Activity- and pharmacology-dependent modulation of adult neurogenesis in relation to Alzheimer's disease

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Chapter 2: Alzheimer's disease and adult neurogenesis: Are endogenous neural stem cells part of the solution?

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Abstract

The human brain produces new neurons mediating hippocampal plasticity but also having a potential role in hippocampal-related disorders, such as Alzheimer's disease and dementia. Factors such as stress and aging that decrease adult neurogenesis also serve as independent risk factors for Alzheimer's disease. Causality between loss of neurogenesis and hippocampal dysfunction has not been established, however neurogenesis is an attractive research avenue for therapy since it is readily modifiable. Activities such as running and enrichment increase proliferation of neural stem cells and survival of nascent neuroblasts. Adult neurogenesis may alternatively reflect capacity to overcome age-dependent insults and neurodegeneration in the hippocampus. This collectively indicates that stimulation of endogenous cells or transplantation of neural stem cells are potential pathways reversing the behavioural changes associated with neurodegenerative disorders by augmenting structural plasticity of the hippocampus. Continued research in this area and in appropriate animal models of disease is critical for evaluating if neurogenesis-based therapeutic strategies will have the potential to aid those with degenerative conditions.

Preface

Numerous clinical trials are under way to evaluate therapeutic approaches to stop the progression of Alzheimer's disease (AD). Despite the significant efforts towards, for example, clearance of amyloid plaques by vaccination therapies, these approaches may still fall short of cognitive recovery in the AD population as they do not directly focus on the regeneration of damaged tissue and restoration of brain function. Adult neurogenesis is a unique form of structural plasticity in the brain that has important implications in hippocampal-dependent learning and behavior. While not shown to have direct links with AD, adult neurogenesis is carefully regulated by various factors, including ones that impact AD, and should be evaluated independently and in relation to Alzheimer's pathology. Comprehensive therapy would ideally remove the hallmarks of the disease and provide a level of functional recovery, i.e. by increasing neurogenesis. The therapeutic potential of endogenous neuronal stem cells (NSCs) and grafted stem cells in damaged brain regions should therefore be considered in the context of AD. Although the appropriate delivery of exogenous NSCs to restricted areas of the affected AD brain remains a major challenge, ongoing neurogenesis by endogenous NSCs provides an exciting avenue that has the potential to resolve cognitive deficits in people with AD.

Alzheimer's Disease

AD is a fatal and devastating disorder characterized by progressive memory loss and severe cognitive deficits. AD has two pathological hallmarks: amyloid beta (Aβ) plaques, derived from amyloid precursor protein (APP), and neurofibrillary tangles, consisting of hyperphosphorylated tau protein. Tau protein is a microtubule-associated protein (MAP) responsible for cytoskeletal stability. It is implicated in cellular plasticity, migration, division, regulation of the cell-cycle, and neuronal differentiation. Neurofibrillary tangles are accumulations of hyperphosphorylated tau that are well-correlated with cognitive deficits, brain atrophy, and neuronal loss in some brain regions.

Early onset and familial forms of AD are caused by mutations in APP, presenilin-1, or presenilin-2 proteins resulting in overproduction of fibrillogenic Ab species. Most cases (>95%), however, are sporadic late-onset AD not associated with mutations impacting Aβ metabolism. Therapies against Aβ have been forerunners in the field and provide an accurate view of the problems associated with developing an effective therapy. Data from phase I trial immunization, for example, showed clearance of Aβ plaques; however neurofibrillary tangles and cognitive scores were not significantly changed [1].

Adult Neurogenesis

During development and throughout life, endogenous neural stem cells self-renew to produce identical multipotent cells. Astrocytes are the NSCs of the brain and produce neurons, astrocytes and oliogodendrocytes [2,3]. In the adult brain, two zones have been identified where adult neurogenesis occurs. NSCs located in the subgranular zone (SGZ) of the dentate gyrus proliferate and migrate into the granular cell layer [4]. Neurons also develop from stem cells located in the subventricular zones of the lateral ventricles. Here, committed progenitor cells migrate via the rostral migratory stream into the olfactory bulb where they are involved in olfactory discrimination learning [5,6].

The hippocampus has a vital role in higher cognition [7]. While synaptic plasticity is thought to be the main structural change corresponding to cognitive function, ongoing neurogenesis is a novel and unique form of structural plasticity. New neurons generated in the subgranular zone form granule cells in the dentate gyrus of the hippocampus and are thought to have a rather limited input into the adult hippocampus on a short time scale. While the number of new neurons incorporated in the hippocampus may be quite low during aging, adult neurogenesis represents potential for adaptation. This has been described previously as the neurogenic reserve hypothesis; neurogenesis is a special type of brain plasticity that, when the hippocampus is actively engaged, allows for adaptation and resistance to accumulated deleterious insults [8].

Many adult-generated cells die within the first few weeks [9,10] due to selection determined by local neuronal activity and trophic support [11]. Significant proportions of the newborn cells, however, eventually differentiate into fully functional neurons.12 Neurogenesis has a significant role in hippocampal learning and appears to be required for the behavioral effects of antidepressants [13,14].

Recent studies show further that neurogenesis may also occur outside the classical neurogenic niches; rare neurogenesis has been reported in the cortex, amygdala, hypothalamus and substantia nigra

[15–18], notably often in response to insult. Ischemia/reperfusion in the striatum can recruit new neurons from glial precursors in closely related brain regions like the subventricular zone [19,20]. Neurogenesis has also been reported after hippocampal or cortical damage from excitotoxic, ischaemic or epileptic events [21–25]. Interestingly, hypoxia-inducible expression of brain-derived neurotrophic factor, insulin-like growth factor 1, fibroblast growth factor 2, and vascular endothelial growth factor [26–28] are known stimulators of adult neurogenesis [29–31].

Regulation of adult neurogenesis occurs via a wide array of intrinsic growth factors, hormones and environmental factors. Environmental factors, such as enriched housing, learning experiences or physical exercise stimulate neurogenesis; however, aging, glucocorticoid hormones or stress potently inhibit it. Different stimuli can affect different stages of the neurogenic process,[32] each targeting specific populations. Many studies show that adult neurogenesis directly, or indirectly, contributes to adaptations in hippocampal function [33].

Proliferation and neuronal differentiation rates show age-dependent declines in laboratory animals [4,34–37]. Low levels of neurogenesis have been reported in older primates [38,39] and the elderly human brain [40–42]. However, stem cells from aged individuals remain capable of proliferation and neuronal differentiation [37,43]. This in vivo evidence suggests that aging does not affect NSCs capacity for proliferation and neuronal differentiation such that endogenous cells cannot be used therapeutically.

Neurogenesis in the Alzheimer's Brain

A limited number of studies have examined postmortem human brain tissue using various immunocytochemical markers of neurogenesis. These studies have produced different results but collectively they provide crucial evidence. One report describes increases in doublecortin, a marker of immature neurons, in a cohort of senile AD cases, suggesting that neurogenesis is increased in AD [44]. Doublecortin is a MAP linked with migrating neuroblasts [45,46] but has additionally been found to be very sensitive to degradation during post mortem delay [42] and additional studies indicate that it may also be expressed by astrocytes under pathological conditions [47]. A study in a younger cohort of presenile patients did not replicate these results, finding that doublecortin expression was present in only a minority of cases [42].

Significant increases in proliferation have been observed however, these observations are non-specific for ongoing neurogenesis; proliferating Ki-67 antigen positive cells were found in AD but not observed exclusively in the granule cell layer [42]. Other investigators found that expression of the mature neuronal markers, MAP isoforms MAP2a and b, were found to be decreased in AD dentate gyrus, whereas total MAP2, including expression of the immature MAP2c isoform, were less affected. This may suggest that new cells in the AD dentate gyrus do not become mature neurons, although proliferation is increased [48].

Some of the basic questions regarding the relationship between neurogenesis and AD have yet to be answered. Does inflammation, active during the early stages of AD, impact the local microenvironment and ongoing neurogenesis? Do age and disease preclude the use of exogenous stem cells from replacing dysfunctional neurons? If these neurons can successfully integrate will significant behavioral improvements be observed?

Future Directions

To better understand disease progression and underlying mechanisms, various transgenic mouse lines have been developed expressing the AD related proteins amyloid precursor protein, presenilin 1 and/or tau [49,50]. These models recapitulate various aspects of AD and frontal temporal lobe dementia and are inherently useful for understanding the timing of neurogenetic changes in AD progression. Such studies have so far produced conflicting results showing increases [51], non-significant changes [52], and decreases [53] in hippocampal neurogenesis in mouse models that depend, in part, on methodological differences in markers for neurogenesis and the age of the animals. Additional studies have also shown that tau expression is linked to differences in neurogenesis [54]. For reviews, see Thompson et al. [55] and Kuhn et al. [56].

Conclusion

AD is characterized by cognitive deficits and progressive memory loss. In addition to neuropathology in various brain regions, the hippocampus is particularly affected. Stem cells in the SGZ of the dentate gyrus produce new neurons that have acute and long-term consequences for hippocampal dependent learning and memory. The consequences of dysfunctional neurogenesis are unknown but the deleterious conditions known to reduce neurogenesis are also risk factors for AD. A few primary studies have been completed with Alzheimer tissue indicating that neurogenic responses may be initiated, but that new neurons fail to integrate into the DG. Similar results are observed in animal models, where neurogenesis responds to various pathological stimuli, but conclusive evidence has yet to show this phenomenon produces functional neurons that impact behavior.

Whether a neurogenic response can be completed depends on local cues and on the composition of the neurogenic niche, for which vasculature-related and brain derived growth factors are important. But many questions still abound regarding the hippocampal environment, specifically whether successful stimulation of neurogenesis is possible during late aging and under pathological conditions. Indeed, discriminating early hippocampal changes such as gliosis and inflammation, which may suppress neurogenesis, hold the greatest promise for long-term maintenance of this crucial mechanism.

Future research should focus on how neural stem cells respond to chronic and acute insults. This will further improve our understanding of the factors that determine a permissive local microenvironment, and how, by modulation, regenerative responses can be completed successfully.

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