSCs reported no dose-limiting toxicity and serious adverse reactions in both low ( $3.0 \times 10^6$  cells/60 ml) and high ( $6.0 \times 10^6$  cells/60 ml) dose groups.<sup>105</sup> Similar results were observed in a recent study in which 9 mild-to-moderate AD patients were recruited and received low ( $1.0 \times 10^7$  cells/2 ml,  $N = 3$ ) or high ( $3.0 \times 10^7$  cells/2 ml,  $N = 6$ ) doses of human umbilical cord blood-derived MSCs (hUCB-MSCs) through Ommaya reservoirs implanted into the right lateral ventricle. In this study, participants reported only common adverse event like fever, headache, nausea and vomiting within 36 h of cell transplantation.<sup>106</sup> There are many other ongoing clinical trials testing stem cell therapy for AD with results not yet published (Table S1).

Though stem cell transplantation has showed effectiveness in ameliorating AD, the underlying mechanism remains puzzling. Several studies have revealed that exogenous stem cells can mediate anti-AD effects via mechanisms such as secreting neurotrophic factors or moderating innate signaling cascades.<sup>107,108</sup> However, there is little evidence definitely showing that engrafted stem cells proliferate and differentiate into new neurons which can further integrate into and reconstruct the existed neural circuits. Guiding donor stem cells to differentiate into the specific subtype of neurons required is still challenging, since the process of neurogenesis from stem cells is prone to falling victim to the loss of microenvironmental homeostasis in AD brain.<sup>109</sup>

Alternatively, transplanting neural progenitors with defined cell fates instead of stem cells might achieve better outcomes. Indeed, engrafted GABAergic and cholinergic precursors have both exhibited a robust capacity for adding new neurons with typical neuronal morphology and electrophysiology to the AD brain and alleviating cognitive deficits in animal models.<sup>110-113</sup>

## 5.2 | Glia-neuron conversion

Neurogenesis might also be induced by converting innate glial cells to neurons, but there are still controversies over the methodology as well as efficiency of cell reprogramming.

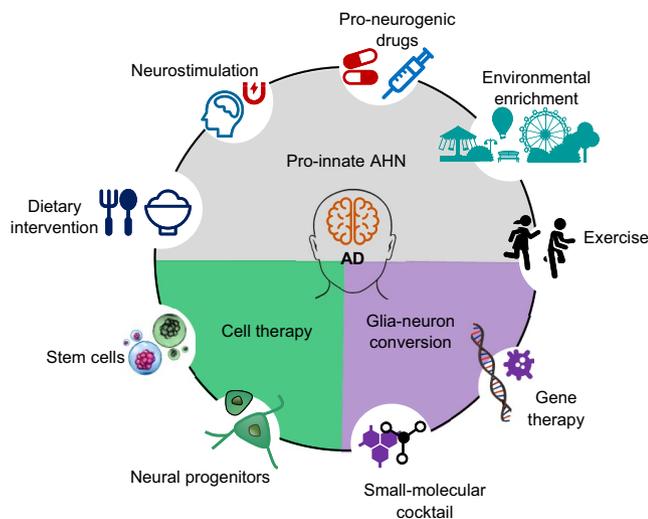
Astrocytes in the brain have shown neurogenic capacity under specific conditions.<sup>7,8</sup> Many researchers believe that eliciting

neurogenesis from astrocytes can kill two birds with one stone since it can add new neurons and simultaneously suppress astrogliosis in the AD brain. It has been reported that combinative and step-wise use of nine small molecule cocktails—LDN193189, SB431542, TTNPB, Tzv, CHIR99021, VPA, DAPT, SAG and Purmo, which overall exert an inhibitory effect on the glial signaling cascade but an active effect on NeuroD1 and the Neurogenin2 pathway—are capable of reprogramming human astrocytes into neurons *in vitro* within 10 days.<sup>114</sup> A subsequent study found that this neuronal conversion can be also induced by chemically modulating only 3~4 signaling pathways from among Notch, glycogen synthase kinase 3 (GSK-3), transforming growth factor- $\beta$  (TGF- $\beta$ ) and bone morphogenetic protein (BMP) pathways.<sup>115</sup>

Viral vector-mediated gene modification is another effective way to induce glia-derived neurogenesis. For example, viral expression of transcription factor Pax6,<sup>116</sup> Ascl1,<sup>117</sup> Sox2<sup>118</sup> or NeuroD1<sup>119-122</sup> in glial cells can direct neurogenesis both *in vitro* and *in vivo*. Genetic suppression of polypyrimidine tract-binding protein 1 (Ptbp1), an RNA-binding protein, by either CRISPR-CasRx,<sup>123</sup> RNAi<sup>124</sup> or antisense oligonucleotide,<sup>125</sup> also successfully induced glia-to-neuron conversion. However, a recent study using stringent lineage tracing with co-expressed fluorescent reporter with NeuroD1 or Ptbp1 knockdown suggested that the previously reported astrocyte-to-neuron conversion mediated by viral vectors might just be the result of nonspecific expression of viral-carried genes,<sup>126</sup> though it could not refute previous studies using chemical cocktails to induce cell reprogramming.

It was previously found in microglia that, similar to astrocytes, exogenous expression of NeuroD1 can also direct neuronal conversion through initially occupying closed chromatin regions associated with bivalent trimethylation of histone H3 at lysine 4 (H3K4me3) and H3K27me3 and subsequently targeting the transcriptional repressors Scrt1 and Meis2.<sup>127</sup> In contrast, a very recent study using lineage tracing has shown that the same titer of lentiviruses as previously used for microglia-to-neuron conversion resulted in nonspecific leakage, and exogenous expression of NeuroD1 did not convert microglia to neurons in mice and even induced microglial cell death.<sup>128</sup> In this model, whether a lower titer and higher selectivity of virus or non-viral chemical agents can reprogram microglia to neurons deserves further investigation.

Despite the controversies, the glia-to-neuron conversion studies have still shed new light on pro-neurogenic therapy for AD. Apart for the examples addressed above, it may also be possible to induce neurogenesis from other subsets of glia such as NG2<sup>+</sup> glial cells<sup>129</sup> or oligodendrocytes. At the same time, glia-derived genesis of selective subgroups of neurons—GABAergic,<sup>130</sup> glutamatergic or cholinergic—might be also achieved by combinative expression of different transcription factors. However, before application in clinical settings, it is important to understand the pathological changes of each subset of neurons and astrocytes in specific region in the AD brain, which as yet remains largely elusive. In addition, more selective gene targets and more reliable genetic editing/delivery tools are needed to promote the clinical testing of glial reprogramming therapy.



**FIGURE 2** Potential pro-neurogenic therapies. Innate AHN can be facilitated by pro-neurogenic drugs, environmental enrichment combined with exercise, neurostimulation and dietary innervation. More extensive neurogenesis can be also induced by transplantation of stem cells or neural progenitors, as well as genetic induction of glia-neuron conversion

## 6 | CONCLUDING REMARKS

AHN is important in maintaining hippocampus-dependent learning and memory. Though innate AHN is finite in type and scale, it still provides us with an opportunity to reconstruct the degenerated hippocampal network, as well as a stable model and a quick means of establishing how AD pathologic factors might determine the outcome of pro-neurogenic treatments. Neurogenesis can be also elicited by external cell grafting and glia cell reprogramming. These pro-neurogenic remedies all shed light on the treatment of AD (Figure 2).

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### CONFLICT OF INTEREST

The authors declare no conflict of interests. Jie Zheng is editorial board member of AMEM, but was excluded from the peer-review process and all editorial decisions related to the publication of this article.

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