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Adult hippocampal neurogenesis and its impairment in Alzheimer's disease

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ABSTRACT

Adult neurogenesis is the creation of new neurons which integrate into the existing neural circuit of the adult brain. Recent evidence suggests that adult hippocampal neurogenesis (AHN) persists throughout life in mammals, including humans. These newborn neurons have been implicated to have a crucial role in brain functions such as learning and memory. Importantly, studies have also found that hippocampal neurogenesis is impaired in neurodegenerative and neuropsychiatric diseases. Alzheimer's disease (AD) is one of the most common forms of dementia affecting millions of people. Cognitive dysfunction is a common symptom of AD patients and progressive memory loss has been attributed to the degeneration of the hippocampus. Therefore, there has been growing interest in identifying how hippocampal neurogenesis is affected in AD. However, the link between cognitive decline and changes in hippocampal neurogenesis in AD is poorly understood. In this review, we summarized the recent literature on AHN and its impairments in AD.

Keywords: Hippocampal function; Adult hippocampal neurogenesis; Cognitive function; Alzheimer's disease; Alzheimer's disease animal models

INTRODUCTION

The mammalian brain is known to generate its full capacity of neurons during their embryonic development stage and perinatal stage (Ming & Song, 2005). This occurs through neurogenesis, the process of generating newborn functional neurons from precursor cells (Kriegstein & Alvarez-Buylla, 2009). However, there are a few regions in the brain that continue to generate newborn cells throughout life. This process is termed adult neurogenesis, which mainly occurs within the hippocampus and the lateral ventricles. Specifically, the subgranular zone (SGZ) of the hippocampus and subventricular zone (SVZ) of the lateral ventricles contain the self-renewing and multipotent neural stem cells responsible for adult neurogenesis (Zhao et al., 2008). The newborn cells in the SGZ generate hippocampal granule cells in the dentate gyrus (DG) while those in the SVZ are found to migrate into the olfactory bulb where they mature into interneurons, especially in rodents (Ming & Song, 2011).

Although the majority of adult born neurons in the hippocampus die (Kempermann et al., 2003), numerous literature points to the fact that they have the potential to synaptically incorporate into the local neural circuit (Alvarez-Buylla & Lim, 2004; Anacker & Hen, 2017; Duan et al., 2008; Gu et al., 2011; Lledo et al., 2006; Toda & Gage, 2018; Vivar et al., 2012). As such, recent research has focused on identifying the hippocampus-engaged functions of these newborn neurons such as cognitive flexibility, learning,

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memory, pattern separation, and mood (Anacker & Hen, 2017; Gu et al., 2012; Kropff et al., 2015; Miller & Sahay, 2019; Sahay & Hen, 2007; Shors et al., 2001; Yassa et al., 2011). Although adult neurogenesis has been rigorously characterized in rodent brains, the topic remains controversial in human brains (Kempermann et al., 2018; Sorrells et al., 2018). However, recent studies have suggested that adult neurogenesis is impaired in the process of aging and neurodegenerative diseases, such as Alzheimer's disease (AD) in both humans and animal models (Dennis et al., 2016; Mathews et al., 2017; Moreno-Jiménez et al., 2019) and may lead to cognitive deficits (Mu & Gage, 2011). Therefore, there is an increasing interest in both the fundamental and clinical aspects of adult neurogenesis.

In this review, we focus on reviewing adult hippocampal neurogenesis (AHN), which occurs in the DG, and its functions. We will then shift the topic to AD and discuss recent studies on the mechanistic understanding of AHN in AD. We also summarize the different animal models that are currently used for AD research and their possible application in advancing neurogenesis studies in AD.

HISTORY AND FUNCTION OF AHN

Over the past few decades, the concept of neurogenesis in the adult mammalian brain has been controversial. With continuous efforts in the neuroscience community, it is now widely accepted that the adult brain continues neurogenesis throughout life in certain regions and it can generate functional newborn neurons. In this section, we will review our current understanding of AHN and its functions focusing on neurogenesis in rodents. We will also briefly discuss adult neurogenesis in different animal species.

History and controversy of adult neurogenesis

The earliest evidence of adult neurogenesis dates to the 1960s when Altman and Das used 3H-thymidine labeling to show newborn neurons in the rat cortex and hippocampus (Altman, 1962; Altman & Das, 1965) followed by Kaplan and Hinds who also found similar results in the rat hippocampus and olfactory bulb in 1977 (Kaplan & Hinds, 1977). However, due to the lack of adequate immunocytochemical markers to label these cells and being strongly against the dogma that neural circuits are fixed in mature brains, the observations were constantly dismissed. The first piece of concrete evidence that the new neurons can be functionally integrated into the existing neuronal network, although not in the hippocampus, emerged from Nottebohm's work in songbirds (Paton & Nottebohm, 1984). This study reported that adult songbirds make new cells as they learn a new song and that these neurons play a role in the memory of the new song. In addition, they showed that the newborn neurons recruited into the existing neural circuit can influence cognitive function. This work was crucial as it helped overturn the criticism and conceptual discrepancies that existed, such as if newborn neurons established connections within the existing neuronal network, this would disturb the already stable network. Nowadays, technological advances such as the use of 5'-bromo-2'-deoxyuridine (BrdU) (Wojtowicz & Kee, 2006), genetic and viral labeling (Enikolopov et al., 2015), and computational network modeling (Aimone, 2016) have allowed adult neurogenesis to settle down as an important field in neuroscience.

The obvious question that follows these observations would be whether adult neurogenesis occurs in adult human brains as well. In 1998, Eriksson et al. (1998) were able to confirm the existence of AHN in the human brain using BrdU labeling and cell-type-specific markers. This observation in the hippocampal DG of human brains was confirmed over the following years from numerous different laboratories (Boldrini et al., 2018; Dennis et al., 2016; Knoth et al., 2010; Kukekov et al., 1999; Mathews et al., 2017; Palmer et al., 1999; Roy et al., 2000; Spalding et al., 2013). However, adult neurogenesis in humans is still controversial as more recent efforts have shown contradicting results where (1) neurogenesis persists in aged humans and (2) neurogenesis declines sharply after infancy and is absent in adults. Spalding et al. (2013) utilized radioactive carbon-13 DNA measurements to provide insight into the cell turnover dynamics and showed that there is substantial neurogenesis throughout life in the human hippocampus. A few years later, Boldrini et al. (2018) suggested that neurogenesis is preserved in humans until almost 79 years of age in the DG followed by a study by Moreno-Jiménez who argued that AHN is robust in healthy human subjects (Moreno-Jiménez et al., 2019). In contrast, Sorrells showed that neurogenesis in the DG declines steeply after birth and is undetectable by adulthood (Sorrells et al., 2018). In addition, recent efforts with single nucleus RNA sequencing have indicated that there is a lack of adult neurogenesis transcriptomic signatures in humans (Franjic et al., 2021). The reasons for these discrepancies are yet to be resolved, although different protocols and quantification methods (e.g. biomarker staining vs. single nucleus RNA sequencing) have been suggested. In addition, the quality of the human brain tissues can depend on the cause of death, postmortem interval, and how long it has been preserved, which could potentially lead to differing results. A recent review paper has extensively compared the differences of the methods used in some of these studies, but more concrete evidence demands novel labeling methods (Kempermann et al., 2018).

The stages of AHN

Along with the debate on the existence of adult neurogenesis in human brains, much progress has been made in animal models, especially rodents. One of the advancements from this is our understanding of the different cell types involved throughout the stages of adult neurogenesis in the DG (Figure 1). AHN begins with quiescent neural stem cells (qNSCs), also known as quiescent radial glia-like (qRGL) cells, which are found in the SGZ of the DG, located between the hilus and granule cell layer. As the name suggests, these cells generally have low metabolic activity and are sensitive to the local environment and physiological stimuli (Urbán et al., 2019). When activated, these RGLs are capable of self-renewing themselves and generate intermediate progenitor cells (type-2a, type-2ab, and type-2b cells) (Bonaguidi et al., 2011; Suh et al., 2007). These cells subsequently become immature neurons and finally mature neurons. Eventually,

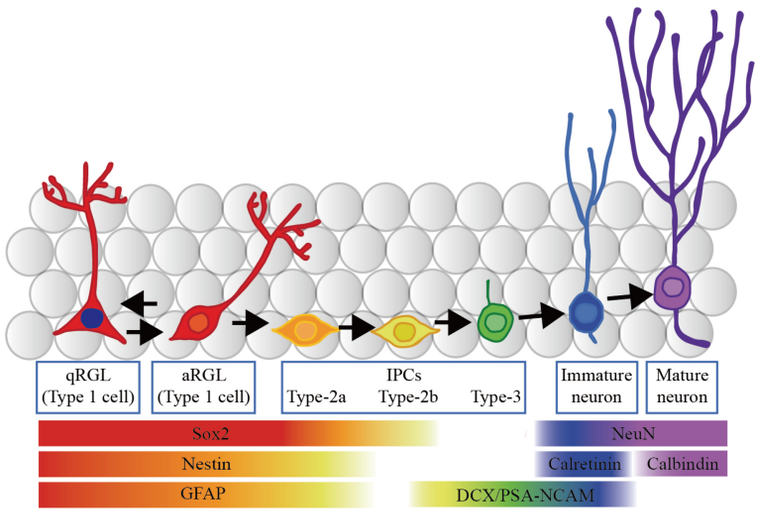

Figure 1 Schematic of AHN in adult rodent brains

A schematic representation of AHN in the adult rodent brain at the subgranular zone. The most left is the radial glial-like cells, followed by the intermediate progenitor cells and finally, the immature and mature neurons. Important biomarkers of neurogenesis are labeled as well. aRGL, active radial glia-like cell; qRGL, quiescent radial glia-like cell; IPCs, intermediate progenitor cells; DCX, doublecortin; GFAP, glial fibrillary acidic protein; NeuN, neuronal nuclear protein; PSA-NCAM, polysialated form of neural cell adhesion molecule.

these cells mature into functional granule cells that integrate into the hippocampal circuitry and have important functions (Gonçalves et al., 2016b; Ming & Song, 2011). Differentiating these stages was a challenge in the 1990s. In the past two decades; however, more and more labeling tools have become available (Enikolopov et al., 2015). For example, by using recently-available immunohistochemical markers specific to the stage and type of cell, researchers are able to identify the cell fate and stage of the developing newborn neurons (Figure 1) (see review from Zhang & Jiao (2015) for a more detailed outline of biomarkers of neurogenesis). The success with biomarker labeling, together with other tools such as viral labeling and transgenic methods, have greatly advanced the study of adult neurogenesis in the past decade. Nevertheless, basic science research has heavily relied on a few immunohistochemical markers such as doublecortin (DCX) and Ki67, while clinical research still lacks concrete biomarkers to measure AHN. Therefore there has been much effort to identify various biomarkers to identify and utilize AHN as therapeutic targets (see review from Gillotin et al.(2021) for a more detailed review on recent efforts on identifying neurogenesis).

Neurogenesis across different animal species

The genesis and circuit integration of new neurons are readily known in the adult brain. However, it remains a challenge to understand the reason why an established neural circuit requires neurogenesis. One idea is to look for the behavioral functions of new neurons in an animal with a simpler neural network than that of humans. Along this journey, although the focus of AHN research has mainly been on rodents and humans, it has indeed been confirmed in many different species. For non-human primates (NHPs), New World monkeys (Gould et al., 1998; Leuner et al., 2007) and old world primates (Gould et al., 1999; Kornack & Rakic, 1999; Perera et al., 2007) have been observed to have AHN although it is thought to decrease significantly after puberty in both species (Jabès et al., 2010). Importantly, a recent study has also provided a single-nucleus transcriptomic atlas of NHPs, allowing us an in-depth view of the age-related changes occurring in different cell types of the primate hippocampus (Zhang et al., 2021a). A huge number of mammals have also been confirmed to display AHN including both wild and domesticated mammals. Some examples include hamsters (Huang et al., 1998), cats (Altman, 1963), dogs (Hwang et al., 2007), moles (Amrein et al., 2014; Peragine et al., 2014), hedgehogs (Alpár et al., 2010), and marsupials (Grabiec et al., 2009; Harman et al., 2003). In contrast, many bat species were found to have very few or absent newborn cells in the adult brain (For a more detailed review, view Amrein (2015)). Interestingly, non-mammalian vertebrates, including fishes, reptiles, amphibians, and birds, were found to have more abundant adult neurogenesis in general (For a more detailed review, view Chapouton et al. (2007)). On the other hand, evidence suggests that cetaceans have a lack of hippocampal neurogenesis (Patzke et al., 2015) and that dolphins also show a lack of neurogenesis in the subventricular zone (Parolisi et al., 2017). Finally, AHN has also been observed in insectivores (Alpár et al., 2010; Bartkowska et al., 2008, 2010).

As AHN is highly conserved across many animal species, one may speculate that AHN has specific functions in the brain. With these lines of advancements in detecting neurogenesis in different types of animals, one would expect some upcoming achievements in showing the function of new neurons. More importantly, further studies on adult neurogenesis may potentially facilitate our understanding of the niche environment necessary for the viability of the stem cells, and how these environments can control the pace of neurogenesis in certain brain regions of different species. Moreover, interdisciplinary studies between species may provide us with insight on the evolutionary meaning of

neurogenesis as the discrepancies between species have been suggested to be linked to adaptation and the functional needs of the species (Kempermann, 2015; Parolisi et al., 2018).

Current evidence showing the functions of neurogenesis

It has been known for a long time now that the hippocampus has a crucial role in memory and learning in humans (Scoville & Milner, 1957). Of the hippocampus, the DG is a unique structure where its dorsal region is thought to be related to cognition and memory, while the ventral region is implicated for mood and stress modulation (Kheirbek et al., 2013; Tannenholz et al., 2014). Moreover, as we have discussed above, the SGZ of the DG is known to be involved in adult neurogenesis. Therefore, it is important to understand the relationship between AHN and hippocampal functions.

Adult neurogenesis is a dynamic process that is sensitive to pharmacological and chemogenetic manipulation, pathological conditions, external stimuli (e.g., exercise and stress) and the local environment (Aimone et al., 2014; Shohayeb et al., 2018; Winner et al., 2011; Winner & Winkler, 2015). As such, together with the desire to understand the fundamentals of biology, there is an increasing interest in the impact these newborn cells have on the existing neural circuitry and the role they have in different brain functions. The hippocampal connectivity has been extensively studied and is now well characterized by the tri-synaptic circuit. The tri-synaptic circuit consists of pyramidal cells in the entorhinal cortex (EC) connecting to the dentate gyrus cells (DGCs) in the DG. The signal is then transferred to the neighboring hippocampal cornu ammonis (CA) 3 followed by the CA1 pyramidal neurons and back to the EC (Amaral & Witter, 1989; Andersen, 1975). Looking more closely at the DG, the DGCs have complex connections with interneurons and CA3 pyramidal neurons (Booker & Vida, 2018; Henze et al., 2000) providing an intricate excitatory and inhibitory balance which play an important role in neural coding and regulating input and output of signals. AHN provides adult-born granule cells that can be integrated into this complex circuitry. Astrocytes (Krzisch et al., 2015; Sultan et al., 2015) and microglia (Rodríguez-Iglesias et al., 2019) have been identified as cell types that can potentially help adult-born DGCs to integrate into the circuit. It has also been discussed that these newborn neurons have different functions and characteristics throughout the process of integrating into the circuitry (Rodríguez-Iglesias et al., 2019). Once successfully integrated into the existing neural circuits, adult born granule cells have unique features that indicate more excitability, heightened plasticity, and a lower threshold for LTP induction (Ge et al., 2007; Gu et al., 2012; Schmidt-Hieber et al., 2004). These features hint that newborn cells potentially play a role in hippocampal functions which include not only learning and memory (Anacker & Hen, 2017; Gu et al., 2012; Hainmueller & Bartos, 2020; Lazarov & Hollands, 2016) but also functions such as anxiety and stress regulation (Surget & Belzung, 2021). Although not reviewed in this paper, it is also important to mention that recent studies have shown that young/immature adult born neurons have a role in learning and memory as well (Baptista & Andrade, 2018; Deng et al., 2010; Dieni et al., 2013; Mongiat et al., 2009).

AHN has been found to be involved in learning and memory which includes cognitive flexibility, emotional memory, spatial navigation, novelty detection and pattern separation (Anacker & Hen, 2017; Gu et al., 2012; Hainmueller & Bartos, 2020; Lazarov & Hollands, 2016). Studies using pharmacological and optogenetic approaches have shown that reduction of newborn cells negatively impacts, or an increase improves, numerous hippocampal-dependent performances including object memory, contextual fear conditioning and extinction learning, spatial learning, pattern separation and forgetting (Akers et al., 2014; Clelland et al., 2009; Danielson et al., 2016; Gao et al., 2018; Gu et al., 2012; Sahay et al., 2011). However, some early studies have found that ablation of new neurons did not affect spatial processing and pattern separation (Groves et al., 2013) or influence subsequent acquisition of spatial memory in the Morris water maze task (Shors et al., 2002). One study even showed that depleting new neurons improved working memory in an 8-arm radial maze (Saxe et al., 2007). These differences may be attributed to the different techniques (e.g. pharmacological vs. chemogenetic vs. optogenetic depletion) used to deplete the new neurons. These techniques may potentially cause off-target effects as it is challenging to selectively disrupt neurogenesis without disrupting the nearby structures. Moreover, behavioral paradigms such as the Morris water maze and contextual fear learning are hippocampus-dependent learning tasks. Therefore, it is also important to examine DG functionality specifically in relation to AHN. Most commonly, pattern separation has been associated with the DG (Bakker et al., 2008; Berron et al., 2016; Leutgeb et al., 2007). Unfortunately, pattern separation studies have also provided us with conflicting results where some have found newborn granule cells to have a critical role in pattern separation (Clelland et al., 2009; Nakashiba et al., 2012; Sahay et al., 2011) while other have not (Swan et al., 2014; Whoolery et al., 2020). Nevertheless, accumulating studies have suggested that the adult born neurons play a significant role in hippocampal-related functions (Toda et al., 2019).

The contradictory conclusion of the role of newborn neurons can also be seen in the emotional tests tackling the function of newborn neurons. For example, studies have shown contradictory evidence on whether AHN has a role in anxiety. In 1999, Lemaire et al. (1999) suggested that stress is closely related to AHN by showing decreased neurogenesis in rats with higher stress induced corticosterone. He also provided evidence that prenatal stress reduced AHN in rats (Lemaire et al., 2000). However, Shors et al. (2002) provided evidence that new neuron depletion does not affect anxiety-like behavior in an elevated plus maze. With different manipulating tools, recent studies have provided a clearer picture of the relationship between anxiety and AHN. One study has found that excessive anxiety leads to a decrease in the number of new neurons (Revest et al., 2009). However, some studies point towards AHN having a role in stress-induced anxiety. Increased AHN reduced anxiety levels measured through behavioral tests in mice (Hill et al., 2015) and AHN was also reported to provide resilience to stress-induced anxiety-like behavior (Anacker et al., 2018; Snyder et al., 2011). Putting all

this together, it seems that AHN and anxiety have a bidirectional relationship where one can influence the other. However, further investigation will be needed to understand which comes first. There have also been recent efforts to identify a relationship between AHN and social behavior. Both social recognition memory (Garrett et al., 2015) and stress-induced social avoidance (Lagace et al., 2010) have been shown to be associated with AHN, where mice with lower levels of AHN had problems with remembering previously encountered mice. These lines of evidence suggest that the effects AHN has on social memory and anxiety may not be individual pathways, but rather a complicated and intertwined network that is yet to be fully understood.

Besides these fundamental studies on the function of new neurons, more and more studies allude to a relationship between adult neurogenesis and symptoms observed in patients suffering neuronal degeneration. In a study of neurogenesis using biomarker staining in human AD patients, Tobin et al. (2019) found that a higher number of newly formed neuroblasts was associated with less cognitive impairment based on a correlation analysis. In addition, it has been suggested that decreased AHN is correlated to an increased risk for both AD (Moreno-Jiménez et al., 2019; Tobin et al., 2019) and major depressive disorder (MDD) (Boldrini et al., 2013, 2019; Déry et al., 2013; Kheirbek & Hen, 2011). Moreover, a review by Berger et al. (2020) suggested that AHN could be a potential mediator for an increased risk for AD in those with MDD. Taken together, the potential functions of AHN opens the field to the therapeutic applications for not only aging and neurodegenerative diseases but also for psychiatric diseases including MDD, post-traumatic stress disorder and borderline personality disorder. Therefore, there is an urgent need for thorough investigations of neurogenesis under these pathological conditions. As such, in the next section, we focus on reviewing current updates on the impairment of neurogenesis in AD as an example to discuss neurogenesis under pathological conditions.

NEUROGENESIS IN ALZHEIMER'S DISEASE

Alzheimer's disease currently affects more than 6 million people in the United States taking its place as the most common type of dementia (2021 Alzheimer's disease facts and figures, 2021). The common indicators of AD are the presence of neurofibrillary tangles (NFTs), amyloid plaques, and synaptic loss (Breijyeh & Karaman, 2020). Specifically, the presence of plaques in the hippocampus, and cerebral cortex has been thought to be the major pathogenic factor for AD. As a result, AD patients have symptoms ranging from inability to form new memories to neuropsychiatric problems such as depression (Lyketsos & Lee, 2004; Lyketsos & Olin, 2002; Lyketsos et al., 2011), psychosis (Jeste & Finkel, 2000; Lyketsos et al., 2011), and sleep disturbances (Ju et al., 2014). Despite the technological advances over the years, a definitive diagnosis of AD can only be made through examination of post-mortem brain tissue for NFTs and amyloid plaques (Terry, 2006). In this section, we aim to review the different hypotheses of AD before summarizing the current understanding of AHN in AD, followed by the current and new drug treatments for AD.

Possible causes of Alzheimer's disease

The two main hypotheses for the pathogenesis of AD are the cholinergic and the amyloid hypothesis. The cholinergic hypothesis stems from the idea that acetylcholine (ACh), an organic chemical in the brain, plays a big part in cognitive function. In AD patients, cholinergic neurons were found to degenerate and β-amyloid inhibited choline uptake and ACh release (Babic, 1999; Breijyeh & Karaman, 2020). This has been the foundation for many of the current cholinesterase inhibitor treatments for AD patients. The amyloid hypothesis stems from the observation of fibrillar amyloid β (Aβ) peptides (Aβ40 and Aβ42) being deposited and accumulated in the brain tissue (Glenner & Wong, 1984; Masters et al., 1985). These peptides are neurotoxic eventually leading to neuronal cell death and neurodegeneration. Moreover, multiple genes including APP, PSEN1, and PSEN2, which are related to Aβ formation and accumulation (Paroni et al., 2019), have been identified to be mutated in early-onset AD. The amyloid hypothesis has been the driving force for AD research for over 20 years (Hardy & Allsop, 1991; Hardy & Higgins, 1992; Selkoe, 1991). However, with the failure of many recent drugs that have targeted the Aβ plaques (Yiannopoulou et al., 2019), the vascular hypothesis of Alzheimer's disease has also been gaining interest (De La Torre, 2018; De La Torre & Mussivand, 1993). This idea suggests that reduced cerebral blood flow and cerebral hypoperfusion have implications in the pathogenic pathway of Alzheimer's disease. This allows us to speculate that patients with vascular risk factors may have a higher risk for AD in the future (Cechetto et al., 2008). Another hypothesis that is gaining more momentum is neuroinflammation and microglia in Alzheimer's disease. Reactive microglia have been identified to surround amyloid plaques in human AD brains (Mcgeer et al., 1987) and could produce pro-inflammatory cytokines causing neuroinflammation (Del Bo et al., 1995; Hanisch, 2002). With increasing evidence that Aβ, tau and microglia interact in AD patients, research in this area is becoming more popular (for a more detailed review on microglia and AD, view Leng & Edison (2021)). Finally, one of the most recent hypotheses is the mitochondria-affiliated Endoplasmic Reticulum (ER) membrane (MAM) hypothesis, which relies on the idea that the mitochondria and the ER interact biologically and physically (Area-Gomez & Schon, 2017). In support of this hypothesis, MAMs have been found to be upregulated in AD patients (Area-Gomez et al., 2012).

As reviewed above, AD is a complex disease and has a multitude of risk factors to consider including, but not limited to, genetics, age and environment (Campdelacreu, 2014). However, we are far from understanding the full picture of AD or finding a definitive cure. Therefore, alternative approaches and aspects of AD pathogenesis that have not been extensively studied, such as AHN, must be examined to gain further insight into understanding AD and ameliorating the symptoms.

Impaired neurogenesis in AD

As AD's most common and devastating symptom is memory loss, the hippocampus is of great interest in the field of AD.

From what we reviewed above, one could also speculate that all the potential hypotheses of AD can occur in and significantly impact the hippocampus. We have discussed how the hippocampus is one of the major areas that continues to generate newborn cells throughout life and this AHN has been associated with memory, learning and cognitive function. Therefore, in this section, we will review AHN in AD and how impaired neurogenesis may attribute to cognitive dysfunction in AD mouse models.

Neurogenesis in human AD patients: In the natural process of aging in humans, it has been hypothesized that hippocampal neurogenesis will decline with age as it was observed to decrease in rodents (Ben Abdallah et al., 2010; Gage, 2000; Seib et al., 2013). Indeed, the number of DCX positive cells in human brains was found to decrease with age (Moreno-Jiménez et al., 2019). In addition, Boldrini et al. (2018) also found that there was a decrease in angiogenesis, a smaller quiescent pool, and less neuroplasticity in the aged human brain, indicating reduced, but not absent, neurogenesis. It has also been suggested that the physiological changes that occur with aging are exacerbated in neurodegenerative diseases like AD. Therefore, it has been speculated that adult neurogenesis will decline earlier and more rapidly in AD patients. However, in contrast to the hypothesis, Jin et al. (2004b) reported that there was an increase in neurogenic factors such as DCX, TUC4, and PSA-NCAM in the hippocampus of AD patients. They suggested that there was an increase in AHN in AD patients as a compensatory mechanism to overcome the cell loss that occurs from neurodegeneration. Similarly, Ziabreva et al. (2006) also reported that there was an increase in Nestin-positive stem cells in AD patients. However, it is important to note that the samples are postmortem brains, meaning the medical history of the patients are not completely known, which could provide confounding effects, especially since the sample size for both studies were small. Moreover, the Nestin results from Ziabreva et al. (2006) raised concerns as it has been shown that Nestin expression may be alternatively increased due to reactive astrocytes (Liddelow & Barres, 2017). As such, more recent studies have shown opposite results. Moreno-Jiménez et al. (2019) compared the brains of normal aging patients and AD patients for DCX positive cells. They showed that there was a decrease in the number of immature neurons in AD brains throughout all the ages they examined. Tobin et al. (2019) also found similar results where the number of DCX positive cells and stem cells were decreased in AD patients relative to healthy individuals. They also claimed that DCX positive cells were still visible even in patients over 90 years old. More importantly, this study proposed a correlation between cognitive function and neurogenesis in AD patients. Although a closer examination is needed, this opens the possibility that adult neurogenesis can be used as a measure of cognitive function in AD patients. As such, recent studies have started to focus on *in vivo* imaging of neurogenesis in rodents through technology such as magnetic resonance imaging (MRI) (Vreys et al., 2010), positron emission tomography (PET) (Rueger et al., 2010), 2-photon calcium imaging (Danielson et al., 2016; Gonçalves et al., 2016a), and gradient index lens imaging (Carrier-Ruiz et al., 2021). These methods will allow us to examine the function of newborn granule cells and the changes they go through in pathologic conditions in an *in vivo* setting, which can provide further insight on how to utilize AHN as a target for therapeutic interventions.

Available AD animal models: As there are limitations to examining human tissue for research, animal models have been crucial for examining multiple aspects of AD pathogenesis and phenotypes. Unfortunately, it is not possible to directly extrapolate results from animal models to humans due to variability between species (Kempermann et al., 2018) and the difficulty to design proper cognitive tests (Schubiger et al., 2020). Moreover, AHN studies in non-rodent animals have been challenged due to longer life spans and costs. Nevertheless, the information from animal studies are valuable to provide the foundations and direction for further research. Therefore, we will briefly review the different animal models that are widely used in AD research.

Mouse models: Currently, the most used animal model for AD research is incontestably transgenic (Tg) mice. There are generally two different generations of AD mouse models: the first-generation amyloid precursor protein (APP) overexpressing mouse models and the second-generation APP knock-in (APP-KI) mouse models. The first-generation mice commonly overexpress proteins related to familial AD (FAD) mutant APP, presenilin, or a combination of these. These mice have been useful as they mimic the amyloid beta pathology well in the mouse brain. Although the cerebral amyloid accumulation is replicated well, the onset, size and regional distribution of the plaques differ between mouse models (Table 1). Moreover, driving the gene expression beyond physiological levels brings unwanted artifacts and phenotypes such as disrupting nearby genes (Kuro-O et al., 1997; Saito et al., 2016; Verret et al., 2012) or causing hyperactivity (Rodgers et al., 2012). Most importantly, many of the first-generation mice tend to have cognitive impairment before amyloid beta accumulation (Hsiao et al., 1996; Mucke et al., 2000), which is the opposite of our understanding of the disease in humans (Hardy & Allsop, 1991; Serrano-Pozo et al., 2011).

In order to avoid these pitfalls from the APP overexpression paradigm, there has been much struggle to generate human APP-KI mouse models, which would produce more pathogenic Aβ without overexpressing APP. In 2014, a group led by Saido was able to successfully generate APP-KI models (Saito et al., 2014). These mice also showed all the other AD related pathology observed in the first-generation mice, including gliosis, cell loss, and synaptic loss. Moreover, these mice developed plaques before cognitive impairment, solving many of the problems before. More recently, Denali therapeutics released a novel APP-KI line with the Jackson Lab, allowing more access to APP-KI mice for AD research (Xia et al., 2021). However, both generations so far have failed to generate neurofibrillary tangles, which is also an important hallmark of AD in human patients (For a more detailed overview of the APP mouse models, view Sasaguri et al. (2017)).

Rat models: Overall, rats are closer to humans both physiologically and genetically, making them a great model for

Table 1 Summary of plaque formation, cognitive impairment, and impaired AHN in commonly used AD mouse models

Mouse model	Age of plaque formation (Hippocampus, month)	Age of cognitive impairment (month)	AHN change	Primary paper
J20	6 (Hong et al., 2016)	4 (Cheng et al., 2007; Wright et al., 2013)	3 months ↑ (López-Toledano & Shelanski, 2007) No change (Sun et al., 2009) 5 months ↓ (López-Toledano & Shelanski, 2007) 12 months ↑ (Jin et al., 2004a)	Mucke et al., 2000
5xFAD	6 (Oakley et al., 2006)	4–5 (Devi & Ohno, 2010; Oakley et al., 2006)	2–4 months ↓ (Moon et al., 2014; Zaletel et al., 2018)	Oakley et al., 2006
APPswe/ PS1ΔE9	6 (Jankowsky et al., 2004)	12 (Lalonde et al., 2005; Volianskis et al., 2010)	2 months ↓ (Demars et al., 2010) 6 months ↓ (Verret et al., 2007)	Jankowsky et al., 2004
3xTg	6 (Oddo et al., 2003)	4 (Billings et al., 2005; Stover et al., 2015)	2–4 months ↓ (Hamilton et al., 2015; Rodríguez et al., 2008) 6 months ↓ (Valero et al., 2014) 11, 18 months ↓ (Hamilton et al., 2010)	Oddo et al., 2003
Tg2576	6 (Westerman et al., 2002)	10 (Arendash & King, 2002)	3 months ↑ proliferation / ↓ Survival (Krezymon et al., 2013)	Hsiao et al., 1996
APP NL-G-F Knock-in	4 (Saito et al., 2014)	6 (Saito et al., 2014)	N/A	Saito et al., 2014
AppSAA Knock-in	4 (Xia et al., 2021)	N/A	N/A	Xia et al., 2021

N/A: Not available.

AD research and more ideal for cognitive tests as they mimic human behavior closer than mice (Bryda, 2013). Unfortunately, due to cost and maintenance limitations, as well as the limited genetic manipulation tools in rats (Charreau et al., 1996; Tesson et al., 2005), most studies with rodents are still conducted with mice.

There are three well characterized rat models developed for AD research (Cohen et al., 2013; Leon et al., 2010; Liu et al., 2008). These rats are also generated from expression of FAD mutations, enabling them to have similar phenotypes and limitations to those of the AD mouse models. However, the TgF344-AD rat (Cohen et al., 2013) has been shown to have NFTs, which gives an advantage over most AD mouse models, which do not express NFTs unless crossed with a mutated Tau mouse model. There have also been efforts to generate APP-KI rats, similar to those of the second-generation AD mouse models (Serneels et al., 2020; Tambini & D'adamio, 2020; Tambini et al., 2019, 2020). However, they have failed to exhibit significant AD pathology. Recently, a group from China was able to successfully generate an APP-KI model that exhibits disease progression similar to humans (Pang et al., 2022). Although there are many aspects of this rat line to be characterized, this advancement in genetic manipulation for AD rats is promising.

NHPs: NHPs are an important animal model for studying AD due to their biological proximity to humans, such as their 100% sequence homology with human AB (Camus et al., 2015). Their larger brains allow for more advanced studies including more detailed imaging and more accessible CSF collection. From the existing literature, the rhesus monkey has been shown to be the most well characterized non-human primate model (For a more detailed review on this topic please view this article (Drummond & Wisniewski, 2017)). However, due to the complexity of developing monkey models, although very promising, it may take years before we could see some dramatic advancements in AD study with this type of model.

Lower order animals: Although the genetic make-up of lower order animals is simplified and there is limited genetic homology to humans, drosophila, *Caenorhabditis elegans*, and zebrafish have been used as animal models for AD research. Other than the low cost and the easy maintenance of these models, the main advantage is that genetic manipulations are relatively easy in these species, especially with the wide use of the CRISPR technology. As such, these low order animals can be efficiently used for large scale genetic and drug screenings (For detailed information on these different animal models, please refer to these reviews: *Drosophila*: Giong et al. (2021), Jeon et al. (2020), Tue et al. (2020); *C. elegans*: Paul et al. (2020), Giong et al. (2021); Zebrafish: Caramillo & Echevarria (2017), Giong et al. (2021)).

Adult neurogenesis studies on these AD animal models have mostly been focused on mouse models, which will be discussed in detail in the next section. However, in order to have a better understanding of how AHN is affected in AD, studies in more advanced animal models such as NHPs are needed. Recent efforts with transcriptomic studies have shed more insight onto how AHN may change with aging in multiple different species (Zhang et al., 2021a). Therefore, it will be important to extend these efforts into examining AD animal models to understand the relationship between AHN and AD.

A mechanistic understanding of Impaired AHN in AD: Although it has been challenging to understand AHN in non-rodent AD animals, and the few studies have focused on characterizing the deficits of AHN, we expect more and more mechanistic studies on hippocampal neurogenesis with our advancing understanding of the causes of AD and its impact on the brain network. Having a concrete understanding of how neurogenesis changes in these models will, in turn, facilitate therapeutic developments to rescue altered neurogenesis in AD and potentially alleviate cognitive function. Therefore, in this section, we will dissect the findings on how AHN is affected in AD mouse models, which are relatively more

studied than other animal species. We also provide a summary of the phenotypes for the more commonly used AD models in Table 1.

Young mice (2–4 month old): Ki67 is a marker commonly used to measure proliferation of cells and DCX is a marker that predominantly labels the type-3 IPCs and immature neurons in the SGZ. BrdU can be used to measure proliferation or survival based on the time of injection and when the animal is sacrificed. In 2–4 month AD mice, there has been contradictory evidence on how AHN changes in the SGZ depending on the mouse line. The 5xFAD (Moon et al., 2014; Zaletel et al., 2018; Zhen et al., 2017), 3xTg (Hamilton et al., 2015; Rodríguez et al., 2008), APP/PS1/Nestin-GFP (Zeng et al., 2016), APP/PS1 (Demars et al., 2010; Sun et al., 2009; Zhang et al., 2021c), PS-1 knock-in (Wang et al., 2004), and PS-1 P117L (Wen et al., 2004) mouse models have been shown to have decreased AHN. On the other hand, PS-1 A246E (Chevallier et al., 2005) was shown to have increased AHN. Interestingly, there has been conflicting evidence for AHN in the J20 mouse model. One group found an increase in neurogenesis (López-Toledano & Shelanski, 2007) but other studies have found that there was no significant change (Sun et al., 2009; Zhang et al., 2021b) although the morphology and general trend indicated a decrease in AHN. For the Tg2576 mouse model, the proliferation stage of AHN was found to increase but the survival of newborn cells was decreased in 3 months mice (Krezymon et al., 2013).

Adult mice (5–6 month old): In 5–6 month mice, the 3xTg (Valero et al., 2014), APP/PS1 (Baglietto-Vargas et al., 2017; Verret et al., 2007) and J20 (López-Toledano & Shelanski, 2007) mouse models were shown to have decreased AHN with the former two being more specific for the survival of newborn DGCs and the latter for proliferation. Interestingly though, there was no difference in survival in the J20 mice at this age. However, similar to the young mice, the J20 line showed impaired morphology and maturation (Sun et al., 2009).

Aged mice (10+ month old): By this age, most AD mouse models tend to have widespread plaques in their brains. 3xTg (Hamilton et al., 2010) and PDAPP APPind (Donovan et al., 2006) were found to have significantly decreased AHN, although the latter was suggested to have more abnormal newborn cells in the granule cell layer. However, the J20 line has shown contradictory results as one group found an increase in AHN (Jin et al., 2004a) while another group has shown a decrease at 9 months (Zhang et al., 2021c).

As seen in this section, the overall trend seems to be that AHN is impaired in AD mouse models. However, there are contradictory results between studies and mouse lines. This conflict may be due to technical issues including mouse handling, different protocols, experimental paradigm, and type of markers used (Kempermann et al., 2018). Moreover, it has also been suggested that plaques may induce neurogenesis although the exact timeline for when this happens is not clear (Ermini et al., 2008; Gan et al., 2008). These conflicting results and the possibility for plaque induced neurogenesis highlight the challenges of using the current AD mouse models to study the relationship between AD and AHN. Therefore, there is a need for studies in the improved APP-KI mouse models. In addition, it will be important to have comprehensive studies, such has a monthly analysis of AHN, that handle multiple mouse lines together to examine how AHN changes with age in these AD mouse models. Despite these issues, the ongoing research for AHN in AD is essential to understanding the changes neurodegeneration brings to the adult brain.

IMPAIRED AHN IN AD MOUSE MODELS AND ITS POSSIBLE ASSOCIATION WITH DECLINED COGNITION

Cognitive dysfunction is a main symptom in AD patients and many AD mouse models have also been identified to have similar deficits. However, despite the evidence that AHN is altered in AD mouse models, we lack the knowledge on how the impaired adult neurogenesis directly affects cognitive function. Interestingly, it has been found that the altered AHN occurs before the learning and memory deficits or other common hallmarks like amyloid plaque formation (Li Puma et al., 2021). This allows us to hypothesize that AHN may have a causative role in the cognitive decline of the AD mouse models.

In support of this hypothesis, the APPswe/PS1ΔE9 mouse line shows altered hippocampal circuitry (compromised hippocampal inhibition) and overexcitable hippocampal neurons in response to ablating hippocampal neurogenesis (Hollands et al., 2017). The 5xFAD mouse line also shows that ablation of AHN led to exacerbation of cognitive dysfunction (Choi et al., 2018). On the other hand, the combination of pharmacological stimulation of neurogenesis and physical exercise improved the cognitive deficits and reduced amyloid burden in the 5xFAD mouse line (Choi et al., 2018). Similarly, in the 3xTg-AD mice, exercise alone was sufficient to improve cognitive function (Kim et al., 2019). However, the literature also suggests that the morphology and functional integration of newborn cells in the AD mouse models are abnormal (Krezymon et al., 2013; Richetin et al., 2015; Sun et al., 2009), which could lead to negative consequences in the long term. Therefore, one may also speculate that inhibiting abnormal AHN will improve cognitive function. In contrast to the literature before, Zhang et al. (2021b) reported that ablating adult neural stem cells (aNSC) in the J20 and APP/PS1 mice improved the cognitive and synaptic deficits to normal levels. Another external factor that is known to increase AHN is the use of an enriched environment (EE). EE was found to improve cognitive function in APP/PS1 mice and reduced Aβ load and tau phosphorylation in the hippocampus (Hu et al., 2010; Lazarov et al., 2005; Zhang et al., 2021c).

Additional studies have also supported the hypothesis that AHN improves cognitive function in AD. One study used adult bone marrow-derived mesenchymal stem cell transplantation in APP/PS1 mice to increase AHN, which improved memory and cognitive function (Yan et al., 2014). More recent studies have shown that micro-RNAs from NSCs have a role in AD as well. Micci et al. (2019) reported that micro-RNAs from NSCs improved memory deficits and protected the hippocampus from Aβ and Walgrave et al. (2021) demonstrated that replacement of miR-132, a downregulated micro-RNA in AD, improved AHN and memory deficits.

In conclusion, these studies demonstrate that adult neurogenesis very likely influences cognitive function of AD

mouse models especially by increasing healthy adult neurogenesis and ablating abnormal adult neurogenesis. Moreover, many of the studies show that neurogenesis has a role in decreasing Aβ levels, which suggests that neurogenesis may also have a role in clearance or degradation of Aβ. However, there is a lack of consistency between different AD mouse models and the overexpression of APP in the first-generation AD mouse models has consistently been questioned as a factor for influencing the results. Therefore, further confirmation and mechanistic investigation of neurogenesis is required in the newer models such as the APP-KI mice.

CURRENT TREATMENTS FOR AD, POSSIBLY LINKED WITH AHN?

Pharmacological treatments for AD have been focused on treating the symptoms of patients to increase their quality of life. The most commonly used non-disease altering drugs include Donepezil, Galantamine, and Rivastigmine, which are FDA approved cholinesterase inhibitors used for mild to moderate AD. Donepezil treats cognitive function and behavioral functions and is used for mild to moderate cases of AD (Birks & Harvey, 2018; Knowles, 2006; Tan et al., 2014). Galantamine also showed advantages to cognitive function and is used in cases where mild to moderate dementia is present (Tan et al., 2014). Rivastigmine showed effectiveness in patients with mild to moderate dementia, and like the other cholinesterase inhibitors, its main target is cognitive functions (Birks & Evans, 2015; Tan et al., 2014). Unfortunately, our understanding of how cholinesterase inhibitors help relieve the symptoms of AD is yet unclear. However, it is speculated that by preventing the breakdown of acetylcholine, a chemical thought to play a role in memory and thinking, the drugs are improving cognitive function in these patients (Birks, 2006). Nevertheless, the AD brain produces less acetylcholine as the disease progresses, eventually rendering the drugs ineffective.

The drug Memantine is an uncompetitive N-methyl-D-aspartate receptor (NMDAR) modulator/antagonist that is used for moderate to severe AD. Overstimulation of NMDARs causes unusual calcium levels and glutamate overproduction, resulting in a decrease in cognitive function and learning and memory deficits. Memantine blocks the channels of NMDARs preventing the overstimulation of NMDARs, which occurs in AD. Those with moderate to severe Alzheimer's disease who took memantine saw an improvement in their cognitive, functional, and behavioral declines (Tan et al., 2014).

Opposed to the pharmacological treatments described above, Disease-Modifying treatments (DMTs) have shown promising results (Thomas et al., 2021). Aducanumad and Gantenerumab are 2 examples. Aducanumab is a recent antibody treatment that has been FDA approved. It is a human IgG1 anti-Aβ monoclonal antibody that selects for Aβ clusters and removes β-amyloid (Thomas et al., 2021). However, there is still great controversy to whether this drug truly has clinical impact as only a sub-population of clinical trial subjects were found to have improvement (Clinicaltrials.Gov, 2021a, 2021b; Tian et al., 2020). Gantenerumab, another Aβ monoclonal antibody, binds with great attraction towards congregated Aβ. This drug is still in its phase 3 clinical trials and has shown some effects on tau levels (Klein et al., 2019; Ostrowitzki et al., 2017) although it is not certain whether it has clinical efficacy. Another recent drug, ALZ-801 has recently started its phase 3 clinical trials. This drug has been debated to have a higher safety profile for treating AD for its relief of many symptoms that previous medications of AD bring up such as gastrointestinal tract problems. ALZ-801 is a selective anti-oligomer agent that prevents the formation of Aβ42 oligomers (Tolar et al., 2020). However, this drug is an optimized prodrug of tramiprosate, which has been shown to have its clinical efficacy limited to high-risk APOE4 carriers only. Nevertheless, these drugs are very promising in, alleviating some AD symptoms but it remains to be studied whether these drugs can improve the deficits seen with AHN, or whether the alleviation of symptoms requires the participation of AHN. This is especially important as emerging studies have shown that commonly used drugs have an effect on AHN in animal models (Gillotin et al., 2021) and there is also an effort to repurpose pre-existing drugs for AD (Taubes et al., 2021). Moreover, one study showed the genetic and pharmacological stimulation of AHN with the combination of pharmacologically increasing brain-derived neurotrophic factor improved cognition in AD mice (Choi et al., 2018). Therefore, there is a great need for research on how AHN is affected by AD related drugs in both animal models and humans.

CONCLUSION AND PERSPECTIVES

In this review, we first summarized our current understanding of AHN and its functions, focusing on cognitive function and stress. We also described how AHN was preserved across many different species. Next, we examined the different hypotheses of Alzheimer's disease and the relationship between AHN and AD. We then discussed about the idea that impaired AHN in AD animal models indeed has a role in the declining cognitive function seen in AD. We also pointed out some of the common and new animal models used for AD research, which will potentially advance the studies of neurogenesis impairment in AD. Finally, we touched upon the current treatments and the potential for AHN to be a target for future AD drugs.

Although AHN has been a topic of interest in the field of AD, there is much that is not known and needs extensive investigation. However, the recent advent of APP-KI mice allows us to explore neurogenesis in the context of improved AD mouse models and we hope that these studies will be more transferable to human subjects. As technology continues to rapidly develop, we will also be able to examine neurogenesis more concretely in the human brain and develop more efficient methods to conduct research. As such, it is important to continue our efforts to explore adult neurogenesis in both human AD patients and AD animal models to further our understanding of AD. Most importantly, tackling hippocampal neurogenesis may provide us a window to mitigate the damage from AD and provide novel therapeutic approaches to treat AD. Numerous studies have tried to influence AHN in AD animal models through different approaches including genetic/pharmacological (Choi et al., 2018), dietary (Cao et al., 2009; Lee et al., 2002; Morello et

al., 2018; Qin et al., 2006) and behavioral interventions (discussed in section above). However, there is a lingering question of what the optimal time point is for these interventions. Once this question is addressed, it may also be possible to combine multiple treatments to develop novel approaches to treat AD through AHN.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

T.A.K. conceived the review. T.A.K., M.D.S., and K.W. wrote the manuscript with input from all authors. T.A.K., M.D.S., and K.W. prepared the illustration and table. S.G. provided valuable suggestions. All authors read and approved the final version of the manuscript.

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