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DOI
10.1007/978-1-4939-1908-6_4

Publication date
2015

Document Version
Final published version

Published in
Neural Stem Cells in Development, Adulthood and Disease

Stem Cells and Neurogenesis in Relation to Dementia and Alzheimer's Disease Mouse Models

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Introduction

Dementia is a neurodegenerative disorder that results in progressive memory loss and cognitive deficits and affects millions of people in the Western world. The most common form is *sporadic* Alzheimer's disease (AD). It is characterized by a late onset and the gradual accumulation of β-amyloid peptide (Aβ)-containing senile plaques, which are derived from the amyloid precursor protein (APP). Also many neurofibrillary tangles (NFTs) are found that contain hyperphosphorylated tau protein and correlate well with cognitive decline. Early onset forms of AD exist as well, but these are rare and mostly familial. They are caused by mutations in the APP or presenilin 1 or 2 (PS1/2) genes, which eventually all result in the overproduction of the longer Aβ species. Alterations in intracellular APP processing by specific secretases are thought to cause accumulation of mainly the longer forms of beta amyloid (Aβ1-42/43) that are secreted and, over time, aggregate in extracellular amyloid plaques. As the toxic forms are most likely the oligomeric forms of Aβ that, prior to

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H.G. Kuhn, A.J. Eisch (eds.), *Neural Stem Cells in Development, Adulthood and Disease*, Stem Cell Biology and Regenerative Medicine,
DOI 10.1007/978-1-4939-1908-6_4

accumulation in extracellular plaques, may form already intracellularly, increasing attention is nowadays paid to a role for different forms of intraneuronal Aβ as well (Bayer and Wirths 2011, 2014; Gouras et al. 2010).

In addition to β-amyloid plaques, extensive numbers of neurofibrillary tangles are found in the AD brain. In AD, the neurofibrillary tangles are based on tau protein that is hyperphosphorylated at numerous sites by specific kinases. Protein tau is a microtubule-associated protein (MAP) involved in cytoskeletal stability and internal vesicle transport. Its hyperphosphorylation is thought to contribute directly to neuronal dysfunction. In support, the extent of neurofibrillary tangle pathology correlates well with cognitive decline in AD (Nelson et al. 2012), which is not the case for the amyloid plaque load, where considerable overlap exists between control subjects and AD patients (Musiek and Holtzman 2012; Perl 2010).

In addition to AD, frontotemporal dementia is a specific form of dementia that lacks amyloid deposits but is characterized by the select and abundant presence of neurofibrillary tangles. These "tangle-only" forms of dementia are caused by specific mutations in tau or tau-related proteins like progranulin (van Swieten and Heutink 2008; Seelaar et al. 2011). Together, the gradual accumulation in the brain of amyloid and tau neuropathology is thought to induce progressive neuronal dysfunction and degeneration, which eventually results in cognitive deficits, brain atrophy, and limited cell death in distinct subregions of the AD brain (Duyckaerts and Hauw 1997; Masters et al. 2006; Perl 2010; Ferrer 2012; Krstic and Knuesel 2013; Ferrer 2012).

AD is furthermore a very heterogeneous disorder with a wide variation in age of onset, disease duration, as well as in the extent of neuropathology between brain regions. In many instances, e.g., amyloid plaque load does not correlate well with the patients' symptoms, and despite considerable progress in understanding the biochemical, genetic, and molecular mechanisms underlying AD and despite promising trials aimed at inhibition of secretases or at vaccination against amyloid (Pul et al. 2011; Lambracht-Washington and Rosenberg 2013; Wisniewski and Goñi 2014), knowledge of the exact AD etiology is poor and effective treatment or prevention remains elusive.

While many of the current therapeutic strategies are aimed to slow down or stop the degenerative process of amyloid accumulation, novel strategies could focus on other substrates like tau and tangle pathology as well as on the regeneration of damaged tissue. This could take place by utilizing the therapeutic potential of stem cells that could in theory be introduced and/or recruited into damaged brain regions where they could be stimulated to differentiate into new neurons. The proper delivery of exogenous neural stem cells to restricted areas of the affected AD brain still remains a major challenge, but the discovery of ongoing neurogenesis and the presence of endogenous stem cells in the adult brain, and their regenerative potential, holds considerable promise for recruiting endogenous populations and potentially restoring neuronal populations and improving functional neural circuits.

As various studies have now shown that it is the local microenvironment that determines the neurogenic potential and properties of endogenous as well as exogenously transplanted stem cells, it will be critical to first obtain a better understanding of the effects of the different elements of the AD disease process and its

main mediators, on the endogenous stem cell population. In this chapter, we will therefore review the state of the art on stem cells in the brain and their responses in relation to Alzheimer pathology. We focus on hippocampal neurogenesis and available AD mouse models.

Hippocampal Neurogenesis

The hippocampus is well known for its involvement in cognitive processes, such as learning and memory (Morris et al. 1982; Jaffard and Meunier 1993), and is severely affected in the dementias. It is furthermore unique as it is one of the very few brain regions where neurogenesis continues to occur in adult individuals (Altman 1962). Stem cells located in the subgranular zone (SGZ) of the adult hippocampal dentate gyrus (DG) undergo extensive proliferation before they migrate into its granular cell layer. In young adult rats, approximately 9,000 new hippocampal cells are born per day. Many of these adult-generated cells die within the first few weeks (Dayer et al. 2003), due to a selection probably determined by local neuronal activity and trophic support (Deisseroth et al. 2004). Significant proportions of the new cells survive and differentiate in about 3–4 weeks into mature neurons. During this process, they are eventually incorporated into the adult hippocampal circuitry where they become functionally active and contribute to the properties of the DG network. Various molecular (Schouten et al. 2012) and epigenetic factors have been identified that modulate this process, e.g., in relation to Alzheimer-related factors (Fitzsimons et al. 2014; Mu and Gage 2011).

In addition to the DG, neurogenesis occurs in the subventricular zone (SVZ) of the lateral ventricle. Here, committed progenitor cells migrate via the rostral migratory stream (RMS) into the olfactory bulb (OB) where they differentiate into interneurons that are involved in olfactory discrimination learning (Gheusi et al. 2000; Alonso et al. 2006). The location of these two adult neurogenic zones in the hippocampus and the lateral ventricle wall, i.e., close to the corpus callosum and neocortex, indicates strategic positions for potential repair processes. However, the generation of new neurons is involved in cognitive function and could, therefore, also be influenced by disease pathology. Moreover, aberrant neurogenic responses or mechanisms could even be a part of the pathological events of neurodegenerative diseases, as will be discussed below.

Adult hippocampal neurogenesis is prominent in young rodents, but the amount of neuronal progenitors decreases over time (Kuhn et al. 1996; Bondolfi et al. 2004; Heine et al. 2004; Kronenberg et al. 2006; Montaron et al. 2006; Shetty et al. 2005; Jinno 2011) to low levels in middle-aged and particularly aged animals. Additional studies have shown that similar levels exist in older primates (Gould et al. 1999; Kornack and Rakic 1999). The very few studies on this subject indicate that the adult and elderly human brain is no exception in this respect: while the extent of neurogenesis and its different stages is difficult to study in a controlled manner in the postmortem human brain or under in vivo conditions, these numbers are likely

low and, as in rodents, appear to decrease with advancing age (Couillard-Després 2013; Manganas et al. 2007; Spalding et al. 2013; Knoth et al. 2010; Mirochnic et al. 2009; Eriksson et al. 1998; Curtis et al. 2011; Ho et al. 2013).

Regulation of Neurogenesis

The fact that neurogenesis occurs in many different animal species suggests an important functional role that is conserved throughout evolution. Interestingly, the process is not only changed with age but also highly susceptible to environmental- or experience-dependent modulation: voluntary exercise and environmental enrichment, e.g., are well known to change the in vivo fates of the newborn cells. Various studies have identified factors that can regulate production, maturation, and survival of the new hippocampal neurons during rodent adulthood. Some, like estrogen, environmental complexity, antidepressants, learning, physical exercise, and NMDA-related excitatory input, positively regulate neurogenesis, whereas factors like stress, cholinergic denervation, drugs of abuse, and aging decrease levels of neurogenesis (Marlatt and Lucassen 2010; Marlatt et al. 2012, 2013; Lee et al. 2012; Cooper-Kuhn et al. 2004; Mohapel et al. 2005; Lucassen et al. 2010; Schouten et al. 2012; Bruel-Jungerman et al. 2011; Zhao et al. 2008).

Although it seems somewhat counterintuitive, acute and chronic brain disorders or insults also stimulate the endogenous NSC population. For instance, head injury, epileptic seizures, and transient global and focal ischemia increase hippocampal proliferation and neurogenesis. The effects of insults on hippocampal circuit properties and characteristics of a slowly developing disorder like AD, however, are variable, depend probably on the stage of the disease, and are in general poorly understood (Winner et al. 2011; Coras et al. 2010; Gomez-Nicola et al. 2014; Perry et al. 2012). It is important to note that a variety of stimuli can affect different stages of the neurogenic process independently, e.g., each targeting specific populations of proliferating versus differentiating adult-generated cells.

Consistent with the important role of the hippocampus in cognition, many studies have found changes in adult neurogenesis to be paralleled by changes in hippocampal functional plasticity and/or cognition (Drapeau et al. 2007; Koehl and Abrous 2011). For example, housing rodents in an enriched environment, or allowing them access to a running wheel, not only increases the survival of progenitor cells, but also leads to an enhanced performance in the hippocampus-dependent water maze learning task (van Praag et al. 1999). Conversely, factors like stress, which are linked to a decrease in neurogenesis, impair behavioral performance on such tasks (Abrous et al. 2005; Brummelte and Galea 2010; Gould et al. 1999; Lucassen et al. 2010).

One of the most direct studies to address the relation between neurogenesis and cognition utilized an inducible transgenic model to ablate adult-born hippocampal neurons through expression of the proapoptotic gene *Bax* in hippocampal neural precursors. These mice showed impairment of spatial memory while less complex

forms of spatial memory were unaltered. Previous work has established that spatial learning requires different phases of cellular plasticity. Moreover, learning increases levels of newborn cells and their dendritic spines, which is associated with improved cognitive performance. Thus, cellular plasticity and neurogenesis contribute to various types of hippocampus-dependent learning and memory particularly when learning is challenging and difficult (Abrous et al. 2005; Curlik and Shors 2011; Dupret et al. 2007; Zhao et al. 2008; Cameron and Glover 2014).

One of the first demonstrations of a functional role for newly born cells was by a study that substantially reduced the number of newly generated granule cells using treatment with the antimitotic agent MAM, which also disrupted trace eyeblink conditioning and trace fear conditioning, both known to be hippocampus-dependent tasks (Shors et al. 2002; Anderson et al. 2011). Notably, the reduction in new neurons had no effect on learning during tasks that were hippocampus-independent. Additional studies showed a functional incorporation of adult-generated cells into the hippocampal circuit (van Praag et al. 2002), while hippocampal learning itself also increased neurogenesis, which depended on the difficulty of the task (Gould et al. 1999; Curlik and Shors 2011). Together, this directly implicates adult neurogenesis in hippocampal function. Subsequent studies utilizing irradiation or genetic modification aimed to eliminate adult neurogenesis in rodent models observed an impaired performance of the animals in spatial-navigation learning, spatial memory, spatial pattern discrimination, and fear conditioning tasks. Later studies revealed a reorganization of memory to extrahippocampal substrates, a role for adult neurogenesis in spatiotemporal learning and memory and the encoding of time in new memories with pattern separation as one of the most prominent tasks (Sahay et al. 2011; Clelland et al. 2009). Thus, neurogenesis is involved in several aspects of hippocampal function and may prove important in disorders associated with cognitive impairments, like AD (Abrous et al. 2005; Zhao et al. 2008; Oomen et al. 2014).

Regulation of Plasticity by Disease

In contrast to many of the stimuli mentioned above, and important for the context of this review, pathological alterations involving the hippocampal trisynaptic circuit can trigger changes in neurogenesis as well. Neurogenesis is e.g. modified by hippocampal and cortical damage. This includes acute excitotoxic, ischemic, or epileptic insults or by more gradual accumulation of aberrant proteins (Parent et al. 1997; Covolan et al. 2000; Blumcke et al. 2001; Jiang et al. 2001; Jin et al. 2001; Mu and Gage 2011). Whereas the extent and severity of the insult may modulate the extent of the neurogenic response, it is generally insufficient in functional terms as many of the newly formed cells turn into glial cells and/or contribute to the formation of scar tissue. In fact, in epilepsy, a popular concept even implicates neurogenesis in its etiology, assuming that the neurogenic response that occurs following the initial, and damaging, status epilepticus contributes to the occurrence of chronic epilepsy due to the fact that new neurons “rewire” inappropriately and form new contacts, such as new excitatory synapses on previously inhibitory synapses.

Thereby, neurogenesis may hamper the restoration of the damaged circuit and/or contribute to the emergence of chronic epilepsy and disease progression (Parent et al. 1997; Bielefeld et al. 2014), a possibility that may be of interest for AD etiology as well (Palop and Mucke 2010; Yan et al. 2012).

Some of the regulatory factors involved in the neurogenic responses could be growth-related peptides like BDNF, IGF-1, FGF-2, and VEGF, which are upregulated after ischemic damage (Kiyota et al. 1991; Gluckman et al. 1992; Plate et al. 1999; Schmidt-Kastner et al. 2001) and which are known stimulators of adult neurogenesis when studied in isolated conditions (Kuhn et al. 1997; Zigova et al. 1998; Aberg et al. 2000; Schänzer et al. 2004; Van Tijn et al. 2011; Marlatt et al. 2012, 2013). Much less is known about whether neurogenesis is also increased after *chronic* lesions, or during "slow" neurodegenerative processes, like those expected in AD, and in close relation to the neuropathology (Marlatt et al. 2014). To address the spatiotemporal characteristics of these responses, animal models have provided important tools, as will be discussed later.

Cell Cycle Markers in the Alzheimer Brain

Earlier studies had already suggested that cellular plasticity responses occur during AD. These were based on the presence of marker proteins selectively identifying specific stages of the cell cycle. Despite the fact that they were not expected to be present in the adult postmitotic brain, considerably more cells actively engaged in cell cycle were found in the AD hippocampus compared to control (Smith and Lippa 1995; Arendt et al. 1996; Kondratick and Vandré 1996; McShea et al. 1997; Nagy et al. 1997; Vincent et al. 1997; Busser et al. 1998; Yang et al. 2003). For instance, neurons containing neurofibrillary tangles in both the "dynamic" DG to which new neurons are added every day, as well as in the more "stable" cornu ammonis (CA) areas, co-express various cyclins, mitotic phosphoepitopes, and cyclin-dependent kinases (Smith and Lippa 1995; Arendt et al. 1996; Kondratick and Vandré 1996; McShea et al. 1997; Vincent et al. 1997; Busser et al. 1998). While on the one hand seen as endangered neurons that attempt to reenter the cell cycle (Smith and Lippa 1995; Kondratick and Vandré 1996; Busser et al. 1998; Herrup et al. 2004), cell cycle marker re-expression was on the other hand considered part of a more general regenerative process associated with neurogenic cells in the adult brain that depends on the "permissiveness" of the local environment.

Thus far, evidence from mouse models demonstrates that the induction of cell cycle changes after the onset of amyloid pathology is limited (Yang et al. 2006). This could depend on the limited age of the mice studied or on the artificial condition of transgene-controlled protein expression that is intrinsically different from the human situation. The re-expression of these markers in mature human neurons could also induce an abortive exit of the cell cycle or lead to cell cycle arrest, followed by lasting cellular dysfunction. Cell cycle protein expression in mature neurons is regarded as a maladaptive response of cells "stuck" in a cycle they cannot complete that is expected to precede cell death (Yang et al. 2003; Herrup et al. 2004).

Cellular Plasticity and Neurogenesis in the Human and Alzheimer Brain

After the initial studies using cell cycle markers, interest quickly turned to a possible role of stem cells and neurogenesis in the human brain. While BrdU pulse-chase and viral labeling have been instrumental in a better understanding of stem cell kinetics and regulation in rodents, such studies were not possible in living AD patients. Also, they were hampered by intrinsic difficulties with obtaining human postmortem tissue of sufficient quality but also by the lack of reliable makers to identify the different stages of the neurogenic process in postmortem tissue. Although specialized immunocytochemical markers, e.g., from the tumor research field, had been promising, the methodological issues of postmortem delay, specificity and fixation turned out to be not trivial. One example was doublecortin (DCX), a reliable and common marker to detect adult neurogenesis in rodents (Brown et al. 2003; Rao and Shetty 2004; Couillard-Despres et al. 2005). Unlike BrdU, detection of DCX does not require prior BrdU injections in living subjects, which made DCX a promising candidate marker. However, DCX, like many other microtubule-associated proteins (MAP) (Swaab and Uylings 1988), is very sensitive to degradation during postmortem delay (Boekhoorn et al. 2006a) and also labels subsets of astrocytes (Verwer et al. 2007). Hence, this marker has its drawbacks when used for detecting quantitative differences in neurogenesis in the human brain.

So far, only a few studies have reported changes in these and other young neuronal markers in human healthy or AD brain (Curtis et al. 2011; Winner et al. 2011; Zhao et al. 2008; Knoth et al. 2010). One report showed increases in various immature neuronal markers in a cohort of senile AD cases, suggesting that neurogenesis could be increased in AD (Jin et al. 2004b). In another study in younger, presenile patients, these results could not be replicated (Boekhoorn et al. 2006a). Although a significant increase in the number of Ki-67 positive, proliferating cells was found, quantification revealed that these cells were mostly located in nonneuronal compartments and associated with glial cells and the vasculature, while for proliferating cells located in neuronal layers, no differences were found between control subjects and AD patients. Additional causes for these discrepancies could be the age difference between the cohorts. Senile dementia is generally associated with a slower deterioration of cognition over time, whereas pathology in presenile dementia is often more severe, and reactions to hippocampal injury were thus expected to be more prominent in the younger group. Regardless of this, no indications were found for changes in cellular plasticity of neurons in presenile AD (Boekhoorn et al. 2006b) as was later confirmed for senile cases too (Marlatt et al. 2014).

Later studies have also used other markers like Musashi-1, nestin, and PSA-NCAM to show that neurogenic abnormalities in AD differ between phases and areas of neurogenesis and stages of AD: while hippocampal stem cells (Musashi-1) decrease, proliferation increases and differentiation/migration phase as well as axonal/dendritic targeting (DCX and β-III-tubulin) remain unchanged. This suggests an attenuation of stem cells together with compensatory increased proliferation that, however, does not result in an increased number of migratory neuroblasts and differentiated neurons in AD (Perry et al. 2012). Similar findings on microtubule-associated

protein isoforms showed that the mature high-molecular weight isoforms MAP2a and b were dramatically decreased in the AD dentate gyrus. The total amount of MAP2 protein, including expression of the immature neuronal marker, the MAP2c isoform, was less affected. These findings suggest that newly generated neurons in AD dentate gyrus do not become mature neurons, although proliferation is increased, confirming this general picture (Taupin 2009). Another study reported a decrease in DCX- and sex-determining region Y-box 2 (Sox2)-positive cells in human AD but an increase in bone morphogenetic protein 6 (BMP6) levels that was also found in APP transgenic mice, suggesting a role in defective neurogenesis in AD (Crews et al. 2010a, b).

In 1998, co-labeling of BrdU was shown with neuronal markers in human postmortem hippocampus in a unique patient cohort (Eriksson et al. 1998). Although this study was the first to show definite proof of adult neurogenesis in the human hippocampus, the methodology and cohort was unique and not suitable for experiments at larger scales in different populations. More recent methods used MRS spectroscopy (Manganas et al. 2007; Ho et al. 2013) or carbon dating in human postmortem tissue (Spalding et al. 2005, 2013). The latter technique takes advantage of the fact that during the 1950s and 1960s, radioactive atmospheric ^{14}C levels were increased due to nuclear testing and gradually declined after the ban in 1963. Similar to normal carbon, ^{14}C is stably incorporated into the DNA of dividing cells, and its level can accurately predict the age of any neuron derived from tissue. In this manner, it has been shown that in contrast to the cortex, a significant proportion of hippocampal neurons is born during adulthood (Spalding et al. 2013). In contrast to a common view in the field that adult hippocampal neurogenesis in the human brain should be a very limited phenomenon, this study demonstrated that about one-third of the hippocampal neurons present at birth is replaced during life and that the rate of neurogenesis in middle-aged individuals is comparable to that found in mice (Spalding et al. 2013). Also, extensive cell birth was identified in the human striatum (Ernst et al. 2014). So far, however, this technique has not yet been applied to AD material, but it could require definite proof as to how much neurogenesis is actually affected during AD.

Given the methodological pitfalls, the limited availability, presence of medication, and the variation between individual patients, together with the "end-stage" quality of human postmortem AD tissue, various research groups now focus on mouse models that overexpress AD-related proteins, like APP, PS, or tau (Crews et al. 2010a; Marlatt and Lucassen 2010; Mu and Gage 2011; Webster et al. 2014). Although aspects of redundancy, artifical overexpression of a transgene and indirect effects are of course important, these models recapitulate aspects of AD and FTD and provide a basis to address cause and effect and the temporal aspects of neurogenesis in response to AD neuropathology.

Neurogenesis and AD Mouse Models

The extent of neurogenesis may influence vulnerability to accumulating deleterious events, e.g., during aging, and as such may to some extent also reflect susceptibility to brain disorders like AD (Thompson et al. 2008; Zhao et al. 2008). Hippocampal neurogenesis is modulated by the expression of AD-related genes with the direction of the

effect often depending on the age and brain region under study, on the presence of neuropathology, and/or on the promoter used (Kuhn et al. 2007; Thompson et al. 2008; Crews et al. 2010a; Marlatt and Lucassen 2010; Mu and Gage 2011; Webster et al. 2014). In Alzheimer mouse models, APP, PS1, and APP/PS1 mutations generally cause reductions in neurogenesis when neuropathology is apparent, but also stimulatory effects have been reported but then mostly at earlier ages. Effects of mutated tau on neurogenesis are less well characterized or have been studied only postnatally and/or at young ages (Boekhoorn et al. 2006b; Sennvik et al. 2007).

In an attempt to link changes in neurogenesis to specific aspects of the disease, such as tauopathy or amyloid pathology, various mouse models of AD have been studied, either under naive conditions or under conditions when neurogenesis was modulated, e.g., by exercise, drugs, enrichment, or stress (Kronenberg et al. 2006; Hu et al. 2010; Cotel et al. 2012; Chadwick et al. 2011; Crews et al. 2010a; Marlatt and Lucassen 2010; Mu and Gage 2011; Marlatt and Lucassen 2010; Marlatt et al. 2010, 2013; Lazarov et al. 2005; Webster et al. 2014; Rodríguez et al. 2011). The majority of these have been APP- and/or PS1-based mouse models and, to a lesser extent, tau transgenic mice. Even though the exact cause of the age-associated decline in neurogenesis remains to be determined, the loss of growth factors from the local hippocampal microenvironment, such as FGF-2, IGF-1, BDNF, and VEGF, which are potent stimulators of adult hippocampal neurogenesis and neural stem cell growth in vitro, suggests a reduced neurogenic potential with age (Hattiangady et al. 2005; Shetty et al. 2005). This bears considerable relevance for AD itself, where many of these growth factors are reduced in their expression as well. Given the stimulatory effects of growth factors and of Aβ on stem cells in vitro, this could provide a putative mechanism for an impairment of neurogenesis in AD. Similar arguments hold for the prominent loss of cholinergic neurons and innervation in AD, which may contribute to impaired neurogenesis (Cooper-Kuhn et al. 2004; Mohapel et al. 2005; Bruel-Jungerman et al. 2011). Even though the exact function of APP remains elusive, PS1 has a well-established role in γ-secretase cleavage, and is also known for its prominent role in regulating β-catenin, a protein involved in Wnt signaling, which regulates hippocampal neurogenesis (Lie et al. 2005; Inestrosa and Varela-Nallar 2014). In addition, neurogenesis may be changed in AD mice due to a "loss of function" of normal APP and PS1.

In different transgenic models, adult neurogenesis is compromised in AD and generally precedes neuronal loss: dysfunctional neurogenesis, both decreased and increased, has been reported for AD transgenic models in both regions of adult neurogenesis, i.e., the SVZ and SGZ (Marlatt and Lucassen 2010; Mu and Gage 2011; Webster et al. 2014; Rodríguez and Verkhratsky 2011). Importantly, experimental conditions in these animal studies largely differ, depending on the use of transgenic expression of PSEN1, PSEN2, or of different APP single mutations, or knock-ins, or combinations thereof. Importantly, Aβ is not the only product of APP processing, and different APP metabolites may have different effects on different stages of neurogenesis (Mu and Gage 2011; Lazarov et al. 2010). For example, whereas the APP intracellular domain (AICD) negatively regulates proliferation and survival in the hippocampus, the soluble APP produced by α secretase may even stimulate neurogenesis (Ghosal et al. 2010; Demars et al. 2013; Winner et al. 2011). Therefore, the

net outcome will depend on the differential contributions of each APP metabolite produced within a certain model and how they are influenced by experimental conditions. In addition, BrdU regimens, doses, the time points analyzed after BrdU treatment, the genetic backgrounds of the mice, and the brain regions investigated vary considerably (Demars et al. 2010; Marlatt and Lucassen 2010; Lazarov and Marr 2010; Rodríguez and Verkhratsky 2011).

Furthermore, promoters determine expression in specific neuronal populations and thus the topographical distribution of the overexpressed transgene. For example, the use of the platelet-derived growth factor (PDGF) promoter results in the production of diffuse plaques, whereas prion protein and mouse thymocyte differentiation antigen 1 (mThy1) promoters favor plaque formation in the hippocampus and neocortex, etc. We will first discuss APP and PS1 mutant or deletion studies and then proceed to the discussion of tau mutant studies.

Amyloid Precursor Protein Transgenic Mice

Popular transgenic models of AD include mice expressing mutant APP. As single APP transgene, the FAD V717F (Indiana) mutation has negative effects on adult neurogenesis at an aged and symptomatic stage, mainly after amyloid deposition (Donovan et al. 2006). Double K670N M671L (Swedish) and triple (Swedish and Indiana) mutations of APP under many circumstances result in increased proliferation, and, in some cases, increased survival of the new neurons (Mirochnic et al. 2009; Haughey et al. 2002). Most earlier studies indicated that hippocampal neurogenesis is decreased in mice overexpressing the APP Swedish mutation that elevate Aβ (Donovan et al. 2006; Dong et al. 2004). In either an Aβ peptide injection model or in a mouse model expressing the APP mutant under control of the platelet-derived growth factor promoter (PDGF-APP), neurogenesis was found to be unaltered as long as Aβ pathology was absent, but its rate decreased as soon as plaque pathology developed (Haughey et al. 2002; Donovan et al. 2006). In contrast to the decreased number of dividing cells within the SGZ, PDGF-APP mice had significantly increased numbers of immature neurons in the outer portion of the granule cell layer. Whether the occurrence of these ectopic cells is due to abnormal APP function awaits further study, but changes in this subregion may at least explain some of the discrepancies with previous studies that combined all DG subregions in their quantitative analyses. Neurogenesis was also decreased in mouse models carrying three PS1 mutations (M146V, P117L, or A246E) (Wang et al. 2004; Wen et al. 2004; Chevallier et al. 2005). Also in a commonly used AD model, the triple transgenic AD mice (3xTg) harboring three mutant genes (PS1(M146V), APP(Swe), and tau(P301L)), decreased proliferation was found in male mice. This reduction in proliferation was directly associated with the occurrence of the first Aβ plaques and an increase in the number of Aβ-containing neurons in the hippocampus, which, in the case of 3xTg females, was directly correlated (Rodríguez et al. 2008).

In contrast to the abovementioned using PDGF-APP mice, Jin and colleagues have shown an increase in hippocampal neurogenesis in these mice that bear both the

Swedish and Indiana mutations (Jin et al. 2004a). These effects were found at 3 months of age, still in the absence of plaques, and at 1 year of age, at which time the hippocampus contained many plaques. Of importance, a considerable number of BrdU-positive cells in the hilus and molecular layer contribute to the total number of newborn cells that incorporate in the DG cell layer (Jin et al. 2004a; Donovan et al. 2006). These studies differ from others regarding the SVZ, where, at 3 months of age, no difference was found in the number of dividing cells; however, they detected a significant increase at 1 year of age (Jin et al. 2004a). These data suggest an opposite hypothesis, namely, that amyloid pathology, at least to the extent that it is derived from two different types of APP mutations, i.e., APPswe and APPind, increases neurogenesis. Alternative triggers, such as soluble or intraneuronal forms of amyloid, are still poorly studied in this respect.

In different strains of APPswe mutant mice, various cell cycle events were found to be increased (Yang et al. 2006), which resembles the situation in human AD where aberrant and ectopic expression of cell cycle markers has also been reported repeatedly. In contrast to the conclusion of Jin et al. (2004b), an alternative explanation is that expression of cell cycle markers selectively occurs in cells destined to die. In addition, this suggests that amyloid not only affects cell division but also survival of neurons.

Together, these studies suggest that the emergence of Aβ in the early stages of the pathology decreases, rather than increases, neurogenesis in mice (Jin et al. 2004a; Yang et al. 2006). It is important to note that changes in neurogenesis further depend on the pathological state of the AD-related protein, be it aggregated or mutated, or overexpressed (Haughey et al. 2002; Donovan et al. 2006), an assumption that was supported by Wen et al. who reported increases in hippocampal neurogenesis in a cohort of mice overexpressing the wild type but not mutated (P117L) form of PS1 (Wen et al. 2002).

Presenilin 1 Transgenic Mice

Interest in γ-secretase, the enzyme that generates highly fibrillogenic Aβ42, has led to the development of PS1 transgenic mice expressing mutant PS1. While PS1 is part of the γ-secretase complex, this pleiotropic gene also participates in mechanisms regulating cellular proliferation. PS1 is a key regulator in e.g., Notch and Wnt signaling mechanisms, but there is no direct evidence demonstrating that familial PS1 can influence proliferation or survival of NPCs in humans. PS1 signaling is responsible for the developmental maturation of glia and neurons. In Wnt signaling, PS1 is directly involved in β-catenin turnover, a mechanism responsible for proliferation of progenitor cells in the developing brain (Inestrosa and Varela-Nallar 2014). Normal PS1 facilitates phosphorylation of β-catenin, which leads to proteosomal degradation; mutant PS1 cells have an increased stability of β-catenin that leads to downstream nuclear signaling events. It is therefore not surprising that neuronal expression of mutant PS1 using a Thy1 promoter increased cell proliferation in the DG of 4-month-old transgenic mice. An increased cell proliferation did not result, however, in, an increased neuron survival in the hippocampus of these mice (Wen et al. 2002, 2004).

In a follow-up study, the same authors found decreased neurogenesis in mice overexpressing mutant PS1, whereas no effect was found of WT overexpression (Wen et al. 2004). The only difference with the previous study was that now older mice were used. Hence, the effects of WT PS1 on neurogenesis are either positive or neutral, whereas mutated PS1 had a neutral or negative effect on neurogenesis, with a clear age-dependency for the neurogenic effects of PS1.

Animal models for AD based on familial PS mutations (Elder et al. 2010) show elevated generation of Aβ42. Chevallier et al. (2005) used PS1 A246E mutant mice and determined an increased proliferation of subgranular progenitor cells in the DG, but only 25 % of the newly generated cells survived after four weeks. In the PS1 M146V knock-in mice, Wang et al. (2004) observed that neurogenesis was decreased as supported by decreases in proliferation, differentiation, and survival of precursor cells, while the P117L mutation also decreases neuronal differentiation of embryonic murine neural progenitor cells (Wen et al. 2004; Eder-Colli et al. 2009).

Mice deficient for both PS1 and PS2 were found to have increased proliferation and survival when evaluated at two ages (Chevallier et al. 2005). A study of PS1 expressed under the neuron-specific enolase (NSE) promoter found that cell proliferation was reduced by both wild-type and mutant P117L PS1 (Wen et al. 2004; Eder-Colli et al. 2009). Interestingly, wild-type PS1 mice had increased survival of immature neurons, whereas the mutants did not. A follow-up to this study incorporated groups with environmental enrichment and found that expression of the wild-type protein was sufficient to increase survival of immature neurons. Enriched environmental housing in these mice increased proliferation and newborn cell survival compared to the non-enriched group. This normal physiology was not preserved in mice expressing mutant PS1; enrichment increased proliferation, but there were no changes in Tuj1 expression and lower numbers were found of less surviving BrdU-positive cells. A more sensitive experiment was produced by crossing mutant PS1 M146V knock-in mice with PS1-deficient mice. Investigators generated mice with one mutant copy of PS1. Expression of mutant PS1 resulted in impaired learning in a contextual fear conditioning test. This impaired associative learning was positively correlated with impaired neurogenesis. The investigators, by comparing with the parental knock-in line, concluded that expression of wild-type PS1 can override the mutant PS1 gene. Although the expression of human PS1 transgenes does impact on neurogenesis, it is difficult to assess whether behavioral changes are due to increased neurogenesis or to the expression of the transgene per se (Wang et al. 2004; Elder et al. 2010).

APP/PS Bigenic Mice

As murine APP does not generate fibrillogenic peptides, typically bigenic mice are generated that express mutant PS1 and human mutant APP. As reviewed before, most APP and APP/PS1 mouse models show reductions in cell proliferation (Lazarov et al. 2010; Marlatt and Lucassen 2010; Mu and Gage 2011. A study evaluating mutant APPswe and APP-PS1L166P mice showed that APP mice had no difference in hippocampal neurogenesis when evaluated by BrdU incorporation at

5 months of age. At this age, the mice do not have amyloid deposits, but when evaluated at 25 months of age, APP mice exhibited significant increases in the number of BrdU- and DCX-positive cells (Ermini et al. 2008). A separate study utilizing different APP-PS1 mice at 8 months of age showed increased BrdU- and NeuN-positive cells compared to controls despite findings that APP-PS1x nestin-GFP mice exhibited decreases in nonproliferative, nestin-positive NPCs (Gan et al. 2008). Hence, endogenous neurogenesis appears to be elevated early in response to pathology, and to later decrease again. However, the molecular mechanisms and functionality of these new neurons remains unclear.

Aβ pathology reduces neurogenesis in several mouse lines (Haughey et al. 2002; Dong et al. 2004; Wang et al. 2004; Donovan et al. 2006), and, with the exception of in vitro data (Lopez-Toledano and Shelanski 2004), that lack true neuropathology (Feng et al. 2001; Caille et al. 2004; Yasuoka et al. 2004), many of these studies are consistent with the hypothesis that AD initially stimulates neurogenesis, and later decreases it, coinciding with the accumulation of amyloid pathology. Considering the roles of both APP and PS1 in embryonic development, e.g., as regulators of Wnt signaling (Caricasole et al. 2003; Chevallier et al. 2005; Wines-Samuelson and Shen 2005; Chen and Tang 2006), both genes are likely to be of general importance during both developmental and adult neurogenesis. Therefore, stimulatory effects of APP on increased neurogenesis could reflect a delayed or repeated developmental role rather than a pathological one. A developmental role is further supported by the fact that the total number of neurons was increased at 8 months of age (when no pathology is present) in the neocortex of APP23 mice overexpressing the Swedish mutation. However, at 27 months of age, these mice have developed a considerable plaque load that negatively correlated with the number of neurons (Bondolfi et al. 2002). In a related model, also cortical changes were found (Lemmens et al. 2011).

In other studies, Zhang et al. (2007) used APP, PS1, and both APP-PS1 mutants and only observed diminished neurogenesis in the double knock-in mice (Zhang et al. 2007). Jin et al. (2004a) observed an increased neurogenesis in PDGF-APP(Sw,Ind) mice, which express human APP isoforms APP695, APP751, and APP770 with the FAD's Indiana (V717F) and Swedish (K670N M671L) mutations driven by a platelet-derived growth factor promoter. They observed elevated neurogenesis in AD mice, which suggested that a compensatory mechanism may be active and that neurogenesis is increased in the early phases in response to emerging pathology, consistent with findings of others (Yu et al. 2009).

Tau Transgenics

Compared to the many studies on neurogenesis in relation to amyloid pathology, remarkably few studies have addressed a link with protein tau. This is striking since an extensive in vitro literature suggests a prominent role for tau during neuronal development, cytokinesis, neuronal maturation, and neuritic outgrowth (Gonzalez-Billault et al. 2002). Furthermore, tau phosphorylation occurs not only in AD but also during mitosis (Cross et al. 1996; Delobel et al. 2002). Moreover, many of the cell

cycle alterations seen in AD have been linked to tangle pathology (Arendt et al. 1996; Smith and Lippa 1995; Kondratick and Vandré 1996; Busser et al. 1998; Herrup et al. 2004). In vivo, the tau mutation P301S was found to be associated with overexpression of the cell cycle-dependent kinase inhibitors p21/Cip1 and p27/Kip1 (Delobel et al. 2006). Using a knockout–knock-in approach, it was further shown that expression of four repeats (4R) of tau reduces cell proliferation and increases differentiation and neuronal maturation, confirming an important role for tau in neuronal plasticity and differentiation (Sennvik et al. 2007). Moreover, the tau P301L mutation modulates cyclins, inducing cell cycle arrest in the G2 and M phases. In young tau P301L mutant mice, however, no effects were found on neurogenesis despite significant increases, in stead of possible decreases, in long-term potentiation and improved cognitive performance (Boekhoorn et al. 2006b). These data suggest that in the absence of age-related accumulation of tau phosphorylation, this familial tau mutation per se may not impair learning and memory, but rather improve cognition at young ages. Thus, tau protein may play an important beneficial role in hippocampal memory. Conversely, it is most likely not the mutation in tau, but rather the ensuing hyperphosphorylation, that is responsible for the cognitive decline observed in tauopathies (Sennvik et al. 2007; Fuster-Matanzo et al. 2009, 2012).

In a model utilizing human tau with two mutations, induction of hyperphosphorylation and NFTs was found in the hippocampus of in 3–6-month-old animals. Cell bodies of the DG are spared at this young age, but neurites in these areas were immunopositive for the antibody AT8, indicating aberrant phosphorylation of tau, similar to what is found in AD. Compared to non-transgenic mice, transgenic tau mice had twofold higher DCX levels and significantly higher expression of TUC-4 in the DG through 6 months. Mice overexpressing nonmutant human tau also show signs of proliferation; however, this proliferation was identified outside the SGZ and SVZ.

Taken together, the abovementioned data suggest that overexpression of wild-type or mutated tau is unlikely to promote neurogenesis. However, reduced tau expression may be associated with increased neurogenesis, at least within a specific postnatal period (Sennvik et al. 2007), and consistent with an inhibitory role of tau during mitosis, as suggested by others (Delobel et al. 2002, 2006). The fact that tau can inhibit neurogenesis does not imply that neurogenesis is inhibited in AD, where overexpression and aberrant expression of mutated forms of tau occurs. In AD, a large proportion of tau is thought to be hyperphosphorylated, which may lead to reduced microtubule binding and could, therefore, result in reduced tau functioning, which in turn, could lead to increased neurogenesis. While altered APP processing is likely to decrease neurogenesis, increased tau phosphorylation may actually result in the opposite effect. To test these hypotheses, it would be interesting to study the effect of tau phosphorylation on mitosis and neurogenesis in vitro and in vivo.

Environmental Stimulation of Neurogenesis in AD Models

The relationship between Aβ and neurogenesis has also been studied in combination with interventional studies. Environmental enrichment or wheel running in AD mouse models was expected to stimulate neurogenesis, parallel to behavioral

improvements and possible reductions in Aβ plaque load. In some models, environmental enrichment indeed increased newborn cell proliferation, survival, and neurogenesis. These changes corresponded to improved performance in a spatial memory task, but surprisingly, there was often no change in plaque load. Clearly, the neurogenic environment is preserved and permissible, which may allow options for functional recovery. Curiously enough, however, this recovery dissociates structurally from the functional pathology introduced in AD mice (Lazarov and Marr 2010; Marlatt et al. 2013).

Under normal conditions, environmental enrichment generally increases hippocampal neurogenesis; however, in one of the first kind of such studies, i.e., in PS1 knockout mice, which produce less amyloid, hippocampal neurogenesis could not be stimulated (Feng et al. 2001). Interestingly, this was paralleled by neuronal atrophy, increased astrogliosis, and associated with a reduced clearance of hippocampal memory traces. Enriched environment in APP and PSEN1 transgenic mice not only improved memory function but also reduced Aβ deposition (Lazarov et al. 2005), rescued impaired neurogenesis, and significantly enhanced hippocampal LTP in APPswe/PS1DE9 mice (Hu et al. 2010; Lazarov et al. 2005). However, this depends on the mouse models and ages used. The APP/PS1KI mouse model, e.g., failed to show significant improvement after 4 months of continuous enrichment (wheel running activity together with social enrichment), possibly because the mice were not exposed to the enriched environment until after disease onset (Cotel et al. 2012). Physical exercise alone improved cognitive performance in transgenic mouse models of AD (Nichol et al. 2007, 2008).

When both wheel running and enriched environmental housing were combined, the number of newborn granule cells in the DG of APP23 mice was increased and their water maze performance improved (Mirochnic et al. 2009; Wolf et al. 2006). However, environmental enrichment does not enhance neurogenesis in transgenic mice harboring FAD-linked PS1 variants or in forebrain-specific PS1 knockout mice, and it even suppresses neurogenesis in apolipoprotein E (ApoE) epsilon 4 transgenic mice. Taken together, these studies indicate that the effects of exercise and environmental enrichment on adult neurogenesis vary between the mouse models of AD (Lazarov et al. 2010; Lazarov and Marr 2010; Marlatt and Lucassen 2010).

In conclusion, different mouse models of different aspects of AD pathology have shown robust and transient increases in adult cytogenesis or neurogenesis, often parallel to the onset of pathology. The effect on neurogenesis of increased or mutated Aβ production appears to depend on two factors: the developmental stage of the animal and the presence or absence of pathology. Obviously, these two parameters are not independent of each other, since most APP or PS1 mutant mice show increased pathology with age. Altered APP or PS1 expression can increase neurogenesis in younger animals when Aβ pathology is still absent; however, it decreases neurogenesis in later stages when Aβ pathology is present.

Most increases in cytogenesis in AD mice are nonspecific and likely involved in gliogenesis and will at least not result in acute functional neuronal recovery, possibly because the microenvironment at the age when AD pathology becomes apparent is no longer permissive enough to support stem cell proliferation or neuronal differentiation (Doorn et al. 2014; Marlatt et al. 2014).

Utilizing neurogenesis for healthy aging would require its occurrence and stimulation over longer durations. Hence, it may perhaps be most beneficial if activity is established and maintained from midlife (or earlier) onwards to preserve adult neurogenesis prior to the onset of AD neuropathology or clinical presentation with dementia or AD. As neurons born in aged mammals are just as functional as the ones generated during developmental neurogenesis in young mammals, maintenance of stem cell proliferation and of the local microenvironment that enables a proper migration and connection is necessary to fully understand the dynamics of the neurogenic niche during aging and AD.

If we were to translate the data from animal models to the human familial AD situation, one would expect neurogenesis to be decreased rather than increased, with APP and/or PS1 as risk factors. Clearly, this contrasts from recent literature where plasticity markers were reported to be either increased or unaffected in a sporadic, senile cohort (Jin et al. 2004b) or in a presenile cohort (Boekhoorn et al. 2006a) respectively, possibly depending on the stage and severity of AD (Gomez-Nicola et al. 2014; Brain 2014; Enikomou et al. 2014; Biol Psych 2014). Aside from different methodologies, one obvious explanation could be that human AD pathology is more complex than altered APP expression alone, and, e.g., also other pathological changes such as in tau and, e.g., a longer disease duration and differences in metabolism between human and rodent brain are implicated. Moreover, although APP pathology may not directly stimulate neurogenesis, the resulting neuronal dysfunction, damage, and cell loss could later increase cell birth in an indirect manner, similar to brain injuries like ischemia.

Preventive Strategies for AD

Although there is currently no cure for AD, significant progress has been made in defining lifestyle conditions that promote healthy brain aging and, to some extent, delay the onset of AD. In clinical studies, poor social interaction, lack of physical exercise, malnutrition, and lack of cognitive stimulation have been singled out as risk factors of AD onset and progression (Laurin et al. 2001; Bennett et al. 2006; Scarmeas et al. 2006; Sitzer et al. 2006). In parallel, experimental studies found positive effects of enriched environment, physical exercise, and caloric restriction on accumulation of plaques in transgenic AD models (Adlard et al. 2005; Lazarov et al. 2005; Patel et al. 2005; Wolf et al. 2006). Although the functional link to neurogenesis and other forms of structural plasticity is not fully established, it is intriguing to note that most all of these lifestyle factors are prominent stimulators of adult hippocampal neurogenesis (Kempermann et al. 1997, 1998; van Praag et al. 1999; Lee et al. 2000) as well as other forms of plasticity (Rosenzweig 1966; Cotman and Berchtold 2002; Chen and Blurton-Jones 2012, Mattson et al. 2001, 2003). It is, therefore, crucial that patients are made aware of the beneficial effects of these lifestyle parameters on neuroplasticity and disease onset, even if a definitive proof of a role for neurogenesis in AD has not yet been provided.

Acknowledgements PJL, AK, and LH are supported by Alzheimer Nederland, AK is supported by an NWO Meervoud grant, and PJL is supported by de HersenStichting Nederland, NWO, and ISAO. HK, LH and AK are supported by ISAO.

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