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Neurogenesis in Alzheimer's disease: a realistic alternative to neuronal degeneration?

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Abstract

Neural stem cells (NSC) are cells that have the capacity to generate multiple types of differentiated brain cells. In conditions in which there is a loss of key functional cell groups, such as neurons, inducing or introducing neural stem cells to replace the function of those cells that were lost during the disease has the greatest potential therapeutic applications. Indeed, the achievement of one of the main objectives of various investigations is already on the horizon for some conditions, such as Alzheimer's disease. It is not known whether impaired neurogenesis contributes to neuronal depletion and cognitive dysfunction in Alzheimer's disease (AD). The results of the different investigations are controversial; some studies have found that neurogenesis is increased in AD brains, but others have not.

Keywords

neurodegenerative disease; Alzheimer's disease; neurogenesis; neural stem cells; cell death

Introduction

One of the main dogmas of neuroscience in the last century was that central nervous system (CNS) regeneration is not possible in adulthood. However, various studies have demonstrated the existence of neurogenesis in adult brain regions [1]. Indeed, this has been confirmed by observing that new cells continue to be generated postnatally and throughout life [2,3].

The most active neurogenic regions in the brain are the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles [3,4,5]. In these two areas of the adult mammalian brain, cells with mitotic activity can be found [6,7]. These cells are called stem cells and have the capacity to generate multiple types of differentiated cells (multipotency) and undergo cell division, in which at least one of the daughter cells maintains its stem-cell potential and, thus, has a capacity for self-renewal [8,9].

Neuronal stem cells (NSCs) in the SVZ predominantly give rise to committed progenitor cells that migrate into the olfactory bulb (OB) via the rostral migratory stream and

differentiate into local interneurons [10,11]; progenitors in the SGZ migrate into the granular cell layer of the hippocampus and also differentiate into neurons [12,13]. Since the discovery of these stem cells, the biggest controversy has been determining the nature of the precursor cells in the adult brain germinal zones. Studies have shown that a specific population of radial glia can give rise to neural precursors, which, in turn, produce neurons and glial cells [14,15].

The identification of new neurons in the brain has generated great expectations among scientists, particularly in the context of the conditions that result in the loss of functional cell groups, such as neurons. The potential therapeutic applications of inducing or introducing NSCs to replace the function of those lost in neurodegenerative diseases such as Alzheimer's disease (AD) has been one of the main objectives in recent years. As the structural and molecular mechanisms governing adult neurogenesis are important in AD, we will review the collective literature findings in this field with a focus on the findings from Alzheimer's mouse models.

Alzheimer's disease and the formation of new neural stem cells

Alzheimer's disease is a particular form of progressive dementia associated with distinct neuropathological changes [16,17]. It is characterized by memory loss and impairment in at least one other area of cognition [18,19,20]. At any time during the disease, patients may also experience changes in behavior or mood. Indeed, several lines of evidence suggest that AD may be a syndrome with overlapping causes that result in identical neuropathological changes, and, if this hypothesis is correct, there will likely be multiple treatment approaches, whose components will vary from patient to patient [21]. Several lines of investigation have proposed different treatment strategies in AD models, including the induction of neurogenesis.

Various evidence supports the idea that the disease symptoms of AD could partly be due to the impaired formation of new hippocampal neurons from endogenous NSCs in the SGZ, which are believed to contribute to mood regulation, learning and memory [22]. However, we still do not know what causes the disease.

In AD, different cellular alterations make the induction of neurogenesis more difficult than expected, and an improved understanding of the factors that govern NSC differentiation is needed before the stimulation or introduction of neural precursors into the brain becomes a viable option for the treatment of this disease. AD is extremely complex because the NSCs would have to be pre-differentiated *in vitro* into many different types of neuroblasts for subsequent implantation into a large number of brain areas. However, there has been evidence showing that endogenous neuronal precursors can proliferate in response to damage [23,24,25]. Neurogenesis was found to be increased in the brains of patients with AD, compared with the brains of age-matched control subjects [26], suggesting that compensatory mechanisms are directed to overcome the loss of function [27]. Currently, it is still unclear how the pathophysiological environment in the AD brain affects neural stem cell biology.

Postmortem analysis of the hippocampus in patients with AD has identified a significant increase in neurogenesis in patients with AD, compared with controls, with the most-severely affected patients displaying the greatest increase [26]. Other evidence has shown that the expression of proteins that are linked to the activation of cell cycle mechanisms and the regulation of chromosomal replication (MCM2, Ki67, and PCNA) are observed in glial cells and neurons in the hippocampus, entorhinal cortex, and white matter in elderly human brains with different extents of AD-type pathology. These proteins trend toward increased expression levels, which are associated with more-advanced Braak stages [28].

Mouse models of AD have provided controversial results. Some studies have demonstrated both increased and decreased hippocampal neurogenesis [29]. One important factor is the disease severity, with a compensatory increase in progenitor proliferation in the early stages and decreased proliferation and survival with in the advanced stages of the pathology [30,31].

Mechanisms that induce neurodegeneration in Alzheimer's disease and their effects on neurogenesis

Alzheimer's disease is the primary cause of dementia in the elderly and begins with a hippocampal pathology [32,33]. This disease is characterized by dysfunctional intracellular and extracellular biochemical processes that result in neuronal death (Figure 1). Various evidence supports a role for the amyloid β (A β) peptide in AD [34,35]. When an autopsy is performed, the AD brain is characterized by a high density of amyloid plaques that are composed primarily of the A β peptide [36,37]. This histological finding is a necessary criterion for a conclusive diagnosis of the disease. The A β peptide isolated from AD brain tissue varies in length from 39–42 amino acids, and the predominant form found in the brains of AD patients is 42 amino acids (A β ⁴²) in length and has pathogenic importance because it can form toxic insoluble fibrils and accumulate in the neuritic plaques isolated from the brains of these patients [38,39]. Although the augmented levels of the pathogenic A β peptide assemblies likely contribute causally to AD [40], there is much debate about whether and how it affects adult neurogenesis in brain tissue.

Studies have provided evidence of the adverse effects of A β on the proliferation, differentiation, and survival of adult mouse neural progenitor cells (NPCs) in the SVZ. The direct exposure of the human embryonic cortical NPC to A β results in decreases cell proliferation, whereas the direct exposure of differentiating neurospheres to A β induces the apoptosis of the newly generated neurons [41].

According to the results of transgenic animal studies and cell culture experiments, β -amyloid may also play a role in regulating neurogenesis, although the results of these experimental studies are inconsistent. Different studies have reported that the amyloid protein either reduces [42,43,44] or induces neurogenesis in adult transgenic animals [26,45].

The exposure of cell cultures derived from the adult mouse SVZ to A β (25–35 and 1–42) have demonstrated that A β peptides can influence the fate (but not the proliferation) of NSCs by driving their differentiation toward a neuronal lineage [46]. Different results have also come from studies using bromodeoxyuridine (BrdU) labeling and neuronal or glial markers in different lines of transgenic mice expressing the human amyloid precursor protein [41,47,48,49].

The basis of the effects of A β on the proliferation, differentiation, and survival of NSCs remains to be fully determined. Multiple analyses have documented that this process is regulated by different growth factors that are abundant during development, dramatically decline with age, and can contribute to reduced neurogenic potential [50,51]. Other studies have postulated that A β induces an increase in GABAergic neurotransmission, or an imbalance between GABAergic and glutamatergic circuits may contribute to impairment in AD [52].

Neurofibrillary alterations in AD

The brains of AD patients are characterized by hyperphosphorylated tau and the formation of neurofibrillary lesions, which constitute the intracellular deposits that form neurofibrillary

tangles (NFTs) in neuronal cell bodies and apical dendrites, neuropil threads in the distal dendrites and axons and the dystrophic neurites that are associated with neuritic plaques [53,54]. Tau hyperphosphorylation and aggregation appear to have distinct effects on cell differentiation and death. Although some reports have proposed a protective role for tau hyperphosphorylation [55,56], tau aggregation is postulated to induce neuronal death [57]. Tau hyperphosphorylation has been shown to be reversible, whereas tau aggregation is not [58]. Schindowski, et al. (2008) generated a novel transgenic mouse line (THY-Tau22, which has the typical biochemical phosphorylation pattern of human tau in AD) and demonstrated an increase in neurogenesis during tau hyperphosphorylation, cell cycle events during abnormal tau phosphorylation, and tau aggregation preceding neuronal death and neurodegeneration [59]. These authors stated that their findings have also been observed in other tau transgenic mouse models with the following tau mutations: P301S [60], P301L [61,62], V337M [63] and R406W [64,65].

Recent studies have suggested that tau phosphorylation is essential for hippocampal neurogenesis [66]. A set of different protein kinases, including glycogen synthase kinase 3b (GSK3b), MAP kinase, the cyclin-dependent kinase 5 (Cdk5) system and others [67], is involved in tau phosphorylation. These kinases might be sensitive to changes in their regulatory patterns or at the structural level and, thus, participate in the molecular pathway leading to neurodegeneration. In this context, there are evidences of mutations of the amyloid precursor protein provoke an increase in GSK3 activity that facilitate tau phosphorylation and cell toxicity [68].

Evidence suggests that the manipulation of tau phosphorylation may compensate for neuronal loss in neurological disorders, including AD. Other investigations have examined the expression of phosphorylated tau in the SVZ and its role in adult neurogenesis. They found that tau colocalized with some SVZ neural precursors. However, it is not known the implications of this findings and the mechanism that participate in the molecular pathway leading to tau and neural precursors.

Reactive gliosis

In the last decade, evidence has converged regarding the roles of glial cells, alterations in their function and their implications for neuronal degeneration [69,70]. Reactive astrocytes have been found to be increased in the cortex and hippocampus of patients with AD. Although astrogliosis is an important neuropathological feature of AD, its significance is not completely clear. Some studies have suggested that the combined effects of cytokines derived from activated astroglial and microglial cells and A β mediate neuronal death. The generation of a cytokine milieu, which includes the up-regulation of tumor necrosis factor α (TNF α), interleukin-1 β (IL-1 β), transforming growth factor β (TGF β) and IL-6, at A β plaques in the brain potentially suppresses neurogenesis [71,72,73,74].

The increased expression of IL-6 in the aged brain is potentially significant, because this cytokine can be neurotoxic [75]. It has been shown that neurogenesis is decreased by 63% in the SGZ of adult transgenic mice whose astrocytes overexpress IL-6, and the proliferation, survival, and differentiation of neural progenitor cells labeled with thymidine are all reduced in the granule cell layers of these mice [76]. Embryonic cerebral precursor cells have also been shown to differentiate into astroglia when they are cultured in the presence of IL-6 or other cytokines; this mechanism is mediated by the Janus kinase signaling pathway [77]. Thus, IL-6 may restrain neurogenesis in the aged brain by redirecting progenitor cells toward a glial cell lineage [78].

TNF α is a key player in many pathological processes and is increased in some conditions, such as mild cognitive impairment and AD [79]. This cytokine and its receptors play

important roles in neurogenesis in the adult brain [80,81]. Both receptors have been proposed to mediate distinct TNF α effects in the CNS, with TNF-R1 contributing to neuronal damage and TNF-R2 providing neuroprotection [82,83,84]. These results have been tested under both physiological and pathological conditions by activating these two receptors and observing their differential effects on proliferation and survival [72].

The cholinergic system in AD and its relationship with neurogenesis

Cholinergic deficits in AD are well established and include decreased levels of choline acetyltransferase (CAT), the biosynthetic enzyme for acetylcholine (ACh), decreased levels of acetylcholinesterase (AChE), the enzyme that degrades synaptic acetylcholine, and decreased levels of acetylcholine in the cortex [85]. These deficiencies are associated with a loss of neurons in the basal nucleus of Meynert [86]. A deficiency in cholinergic neurotransmission may account for some of the cognitive impairment observed in AD, and it correlates with the severity of dementia in multiple neocortical regions [88].

The cholinergic system plays an important role in neurogenesis because acetylcholine acts as growth regulatory signal in the brain. Ma et al. (2000) showed that ACh can stimulate the proliferation of NSCs and stem cell-derived progenitor cells during neural cell lineage progression *in vitro* [89]. In a transgenic mouse model, it has been shown that a diminution in the cholinergic innervation of the cortex is associated with different impairments in synaptic plasticity, and an acute increase in the availability of acetylcholine rescues these alterations in synaptic plasticity. The authors suggest that the cholinergic system mediates the impairment of cortical plasticity [90]. In addition, another study has provided *in vivo* evidence that the experience-dependent plasticity of the human auditory cortex is modulated by acetylcholine [91]. In spite of these results, few investigations have focused on clarifying the role of this system in neurogenesis and this condition.

Concluding remarks

One of the greatest challenges in elucidating the etiology of AD is the difficulty of studying the earliest changes in the neuronal function of the brain and correlating these changes with antemortem cognitive and behavioral function. Although suitable tissue specimens from patients with AD are very difficult to obtain, they are the most important and logical tools for understanding the causes of this disease. In this context, different mouse models of AD have been used to try to clarify the mechanism that induces this disease.

The discovery of neurogenesis in the adult brain and the regenerative potential of NSCs hold the promise of restoring the neural populations and regenerating the neural circuits that are necessary for cerebral function. Indeed, the core factors that drive neurogenesis in AD have not been elucidated. The induction of neurogenesis is of particular interest because the pathological manifestations of AD occur in the brain regions that are involved in learning and memory. Continued research in this area and the use of animal models are critical for evaluating whether neurogenesis-based therapeutic strategies will have the potential to aid those individuals with degenerative conditions.

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Figure 1.
Mechanisms of neurodegeneration in AD. Defective cellular and genetic processes can lead to different defects, synaptic damage and cell death.