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Alzheimer's Disease and Hippocampal Adult Neurogenesis; Exploring Shared Mechanisms

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New neurons incorporate into the granular cell layer of the dentate gyrus throughout life. Neurogenesis is modulated by behavior and plays a major role in hippocampal plasticity. Along with older mature neurons, new neurons structure the dentate gyrus, and determine its function. Recent data suggest that the level of hippocampal neurogenesis is substantial in the human brain, suggesting that neurogenesis may have important implications for human cognition. In support of that, impaired neurogenesis compromises hippocampal function and plays a role in cognitive deficits in Alzheimer's disease mouse models. We review current work suggesting that neuronal differentiation is defective in Alzheimer's disease, leading to dysfunction of the dentate gyrus. Additionally, alterations in critical signals regulating neurogenesis, such as presenilin-1, Notch 1, soluble amyloid precursor protein, CREB, and β-catenin underlie dysfunctional neurogenesis in Alzheimer's disease. Lastly, we discuss the detectability of neurogenesis in the live mouse and human brain, as well as the therapeutic implications of enhancing neurogenesis for the treatment of cognitive deficits and Alzheimer's disease.

Keywords: hippocampus, neurogenesis, Alzheimer's disease, cognition, learning and memory

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INTRODUCTION

In early development neurons are rapidly produced to form the intricate complexity of the brain and peripheral nervous system. Postnatally, the role of neurogenesis is shifted from brain development into brain plasticity. From then on, neurogenesis takes place only in specific niches in the adult brain, in the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus and the subventricular zone (Kempermann et al., 2015). Recent evidence suggests substantial levels of hippocampal neurogenesis in the human brain, estimating about 700 new neurons a day in the DG (Spalding et al., 2013). Humans replace ∼35% of the DG, while rodents are estimated to replace only 10% (Ninkovic and Gotz, 2007; Imayoshi et al., 2008). Recent information also suggests that in humans, the striatum may be a source of adult neurogenesis as well (Ernst et al., 2014). The existence of adult neurogenesis in the human brain supports the notion that neurogenesis has important functional significance and implications for cognitive disorders and their therapy (Eriksson et al., 1998; Ninkovic and Gotz, 2007; Imayoshi et al., 2008; Lazarov and Marr, 2013; Spalding et al., 2013).

The circuitry of the DG, of which new neurons are part, promotes several important functions, namely, pattern separation, conjunctive encoding of multiple sensory output to the dorsal CA3, facilitation of encoding of spatial information based on its output to the dorsal CA3, and encoding of time in new memories (for review, Lazarov and Hollands, 2016).

In support of the role of hippocampal neurogenesis in plasticity, learning and memory, increasing evidence suggests that cognitive deficits, difficulty learning new information and memory loss, as occurs in Alzheimer's disease (AD), may be, at least in part, due to impairments in adult neurogenesis (Demars et al., 2010, 2013; Lazarov and Marr, 2010; Lazarov et al., 2010). Some of the foundation for the association between impairments in adult hippocampal neurogenesis and cognitive deficits leading to AD might be due to the fact that several key signals implicated in AD play a role in regulation of hippocampal neurogenesis (**Figure 1**).

NEUROGENESIS IN AGING, DISEASE STATE, AND COGNITIVE DYSFUNCTION

In the rodent brain, neurogenesis is dramatically decreased during adulthood and further declines during aging (Demars et al., 2013). Recent evidence suggests that in wild type mice reduced proliferation of neural progenitor cells (NPCs) might be one of the processes underlying this phenomenon (Demars et al., 2013). However, other mechanisms, such as altered signaling, increased quiescence of neural stem cells (NSCs) and differentiation toward non-neuronal subtypes have been proposed [see for example Hattiangady and Shetty, 2008]. In humans, the dynamics are less clear. A recent study suggests that there is a moderate decline in neurogenesis with aging (Spalding et al., 2013). However, as of yet, it is unclear how this decline impacts cognitive function in humans or whether similar memory paradigms are regulated by adult neurogenesis as they are in rodents. Observations in humans using high resolution fMRI (Brickman et al., 2014) and cognitive studies (Toner et al., 2009; Stark et al., 2010; Yassa et al., 2011; Brickman et al., 2012) suggest that age-related memory loss begins in the DG. These changes are believed to stem from a decline in the support of the neurogenic niche as well as intrinsic characteristics of NSC (for review Silva-Vargas et al., 2013). Many processes decline in the aging brain along with a decrease in adult neurogenesis. For example, in both rodents and humans the density of synaptic contacts onto granular cells in the DG decreases with age (Flood et al., 1996; Geinisman et al., 2001, 2004). It will be important to determine whether age-dependent decline in neurogenesis compromises the function of the DG and induces susceptibility to memory impairments.

Deficits in adult neurogenesis with age may compromise the structure and function of the entorhinal-hippocampal circuit. This area is particularly vulnerable and heavily affected in AD, the most common form of dementia. AD is characterized by progressive memory loss and cognitive dysfunction (Baulac et al., 2003). Rare, Familail AD (FAD) is caused by mutations in the *amyloid precursor protein* (*APP*) and *presenilin 1* and *2* (*PS1,2*) (Selkoe and Wolfe, 2007). However, the majority of AD cases are sporadic and aging is the greatest risk factor for AD. Research done in mouse models of FAD suggests that declining neurogenesis is an early stage event that can be observed as early as 2–3 months of age (Rodriguez et al., 2008; Demars et al., 2010; Hamilton et al., 2010)(for review Lazarov and Marr, 2010, 2013). Nevertheless, it is important to note that some FAD mouse lines, mostly lines that overexpress APP, exhibit enhanced, rather than reduced, neurogenesis (Jin et al., 2004; Chuang, 2010). As discussed below, this might be attributed to the overexpression of soluble APP (sAPP), a proliferation factor of NPCs (Demars et al., 2011, 2013; Lazarov and Demars, 2012). The manifestations of neurogenic impairments in FAD mice are diverse. They include defective maturation/reduced rate of survival of new neurons in the granular cell layer (GCL), compromised dendritic tree branching (Sun et al., 2009; Bonds et al., 2015), imbalance of GABAergic and glutamatergic input onto new granular neurons (Sun et al., 2009), expression of the less potent proliferation factor sAPPβ at the expense of sAPPα in the neurogenic niche (Demars et al., 2011, 2013) and loss of γ-secretase function in NPCs and new neurons (Gadadhar et al., 2011; Bonds et al., 2015).

Below, we highlight several key signaling factors that are implicated in AD and were recently described to regulate neurogenesis. These factors play a role in aging-dependent behavior, circadian rhythm, inflammation, oxidative stress, neurotrophic signaling, hormonal signaling, neurotransmission, vascular signaling, and others. Thus, the multi- factorial effect on neurogenesis exposes the complex relationship between neurogenesis and the progression of AD pathology (for review Lazarov and Marr, 2010, 2013; Lazarov et al., 2010).

ALTERATIONS IN MOLECULAR SIGNALS DURING AGING AND COGNITIVE DYSFUNCTION ACCOMPANYING NEURODEGENERATIVE DISEASE

Presenillin-1 (PS1) is the catalytic core of γ-secretase, an aspartyl protease, which cleaves numerous substrates, including APP and Notch (De Strooper et al., 1998, 1999). Mutations in PS1 cause FAD, presumably due to loss of γ-secretase function (Xia et al., 2015). A recent paper suggests that PS1 undergoes a conformational change during aging and sporadic AD, and this change may have downstream effects on the processing of its substrates APP and Notch (Wahlster et al., 2013). PS1 regulates NPC differentiation in the adult brain (Gadadhar et al., 2011) via β-catenin, Notch1 and CREB (Bonds et al., 2015). Down regulation of PS1 in hippocampal NPCs compromises the maturation of new neurons, manifested by deficits in their dendritic tree branching, leading to learning and memory deficits (Bonds et al., 2015), suggesting that PS1-induced dysfunction of neurogenesis can impair cognitive function in AD. Transgenic expression of FAD-linked mutant variants of PS1 also impairs neurogenesis and the neurogenic response to experience in an enriched environment (EE) (Wang et al., 2004; Wen et al., 2004; Chevallier et al., 2005; Choi et al., 2008).

Amyloid precursor protein (APP)- APP is a substrate of γ-secretase. Misregulated cleavage of APP in the amyloidogenic pathway is implicated in FAD. While the physiological role of APP is yet to be fully understood, numerous studies suggest a role in synaptic plasticity and neurogenesis (Lazarov and Demars, 2012). The soluble form of APP (sAPPα) regulates NPC proliferation and survival (Demars et al., 2011, 2013). In fact, neurogenesis can be upregulated in the aging mouse

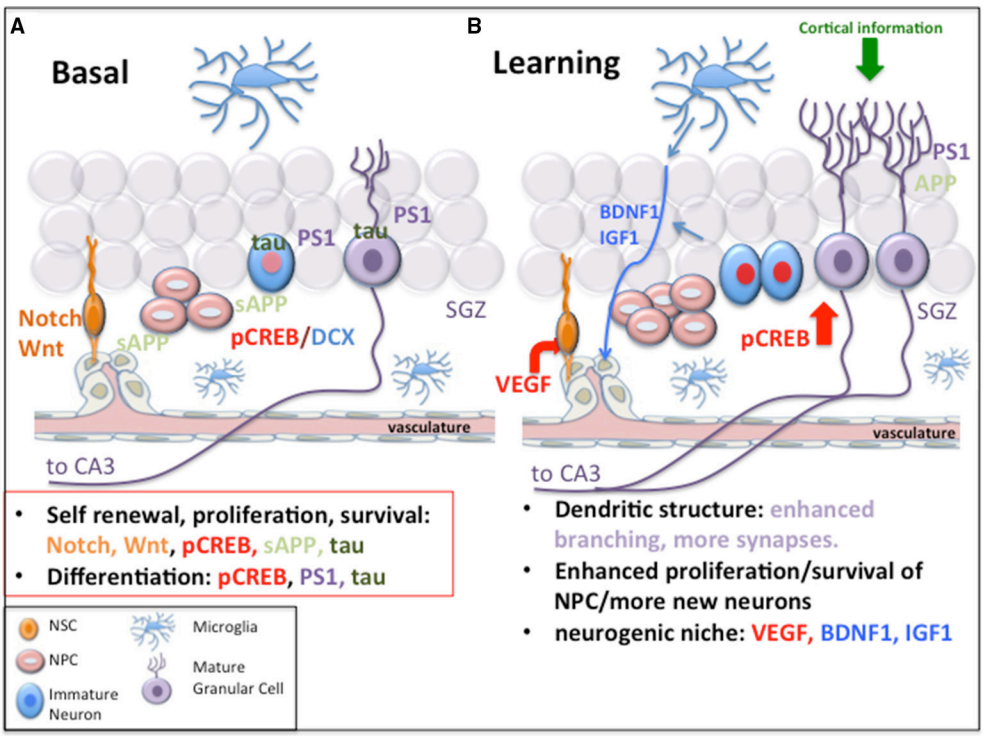

FIGURE 1 | Common mechanisms of neurogenesis and Alzheimer's disease and the implications for learning. (A) Signals that play a role in neurogenesis, such as Notch-1, Wnt/β-catenin, CREB, sAPP, tau, and presenilin-1 are implicated in Alzheimer's disease. **(B)** Following learning, changes in the neurogenic niche include alterations in Notch and sAPP, increased expression of neurotrophins such as VEGF, BDNF, and IGF which enhance angiogenesis and provide support for the neurogenic niche and lead to increased neurogenesis. Upregulation of CREB signaling by neural progenitor cells and neurons may promote survival and maturation of NPCs. Increased dendritic branching of mature neurons and synaptic plasticity may be mediated by presenilin-1 and APP. The factors mediating these processes are dysfunctional or compromised in Alzheimer's disease, suggesting that defective neurogenesis may affect hippocampal function in Alzheimer's disease.

brain following injection of sAPPα into the SVZ (Demars et al., 2013). While APP is extensively researched in regards to AD, the regulation of APP with aging is less well studied. However, there is some evidence that APP processing may be altered during aging, perhaps through dysregulation of the circadian system (Dobrowolska et al., 2014). In FAD, there is upregulation of the less potent sAPPβ counterpart at the expense of sAPPα, which may compromise proliferation of NPCs (Demars et al., 2011, 2013). Interestingly, sAPPα plays an important role in migration of NPC during brain development (Young-Pearse et al., 2007, 2008). Other metabolites of APP, such as AICD and Aβ have been suggested to regulate neurogenesis (for review see Lazarov et al., 2010), but more studies are warranted in order to establish their role.

Tau- is a neuronal microtubule-associated protein, the hyperphosphorylation and aggregation of which plays a key role in AD pathology. Significantly, adult born neurons transiently express the tau-3R isoform during development, overlapping with DCX and NeuN co-expression in the DG (Bullmann et al., 2007; Llorens-Martin et al., 2012). Tau phosphorylation in the DG is also temporally and spatially linked to DCX and neuroD expression with activated GSK-β believed to be the main tau kinase in newborn neurons (Fuster-Matanzo et al., 2009; Hong et al., 2010). The genomic based hTau mouse model exhibited reduction in adult neurogenesis, as a result of decreased proliferation, as early as 2 months of age before the appearance of significant tau pathology (Komuro et al., 2015), which may suggest that either impaired hippocampal neurogenesis is an early hallmark of tau pathology in AD or that there is an association between tau pathology and defective neurogenesis in AD. For a comprehensive review about tau and adult neurogenesis see (Fuster-Matanzo et al., 2012).

Notch 1- is a critical neurogenic signal and a substrate of γ-secretase. The intracellular domain cleavage product, NICD, translocates to the nucleus and drives transcription of factors important for maintaining the NSC pool such as *Hes* and *ErbB2* (for review Pierfelice et al., 2011). Notch signaling occurs when the Notch receptor is activated by one of its ligands in the Jagged or Delta-like family of proteins (for review Kopan and Ilagan, 2009). Following physical activity, NPC proliferation is increased in a Notch-dependent manner in the SGZ of the DG, even in aged mice (Lugert et al., 2010). In contrast, Notch signaling is decreased with age, including in the hippocampus (Lugert et al., 2010; Tseng et al., 2014). Down regulation of PS1 in hippocampal

NPC results in reduced levels of NICD (Bonds et al., 2015). In mature neurons Notch levels are low, and its function is not fully elucidated (for review see Marathe and Alberi, 2015; Marathe et al., 2015).

Wnt/β-catenin- are critical signaling factors in the regulation of hippocampal neurogenesis (Chenn and Walsh, 2003; Sato et al., 2004; Lie et al., 2005; Shimizu et al., 2008). Wnt3 is expressed in the SGZ of the DG, and overexpression of Wnt3 is sufficient to increase neurogenesis (Lie et al., 2005). Wnts are produced by astrocytes in the adult hippocampal niche and support the proliferation and differentiation of neuronally-restricted NPCs (Lie et al., 2005). Wnts regulate NSC self-renewal by inactivating Glycogen synthase kinase 3 (GSK3) and stabilizing β-catenin (Shimizu et al., 2008). Further, β-catenin promotes NPC proliferation through the activation of LEF/TCF transcription factors (Shimizu et al., 2008). Interestingly, nuclear accumulated β-catenin also induces anti-neurogenic hes1 gene expression through the enhancement of Notch1- and RBP-J-mediated transcription. β-catenin can associate with the NICD, and it is present in a nuclear protein-DNA complex containing the hes1 gene promoter. The β-catenin–NICD complex is efficiently formed when transcriptional coactivators p300 and P/CAF are present. Also, significantly, following its cleavage, the PS1CTF/NTF forms a complex with GSK3 and β-catenin (Tesco et al., 1998; Tesco and Tanzi, 2000). PS1 has been implicated as a negative regulator of the Wnt/β-catenin signaling pathway (Xia et al., 2001). Wnt-independent interaction of β-catenin and PS1 has also been described (Kang et al., 2002). Downregulation of PS1 in adult NPCs compromises the phosphorylation of β-catenin, which may affect β-catenin translocation to the nucleus, leading to alterations in the normal development of NPC (Bonds et al., 2015).

CREB- Cyclic-AMP Response Element Binding protein (CREB) is a critical signaling factor for adult brain plasticity and learning (for review Kandel, 2012). Activation of CREB by phosphorylation on Ser133 (pCREB) is observed in the hippocampus and cortical areas following learning and memory tasks (for review Mayr and Montminy, 2001). Importantly, NPCs, neuroblasts and immature neurons constitutively express pCREB, suggesting that pCREB is a critical component of neurogenesis. Indeed, CREB plays a role in neuronal maturation and survival in hippocampal neurogenesis (for review Ge et al., 2006; Jagasia et al., 2009; Herold et al., 2011; Merz et al., 2011). In rodents, CREB signaling components in the hippocampus decrease with age (Chung et al., 2002; Kudo et al., 2005; Porte et al., 2008). However, these observations were made primarily in mature neurons. Thus, the impact of aging on NPC-specific CREB signaling remains unclear. Also unclear is how aging causes a decrease in CREB signaling, although hypotheses suggest that this could occur either by aging-dependent increased levels of reactive oxygen species, or via decreased NMDA receptor and BDNF expression, which are both important for CREB activation (Chung et al., 2002; Kudo et al., 2005; Porte et al., 2008; Ozgen et al., 2010). Interestingly, exposure to young blood increased CREB activation and neurogenesis in the aged hippocampus, suggesting that systemic factors that are altered with aging may play an important role in CREB signaling and neurogenesis in the brain (Villeda et al., 2011; Villeda and Wyss-Coray, 2013). Impaired CREB signaling in AD has been the subject of much study. CREB signaling is dysregulated in both human AD and in mouse models of FAD (Vitolo et al., 2002; Ma et al., 2007; Caccamo et al., 2010; Bartolotti et al., 2015). In addition, down regulation of PS1 expression in NPCs compromises pCREB expression, leading to defective maturation of new neurons and induction of cognitive deficits (Bonds et al., 2015). While the role of CREB signaling in memory via mature neurons is well documented, the contribution of CREB signaling in NPCs to memory is not fully elucidated, and separating out the contribution of CREB to learning and memory via mature neurons or via NPC function is technically challenging and remains to be investigated (for review see Scott Bitner, 2012; Ortega-Martinez, 2015). Likewise, most of the work on CREB signaling in AD has focused on the transient activation in mature neurons during the formation of long-term memories, and so the contribution of CREB signaling in NPC in the context of AD also remains an open question.

NEUROGENESIS AS A BIOMARKER OF COGNITIVE FUNCTION AND AS A THERAPEUTIC APPROACH

While it is clear that hippocampal neurogenesis takes place in the human brain and that the number of new neurons generated is significant (Spalding et al., 2013), information concerning the fate of neurogenesis in aging and cognitively impaired individuals is scarce. Current techniques allow the examination of neurogenesis postmortem. However, because of the dynamic modulation neurogenesis can undergo following numerous stimuli, such as progressive pathology, the development of methodologies for the detection of neurogenesis in live individuals will be crucial. Up to the present time, tools for the detection of neurogenesis in live humans have been limited. The level of ^{14}C in genomic DNA has been used for the estimation of date of birth of hippocampal neurons and their quantification in postmortem tissue (Spalding et al., 2013). A previous study suggests that adult neurogenesis can be specifically detected by proton nuclear magnetic resonance spectroscopy (^{1}H-MRS, Manganas et al., 2007). However, this method was challenged by Loewenbruck et al. (2011), thus, more studies are warranted for the determination of the specificity, sensitivity and feasibility of ^{1}H-MRS for the detection and quantification of neurogenesis.

The association between decline in neurogenesis and cognitive deterioration during aging, coupled with disruption in neurogenesis and cognitive dysfunction in FAD mouse models suggests that enhancing neurogenesis may be a feasible therapeutic approach (**Figure 2**). Successful attempts to enhance neurogenesis in rodents have been described. For example Sahay et al. used genetic manipulation of neurogenic pathways, excising the pro-apoptotic gene *Bax,* to enhance survival of nestin expressing cells (Sahay et al., 2011). They observed enhanced performance in the DG-dependent pattern separation task, where animals must distinguish between two similar contexts. Wang et al. also enhanced cell survival, neuronal differentiation,

Enhancing Neurogenesis	Prospective Readouts of Neurogenesis
Environmental Enrichment; Cognitively complex experiences, Aerobic exercise, social interaction	**Postmortem;** Radioactive isotopes, analysis of neurogenic cellular markers
Anti-depressants; SSRI's	**Imaging;** specific imaging techniques to be developed
Pro-neurogenic small molecules	**Functional MRI;** Behavioral tests (e.g. pattern separation)
Manipulation of neurogenic pathway	**Plasma biomarkers** (learning and memory signals, inflammatory, cytokines, neurogenic signals)
Hormones, neurotransmitters	**Other?**

FIGURE 2 | Therapeutic and translational potential of neurogenesis. Examples of current and prospective methods for the modulation and detection of neurogenesis. Means of enhancing neurogenesis include noninvasive, environmental modulations like cognitively complex activities and exercise, as well as molecular interventions like anti-depressants, pro-neurogenic small molecules, hormones or neurotransmitters, or other manipulations of the neurogenic pathways. While readouts of human neurogenesis are typically done in postmortem tissue using radioactive isotopes or analysis of neurogeneic cell markers, imaging techniques such as fMRI, or blood biomarkers will offer non-invasive avenues to determine neurogenesis during life.

and dendritic complexity in neurogenic regions through activation of ERK5 map kinase (Wang et al., 2014). Following this manipulation, animals had increased performance in spatial learning and memory in the Morris Water Maze (MWM) task. In MWM and the novel object recognition task they also probed long-term memory and saw improvements as well, suggesting that adult neurogenesis may be a key therapeutic target.

Given the evidence from genetic manipulation of neurogenesis in rodents, it is important to consider how neurogenesis could be modulated in humans. One approach is the modulation of lifestyle factors, termed environmental enrichment (EE). Evidence from rodents suggests that EE and running are effective ways to enhance hippocampal plasticity and neurogenesis in particular (Kempermann et al., 1997; van Praag et al., 1999a,b). These behavioral interventions have been found to enhance neurogenesis and ameliorate pathology in AD mouse models (Lazarov et al., 2005; Lazarov and Larson, 2007; Hu et al., 2010, 2013). Significantly, studies have shown that exercise can improve cognitive performance in the elderly (Ahlskog et al., 2011). Brief increases in physical activity (6–12 months) upregulates hippocampal volume and improves both episodic and spatial memory (Klusmann et al., 2010; Erickson et al., 2011; Ruscheweyh et al., 2011). In rodents it has also been shown that EE can increase many of the molecular factors involved in neurogenesis, such as pCREB expression and CRE-gene transcription in the hippocampus of wild-type mice (Hu et al., 2013; Bartolotti et al., 2015). While this observation was not specific to new neurons, it raises the possibility that enhanced CREB signaling may be one mechanism by which EE may increase the survival of new neurons. Nevertheless, EE and running do not target neurogenesis specifically, but have numerous effects on the hippocampus. Several studies describe the manipulation of neurogenesis using small molecules (Longo et al., 2006; Schneider et al., 2008; McNeish et al., 2010; Pieper et al., 2010; Lange et al., 2011; MacMillan et al., 2011; Neely et al., 2012; Petrik et al., 2012; Shi et al., 2013) or pharmacological agents, such as SSRI's or modulators of neurogenic pathways [For example, see Warner-Schmidt and Duman, 2007]. Some of these have been shown to enhance neurogenesis and reverse memory deficits. However, to this point the use of these compounds in AD mouse models has not been explored. In future experiments it will be important to consider the mechanism by which these molecules modulate adult neurogenesis in light of the signaling cascades we have described here. Particularly considering how these cascades are altered in aging and AD, both in rodent models and in humans.

AUTHOR CONTRIBUTIONS

This manuscript is based on data produced by Dr. CH and Mrs. NB. Dr. CH and Ms. NB and Prof. OL wrote this mini-review.

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