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Neurogenesis in Human Hippocampus: Implications for Alzheimer Disease Pathogenesis

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Abstract
Hippocampal neurogenesis, the innate capacity of stem cells in the hippocampus to generate new neurons throughout life, is attracting interest in neurodegenerative disease research as an indicator of neuroplasticity and therefore treatment. Conditions that improve cognitive output and increase neurogenesis are associated with a decreased incidence of Alzheimer disease (AD), and conditions that lead to reduced cognition and neurogenesis are associated with increases in the incidence of AD. Therefore, hippocampal neurogenesis may be of particular relevance in the development of AD, and the modulation of this process can afford an important therapeutic avenue. Nevertheless, apparent contradictions across studies examining all factors of hippocampal neurogenesis in AD have led to a confusing state of affairs regarding the role of this process in the disease, as aberrant cell cycle activation has been advanced as an early pathogenic factor in the development of AD. The objective of this review is to critically examine these contradicting reports and provide additional and alternative insights into the function of hippocampal neurogenesis in AD.

Alzheimer disease (AD) is the most common cause of dementia, and its prevalence is directly related to age [1]. Moreover, the increasing life expectancy, rising from 50 years at the beginning of the last century to approximately 80 years today, inevitably brings a higher incidence of age-related illnesses, including AD, resulting in an increase from 4 million individuals currently affected with AD in the United States to an estimated 14 million by 2050 [2]. In spite of these figures, the lack of progress toward effective therapy is striking.

The hippocampus is among the brain regions affected by AD pathology, particularly neurofibrillary pathology, early in disease [3, 4], a finding that is congruous with the early loss of spatial and episodic memory in AD [5]. Interestingly, the hippocampus is also one of few brain regions capable of neurogenesis in adulthood [6–8]. This property, in conjunction with the potential for exploiting regenerative capabilities of stem cells, offers some hope for a therapeutic intervention distinct from lesion-based therapies that have been disappointing to date.

Hippocampal Neurogenesis

Adult neurons are, in general, terminally differentiated and exist throughout the life of the organism. However, we now know that the dentate gyrus of the hippo-

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campus [6–8], the olfactory bulb [8, 9] and certain areas of the cortex [10–14] retain the capacity to produce neurons during adulthood and that such neurons can integrate into the brain regions, organize, differentiate and become functional. In the adult dentate gyrus, cells divide continuously in the subgranular zone, located between the granular cell layer and the hilus of the hippocampus [15, 16]. Using the reagent bromodeoxyuridine (BrdU), which by incorporating into the DNA of dividing cells allows the identification of these cells in a time-dependent and location-specific manner, hippocampal cells have been shown to divide daily, and after a period of 4 weeks, 67% of the initially counted cells remain. In addition, of these remaining cells, about 50% continue to develop a neuronal phenotype and migrate to the granule cell layer, 15% differentiate into glial cells and the remaining 35% do not differentiate [17].

In adulthood, neurogenesis occurs in a variety of vertebrate species [18–21] including humans [22], and recent work suggests that newly generated granular neurons extend axons and make connections with the hippocampal CA3 region [23–25], receive synaptic input [23] and demonstrate functional properties indistinguishable from mature granule cells in vivo [26] and in vitro [25]. Therefore, neurons of the dentate gyrus of the hippocampus in adulthood can survive, differentiate into mature phenotypes and acquire functional properties indistinguishable from the mature cells of the region. As such, it is reasonable to assume that neurogenesis and the intrinsic capacity of the brain to generate new neurons may play a fundamental role in the various functional aspects of the hippocampus, including cognitive behavior.

Functional Significance

The mechanisms associated with hippocampal neurogenesis and its function and significance to learning and memory are presently being established. Thus far, it has been suggested that neurogenesis sustains the capacity of the dentate gyrus to maintain the continued modulation of cortical input supplied with novel complexities [27]. Interestingly, a substantial reduction in the number of newly generated neurons directly impairs hippocampal-dependent trace conditioning but had no effect on learning during hippocampal-independent tasks, suggesting a direct role for these cells in hippocampal-related memory [28].

Importantly, and as would be expected by the nature of hippocampal memory function, this process is also highly susceptible to environmental/experience-dependent structural changes such that a number of factors can regulate the production and survival of hippocampal neurons developed during rodent adulthood. Factors such as estrogen [29–31], environmental complexity [18, 19, 32–36], exercise [37–39], N-methyl-D-aspartate-related excitatory input [40–42], transient global and focal ischemia [43–46] and epileptic seizures/kindling [47–53] positively regulate neurogenesis. Others such as depression [54–56], stress [20, 57–62], cholinergic denervation [63] and aging [15, 33, 36, 64] decrease the levels of neurogenesis.

Importantly, factors that affect neurogenesis correlate with changes in behavioral performance, further indicating a direct influence of neurogenesis on learning and memory [27, 28, 65–69]. For example, placing rodents in an enriched housing environment [18, 19, 32–36] or undergoing exercise [37–39] increases neurogenesis by increasing the survival of progenitor cells, leading to enhanced performance in the water maze task. Conversely, other factors such as stress, which is linked to a decrease in neurogenesis, impair cognitive performance [20, 57–62]. This involvement of hippocampal neurogenesis in the modulation of hippocampally related cognitive output suggests a potentially important role of this process in degenerative diseases which are associated with severe damage to the hippocampus, the most noteworthy being AD.

Neurogenesis in AD

The process of hippocampal neurogenesis as a potential therapeutic and also a pathogenic mechanism can be applied to the study of AD. In this regard, the positive modulators of neurogenesis and hippocampally controlled memory such as enriched environment [18, 19, 32–36], learning [27, 28, 65–69] and estrogen levels [29–31] have all been associated with a decreased incidence of AD [70–76]. Likewise, factors associated with decreased cognitive output and reduced neurogenesis, such as depression [54–56], stress [20, 57–62], cholinergic denervation [63, 77] and, most importantly, aging [15, 33, 36, 64], are all associated with an increased incidence of AD [1, 78–82]. These striking parallels suggest that AD may be associated with declines in hippocampal neurogenesis. As such, one obvious place to begin examining the possibility that hippocampal neurogenesis is directly associated with AD pathogenesis is by exploring the role of this process in the established animal models of this disease.

Neurogenesis and Animal Models of AD

In this regard, linkage studies show that mutations in at least 3 genes, the amyloid-β protein precursor (AβPP) gene located on chromosome 21 and the 2 homologous genes presenilin 1 and 2 (PS1 and PS2) located on chromosome 14 and 1, respectively, are associated with early-onset AD [83]. Based on these findings, several transgenic mouse models of AD have been generated to mimic the most extensively studied pathological hallmark of AD, namely amyloid-β plaques [84]. The creation of transgenic lines expressing mutated AβPP, a type 1 membrane protein with a large extracellular domain and a short cytoplasmic domain belonging to a larger AβPP family that also includes amyloid precursor-like proteins 1 and 2 [85], or mutations in the genes encoding PS1 and PS2, which are polytopic proteins with 6–8 transmembrane domains that play a central role in intramembrane proteolysis (δ-cleavage) of a number of cell surface proteins including AβPP and that give rise to amyloid-β peptide [86], have been used to establish these models as they share the common feature that they all alter y-secretase cleavage of AβPP to increase the production of amyloid-β_{42}, the primary component of amyloid plaques. Likewise, the fact that the penetrance of the mutations is almost 100% suggests that they play critical roles in neurodegeneration and perhaps, given the parallels between modulators of neurogenesis and incidence factors in AD, these mutations/the overexpression of amyloid-β can also affect neurogenesis.

Two groups of investigators using transgenic animals exhibiting mutations in the AβPP have demonstrated declines in neurogenesis affecting both proliferation and survival of precursor cells [87–89]. Dong and colleagues [89] show declines in neurogenesis as early as 3 months, well before the deposition of amyloid-β plaques begins, suggesting that declines in neurogenesis may be independent of amyloid-β senile plaque formation. However, Haughey and colleagues [87] found that the declines in neurogenesis are restricted to the period when amyloid-β plaque deposition begins (12–14 months), and not in younger animals, suggesting an association with plaque deposition.

In addition to findings in AβPP transgenic animal models of AD, 3 studies in animals expressing the PS1 familial AD mutation also show impaired adult neurogenesis as measured by declines in precursor proliferation [90, 91] and survival [91], as well as various degrees of memory impairment [90, 91]. However, these differences are only visible when the animals are placed in an enriched environment, an intervention that would maximize differences as it is a powerful positive modulator of neurogenesis. Even with the apparent perplexities across studies, research suggests that in AD, whether prior to amyloid-β deposition or during later stages of the disease when amyloid-β deposition is extensive, declines in hippocampal neurogenesis could be a factor related to hippocampal-associated learning and memory deficits readily observed in this disease.

Hippocampal Neurogenesis and Repair

Recent studies suggest a self-repair mechanism to be responsible for increases rather than decreases in hippocampal neurogenesis in AD. Several studies demonstrate that factors such as ischemia [43–46] or seizure-induced brain insults [47–53] lead to increased neurogenesis in the absence of improvements in cognition. Thus, one consideration is that neurogenesis may be activated as an endogenous repair mechanism utilized by the brain to diminish damage from trauma, blood-flow deprivation insults and/or overactivity [53]. This capacity of the brain to seemingly repair itself from these insults has been proposed as major grounds for the use of stem cells in AD [92–94]. To this end, the accumulation of pathological agents like amyloid-β or phosphorylated tau, which are in most cases described as toxic [95, 96], could potentially activate this self-repair mechanism. Even more significant is the fact that both brain trauma and ischemic episodes are associated with an increased incidence of AD. Therefore, the hypothesis that AD-related pathology, similar to ischemia or brain trauma, could drive the brain to attempt to self-regenerate by inducing neurogenesis is now gaining importance. However, based on this assumption, AD would not lead to reduced neurogenesis, as previously described, but to enhanced neurogenesis as suggested in the literature summarized below.

Modulation of Hippocampal Neurogenesis by AD Pathology

Invoking the brain repair theory has permitted investigators to explain the seemingly paradoxical findings concerning the presence of increased neurogenesis in AD [97], in animal models of the disease [98], and after in vitro treatment with amyloid-β [99]. In the latter, the administration of different concentrations of the amyloid-β peptide to neural stem cell cultures of hippocampi from

postnatal day 0 Bl6 mice leads to dose-dependent increases in the total number of cells [99]. Nevertheless, this report contradicts a previous study where treatment of neural stem cells with amyloid-β led to reduced neurogenesis and increased apoptosis of these cells [88]. Postnatal hippocampal cultures which include mature neurons in addition to glia, as those used in the Lopez-Toledano and Shelanski study [99], more closely resemble the hippocampal environment in vivo. Yet the use of amyloid-β_{42}, the peptide produced in the animal models of the disease and also used in the Lopez-Toledano and Shelanski study [99], did not mimic the findings observed in the animal models. Interestingly, in vitro studies have demonstrated that AβPP and its proteolytic fragments (i.e. amyloid-β peptide and secreted AβPP) have mitogenic properties [100–104]; hence, these results may merely reflect an in vitro specific event. Corroboration for the in vitro data is found in a recent study demonstrating that there is increased hippocampal neurogenesis in the brains of AD patients, as well as increased numbers of immature but not mature neuronal markers when compared with age-matched control brains [97]. Perplexingly, another study using animals carrying the Indiana and Swedish versions of the AβPP mutation has recently demonstrated that both young (3 months old) and older (12 months old) transgenic mice show enhanced BrdU labeling in the dentate gyrus [98], directly contradicting the previously mentioned reports [87–89]. These findings point to a possible repair-driven strategy of the AD brain to protect itself from pathology-associated damage. However, one possibility that remains unexplored, with regard to human studies, is that the brain may be attempting self-repair from the ischemic-like insults that occur late in the course of the disease [105], as mentioned before, a factor demonstrated to result in increased neurogenesis [43–46].

Oxidative Stress as a Modulator of Neurogenesis

While amyloid toxicity can be used to explain both increases and decreases in neurogenesis, it cannot simultaneously explain both, and hence, the confusion as to whether increases or decreases in neurogenesis exist in AD remains unresolved. Other processes are tightly associated with AD and can affect neurogenesis multi-dimensionally, and one such factor is oxidative stress. That hippocampal neurogenesis increases fail to yield any significant improvements in cognitive output points to the fact that mechanisms independent of amyloid deposition, whether it is direct toxicity or toxicity-induced self-repair, may be at play. Evidence that the toxic nature of amyloid-β may not play a role in the modulation of neurogenesis stems from the fact that environmental manipulations that maximize hippocampal neurogenesis decrease amyloid-β load [106]. Since previous studies have reported that declines in neurogenesis were only evident in animals that were environmentally enriched [90, 91], when amyloid-β presumably decreases, amyloid-β toxicity does not seem to be the cause of neurogenesis declines.

One modulatory mechanism that can explain this confusing state of affairs, which is a key player in the pathogenesis of AD [107–112] and also a modulator of hippocampal neurogenesis [113–119], is oxidative stress.

In this regard, several reports demonstrate that antioxidant treatment [113–117] or antioxidant-related mechanisms such as caloric restriction [118] promote hippocampal neurogenesis, since oxidative stress precedes the deposition of amyloid-β in the AD brain [112], leading to the examination of an antioxidant role for amyloid-β [120–122]. It is the antioxidant role of amyloid-β that can indeed explain the perplexing results found in the AD neurogenesis literature.

In humans, the deposition of amyloid-β is associated with decreases in oxidative stress; therefore, it would not be the self-repair strategy induced by amyloid-β toxicity that leads to the promotion of neurogenesis in the AD brain but rather its antioxidant function. This could explain the increases in neurogenesis found in AD patients [97] and in cell models of the disease [99]. Thus, based on the above facts, this theory could not explain the declines in neurogenesis observed in animal models of the disease. However, when in excess or out of balance, amyloid-β, like all antioxidants, can act as a pro-oxidant, and hence, in the right circumstances, it can increase oxidative stress and lead to neurogenesis declines.

Finally, another possibility that should be considered is that a repair strategy is indeed implemented, not specifically by promoting hippocampal neurogenesis, but rather by using a parallel mechanism such as trying to reactivate the cell cycling machinery in vulnerable cell populations of the disease. It is well known that oxidative stress is a powerful modulator of the cell cycle and that oxidative stress conditions can lead to cell cycle aberration diseases such as cancer. This molecular event has now been suggested as a possible mechanism for AD pathogenesis and has been extensively reviewed [123–125]. In this regard, the absence of colabeling between BrdU and immature cell populations in the human AD

study [97] allows this theory to remain a possibility. Therefore, the multidimensional capacity of oxidative stress to modulate AD-related pathogenesis as well as cell cycle events establishes it as a viable model explaining AD-related increases and decreases in neurogenesis.

Contradictions

From the literature summarized above, the link between hippocampal neurogenesis and AD remains controversial. In addition to the contradictions in similar studies, many other inconsistencies further complicate this matter. For example, the fact that brain injury, which is associated with an increased incidence of AD, leads to increased hippocampal neurogenesis and that caloric restriction which increases neurogenesis [118], and is thought to be beneficial to normal subjects and to protect from many risk factors associated with AD (i.e. oxidative stress, inflammation), is detrimental or even lethal to the AβPP transgenic [126] contradicts this concept. More importantly, the fact that a recent report demonstrates that animal models of AD show decreased numbers of plaques under enriched environment [106], an intervention that increases neurogenesis and improves learning and memory [27, 28, 65–69], but yet other animal models of AD show that declines in neurogenesis are visible only under enriched environment conditions [90, 91], raises questions about the role of amyloid-β in neurogenesis. Moreover, one study demonstrating that aged animals with higher levels of new cells in the hippocampus show lower cognitive performance than those with fewer cells [127] only lends further confusion by suggesting that increases in neurogenesis, at times, may in fact represent a response to deleterious events and are not always associated with hippocampal 'well-being.'

The findings presented in this review bring to light the inconsistencies within the field of hippocampal neurogenesis in general and in relation to AD and question the validity of the established animal models of this disease. In this regard, it is important to note that the genes associated with the mutations that lead to amyloid-β generation and that are used in these animal models also have powerful roles in neurodevelopment [128]. For example, mutant mice lacking all 3 AβPP genes display early lethality as well as a high incidence of cortical dysplasia, suggesting a critical role in neural development [129]. Moreover, PS1 is involved in γ-cleavage of the Notch receptor, which plays a critical role in determining cell fate during early development [130] and is also involved in degradation [131, 132] resulting in a PS1-deficient mouse with profound developmental abnormalities [133, 134]. Transgenic mice that express constitutively active β-catenin in neuroepithelial precursor cells develop enlarged brains, because a greater proportion of neural precursors re-enter the cell cycle after mitosis [135]. Therefore, since both AβPP and PS1 seem to be tightly involved in cell cycle regulation during development, they are also likely to play a role in hippocampal neurogenesis in animal models of AD independently of any AD-related event, namely overexpression of amyloid-β.

In conclusion, the above stated conflicts suggest that rather than critically examining the true role of hippocampal neurogenesis in a disease such as AD, the field seems to use 'increases' or 'decreases' in neurogenesis as a superficial 'utensil' to fit the hypothesis that amyloid-β is detrimental in AD. If neurogenesis is increased, it is because it is associated with self-repair after amyloid-β toxicity [99], and if it is decreased, it is associated with declining cognition due to amyloid-β deposition [87, 88]. However, the fact that no correlations exist between amyloid-β and neurogenesis in any of these studies, in addition to the other mitogenic or antioxidant properties of this molecule proposed in this review, both of which are capable of altering neurogenesis, makes such assumptions premature. Studies of neurogenesis in models other than APP mice, such as the NGF knockout or SAMP8 mouse, are warranted to further dissect the relationship between adult neurogenesis and AD. Likewise, studies directly targeting hippocampal neurogenesis in normal mice, using AD-associated markers such as amyloid-β infusion, would further help elucidating a direct role between AD, amyloid-β and neurogenesis. Therefore, to date, no compensation or crisis, but rather a chaotic state of affairs seems to be present in the literature regarding the role of neurogenesis in AD, and, judging from the disparity in results across the neurogenesis-Alzheimer studies, the jury is still out on the exact function of neurogenesis.

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