

Alzheimer's Disease and Adult Neurogenesis— Are Endogenous Stem Cells Part of the Solution?

Michael W Marlatt, MSc,¹ Jeroen JM Hoozemans, PhD,² Rob Veerhuis, PhD^{2,3} and Paul J Lucassen, PhD¹

1. Swammerdam Institute for Life Science—Center for Neuroscience, University of Amsterdam; 2. Department of Pathology, VU University Medical Center, Amsterdam; 3. Alzheimer Center/Psychiatry Department and Department of Clinical Chemistry, VU University Medical Center, Amsterdam

Abstract

The human brain produces new neurons that mediate hippocampal plasticity but also have a potential role in hippocampal-related disorders, such as Alzheimer's disease and dementia. Factors such as stress and aging that reduce 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 the 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 behavioral 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 whether neurogenesis-based therapeutic strategies will have the potential to aid those with degenerative conditions.

Keywords

Adult neurogenesis, neural stem cells, structural plasticity, neurogenic reserve, hippocampus, Alzheimer's disease, neurodegeneration

Disclosure: The authors have no conflicts of interest to declare.

Received: November 5, 2008 **Accepted:** June 12, 2009 *DOI:* 10.17925/USN.2009.05.01.12

Correspondence: Paul J Lucassen, PhD, Center for Neuroscience, Swammerdam Institute of Life Sciences, University of Amsterdam, PO Box 94084, 1090 GB Amsterdam, The Netherlands. E: lucassen@science.uva.nl

Numerous clinical trials are under way to evaluate therapeutic approaches to stop the progression of Alzheimer's disease (AD). Despite the significant efforts toward, 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 affect 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 β (A β) plaques, derived from amyloid precursor protein, 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 amyloid precursor protein or presenilin-1 or presenilin-2 proteins, resulting in overproduction of fibrillogenic A β species. Most cases (>95%), however, are sporadic late-onset AD not associated with mutations affecting A β metabolism. Therapies against A β 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 A β 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 oligodendrocytes.^{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 (DG) 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 such as the subventricular zone.^{19,20} Neurogenesis has also been reported after hippocampal or cortical damage from excitotoxic, ischemic, 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 potentially 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 the capacity of NSCs 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 *post mortem* human brain tissue using various immunocytochemical markers of neurogenesis. These studies have produced varying results, but collectively they provide crucial evidence. One report describes increases 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 pre-senile patients did not replicate these results, finding that doublecortin expression was present in 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 were 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, was 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, affect 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 decreases⁵³ 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

Conclusions

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 whether this phenomenon produces functional neurons that affect 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. However, 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, further improving our understanding of the factors that determine a permissive local microenvironment, and how, by its modulation, regenerative responses could be completed successfully. ■

- Holmes C, et al., Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial, *Lancet*, 2008;372(9634):216–23.
- Seri B, et al., Astrocytes give rise to new neurons in the adult mammalian hippocampus, *J Neurosci*, 2001;21(18):7153–60.
- Seri B, et al., Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus, *J Comp Neurol*, 2004;478(4):359–78.
- Kuhn HG, et al., Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation, *J Neurosci*, 1996;16(6):2027–33.
- Gheusi G, et al., Importance of newly generated neurons in the adult olfactory bulb for odor discrimination, *Proc Natl Acad Sci U S A*, 2000;97(4):1823–8.
- Alonso M, et al., Olfactory discrimination learning increases the survival of adult-born neurons in the olfactory bulb, *J Neurosci*, 2006;26(41):10508–13.
- Jaffard R, et al., Role of the hippocampal formation in learning and memory, *Hippocampus*, 1993;3:Spec No 203–17.
- Kempermann G, The neurogenic reserve hypothesis: what is adult hippocampal neurogenesis good for?, *Trends Neurosci*, 2008;31(4):163–9.
- Cameron HA, et al., Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus, *J Comp Neurol*, 2001;435(4):406–17.
- Dayer AG, et al., Short-term and long-term survival of new neurons in the rat dentate gyrus, *J Comp Neurol*, 2003;460(4):563–72.
- Deisseroth K, et al., Excitation-neurogenesis coupling in adult neural stem/progenitor cells, *Neuron*, 2004;42(4):535–52.
- van Praag H, et al., Functional neurogenesis in the adult hippocampus, *Nature*, 2002;415(6875):1030–34.
- Santarelli L, et al., Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants, *Science*, 2003;301(5634):805–9.
- Dupret D, et al., Spatial learning depends on both the addition and removal of new hippocampal neurons, *PLoS Biol*, 2007;5(8):e214.
- Bernier PJ, et al., Newly generated neurons in the amygdala and adjoining cortex of adult primates, *Proc Natl Acad Sci U S A*, 2002;99(17):11464–9.
- Gould E, et al., Neurogenesis in adult mammals: some progress and problems, *J Neurosci*, 2002;22(3):619–23.
- Rakic P, Neurogenesis in adult primate neocortex: an evaluation of the evidence, *Nat Rev Neurosci*, 2002;3(1):65–71.
- Zhao M, et al., Evidence for neurogenesis in the adult mammalian substantia nigra, *Proc Natl Acad Sci U S A*, 2003;100(13):7925–30.
- Lindvall O, et al., Recovery and rehabilitation in stroke: stem cells, *Stroke*, 2004;35(11 Suppl. 1):2691–4.
- Thored P, et al., Persistent production of neurons from adult brain stem cells during recovery after stroke, *Stem Cells*, 2006;24(3):739–47.
- Parent JM, et al., Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus, *J Neurosci*, 1997;17(10):3727–38.
- Covolan L, et al., Cell damage and neurogenesis in the dentate granule cell layer of adult rats after pilocarpine- or kainate-induced status epilepticus, *Hippocampus*, 2000;10(2):169–80.
- Blumcke I, et al., Increase of nestin-immunoreactive neural precursor cells in the dentate gyrus of pediatric patients with early-onset temporal lobe epilepsy, *Hippocampus*, 2001;11(3):311–21.
- Jiang W, et al., Cortical neurogenesis in adult rats after transient middle cerebral artery occlusion, *Stroke*, 2001;32(5):1201–7.
- Jin K, et al., Neurogenesis in dentate subgranular zone and rostral subventricular zone after focal cerebral ischemia in the rat, *Proc Natl Acad Sci U S A*, 2001;98(8):4710–15.
- Kiyota Y, et al., Increase in basic fibroblast growth factor-like immunoreactivity in rat brain after forebrain ischemia, *Brain Res*, 1991;545(1–2):322–8.
- Schmidt-Kastner R, et al., Transient changes of brain-derived neurotrophic factor (BDNF) mRNA expression in hippocampus during moderate ischemia induced by chronic bilateral common carotid artery occlusions in the rat, *Brain Res Mol Brain Res*, 2001;92(1–2):157–66.
- Plate KH, et al., Cell type specific upregulation of vascular endothelial growth factor in an MCA-occlusion model of cerebral infarct, *J Neuropathol Exp Neurol*, 1999;58(6):654–66.
- Kuhn HG, et al., Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain, *J Neurosci*, 1997;17(15):5820–29.
- Zigova T, et al., Intraventricular administration of BDNF increases the number of newly generated neurons in the adult olfactory bulb, *Mol Cell Neurosci*, 1998;11(4):234–45.
- Schanzer A, et al., Direct stimulation of adult neural stem cells *in vitro* and neurogenesis *in vivo* by vascular endothelial growth factor, *Brain Pathol*, 2004;14(3):237–48.
- Kempermann G, et al., Milestones of neuronal development in the adult hippocampus, *Trends Neurosci*, 2004;27(8):447–52.
- Dupret D, et al., Spatial learning depends on both the addition and removal of new hippocampal neurons, *PLoS Biol*, 2007;5(8):e214.
- Heine VM, et al., Prominent decline of newborn cell proliferation, differentiation, and apoptosis in the aging dentate gyrus, in absence of an age-related hypothalamus-pituitary-adrenal axis activation, *Neurobiol Aging*, 2004;25(3):361–75.
- Kronenberg G, et al., Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus, *Neurobiol Aging*, 2006;27(10):1505–13.
- Montaron MF, et al., Lifelong corticosterone level determines age-related decline in neurogenesis and memory, *Neurobiol Aging*, 2006;27(4):645–54.
- Bondolfi L, et al., Impact of age and caloric restriction on neurogenesis in the dentate gyrus of C57BL/6 mice, *Neurobiol Aging*, 2004;25(3):333–40.
- Kornack DR, et al., Continuation of neurogenesis in the hippocampus of the adult macaque monkey, *Proc Natl Acad Sci U S A*, 1999;96(10):5768–73.
- Gould E, et al., Neurogenesis in the neocortex of adult primates, *Science*, 1999;286(5439):548–52.
- Eriksson PS, et al., Neurogenesis in the adult human hippocampus, *Nat Med*, 1998;4(11):1313–17.
- Mangano LN, et al., Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain, *Science*, 2007;318(5852):980–85.
- Boekhoorn K, et al., Increased proliferation reflects glial and vascular-associated changes, but not neurogenesis in the presenilin Alzheimer hippocampus, *Neurobiol Dis*, 2006;24(1):1–14.
- Laplagne DA, et al., Functional convergence of neurons generated in the developing and adult hippocampus, *PLoS Biol*, 2006;4(12):e409.
- Jin K, et al., Increased hippocampal neurogenesis in Alzheimer's disease, *Proc Natl Acad Sci U S A*, 2004;101(1):343–7.
- Rao MS, et al., Efficacy of doublecortin as a marker to analyse the absolute number and dendritic growth of newly generated neurons in the adult dentate gyrus, *Eur J Neurosci*, 2004;19(2):234–46.
- Couillard-Despres S, et al., Doublecortin expression levels in adult brain reflect neurogenesis, *Eur J Neurosci*, 2005;21(1):1–14.
- Verwer CM, et al., Effects of housing condition on experimental outcome in a reproduction toxicity study, *Regul Toxicol Pharmacol*, 2007;48(2):184–93.
- Li B, et al., Failure of neuronal maturation in Alzheimer disease dentate gyrus, *J Neuropathol Exp Neurol*, 2008;67(1):78–84.
- Spires TL, et al., Transgenic models of Alzheimer's disease: learning from animals, *NeuroRx*, 2005;2(3):423–37.
- Gotz J, et al., Transgenic animal models of Alzheimer's disease and related disorders: histopathology, behavior and therapy, *Mol Psychiatry*, 2004;9(7):664–83.
- Jin K, et al., Enhanced neurogenesis in Alzheimer's disease transgenic (PDGF-APPsw,Ind) mice, *Proc Natl Acad Sci U S A*, 2004;101(36):13363–7.
- Chevallier NL, et al., Perturbed neurogenesis in the adult hippocampus associated with presenilin-1 A246E mutation, *Am J Pathol*, 2005;167(1):151–9.
- Zhang C, et al., Long-lasting impairment in hippocampal neurogenesis associated with amyloid deposition in a knock-in mouse model of familial Alzheimer's disease, *Exp Neurol*, 2007;204(1):77–87.
- Sennvik K, et al., Tau-4R suppresses proliferation and promotes neuronal differentiation in the hippocampus of tau knockin/knockout mice, *FASEB J*, 2007;21(9):2149–61.
- Thompson A, et al., Changes in adult neurogenesis in neurodegenerative diseases: cause or consequence?, *Genes Brain Behav*, 2008;7(S1):28Genes, Brain and Behaviour42.
- Kuhn HG, et al., Involvement of adult neurogenesis in dementia and Alzheimer mouse models; what is the functional relevance?, *Eur Arch Gen Psy & Clin Neurosci*, 2007;57(5):281–9.