Adult Hippocampal Neurogenesis in Aging and Alzheimer’s Disease

Lorena Varela-Nallar, Florencia C. Aranguiz, Ana C. Abbott, Paula G. Slater and Nibaldo C. Inestrosa*

Adult neurogenesis occurs in the subgranular zone of the hippocampal dentate gyrus and the subventricular zone of the lateral ventricles. This process is highly regulated by intrinsic and extrinsic factors, which may control the proliferation and/or maturation of neural progenitor cells. Adult-born neurons are integrated in preexisting networks and may have functional implications for adult brain. Here we attempt to summarize relevant findings concerning the physiological role of adult neurogenesis mainly focused on the subgranular zone, and to discuss the reduced neurogenesis observed during aging and the factors that have been involved in this phenomenon. Finally, we focus on hippocampal neurogenesis in Alzheimer’s disease, reviewing animal models of the disease used for the study of this process and the conclusions that have been drawn in this context. Birth Defects Research (Part C) 90:284–296, 2010. © 2010 Wiley-Liss, Inc.

Key words: adult neurogenesis; aging; Alzheimer’s disease

INTRODUCTION

It is currently accepted that neurogenesis in the adult brain mainly occurs in two specific neurogenic regions, the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG), and the subventricular zone (SVZ) of the lateral ventricles. Adult neurogenesis can be separated in different stages: (i) proliferation of neural progenitor cells, (ii) fate specification, and (iii) maturation, which contemplates axon and dendritic targeting, formation of functional synaptic inputs and outputs, and selective survival of newborn neurons. In the SVZ, neural stem cells (NSCs) give rise to neuroblasts that migrate toward the olfactory bulb (OB) through the rostral migratory stream, and within the OB, these neuroblasts differentiate into interneurons (Alvarez-Buylla and Garcia-Verdugo, 2002; Ma et al., 2009a). In the DG, adult-born dentate granule cells (GCs) extend their dendrites into the GC layer and molecular layer and project their axons into the hilus toward the CA3 region (Fig. 1A), giving rise to mature and fully integrated GC (van Praag et al., 2002; Deng et al., 2010). The thymidine analog bromodeoxyuridine (BrdU), which labels DNA during the S-phase, has been used to label dividing cells in adult hippocampus (Miller and Nowakowski, 1988; Kuhn et al., 1996; Eriksson et al., 1998; Kornack and Rakic, 1999), showing that the neuronal progenitor cells divide at the border between the hilus and the GC layer (Fig. 1B). Specific markers are expressed during the different stages of adult neurogenesis (Table 1), providing a helpful tool for the study of this process (Abrus et al., 2005; Ming and Song, 2005; von Bohlen Und Halbach, 2007). A different approach used for the identification of newborn cells in the adult brain is retroviral genetic marking, which is based on the expression of transgenes from some retroviruses that requires integration of the retroviral genome into the host genome during mitosis (Lewis and Emerman, 1994). This approach has been shown to be a very useful tool for studying the morphology and electrophysiology of newborn neurons (van Praag et al., 2002). The capacity to generate new neurons throughout life further demonstrates the plastic ability of the hippocampus, which is one of the most plastic structures in the brain that shows molecular, cellular, and structural changes after different stimulus. This remodeling is important for memory and learning, the most studied roles of the hippocampal region (Squire, 2004; Bast, 2007). Neurogenesis in the SGZ has been shown relevant for memory and learning (Deng et al., 2009), beside other functions that will be discussed later in this review. On the other hand, neurogenesis in the SVZ has been related to...
to olfactory discrimination and odor memory (Gheusi et al., 2000; Rochefort et al., 2002; Magavi et al., 2005).

Adult neurogenesis is modulated by extrinsic and intrinsic factors (Table 2). The SGZ and SVZ microenvironment is a key regulator of the different stages of adult neurogenesis. It provides stem cells with secreted factors and physical contact with their neighboring cells, which have been shown to be relevant for self-renewal, proliferation, differentiation, and fate determination of adult neural progenitors (Table 2). Among the many secreted factors provided by the neurogenic “niches” (reviewed in Suh et al., 2009), Notch and bone morphogenetic protein have been shown as regulators of adult neurogenesis (Johnson et al., 2009), and Wnt ligands have been shown to participate in the proliferation and differentiation of adult neural progenitors (Lie et al., 2005; Jessberger et al., 2009; Inestrosa and Arenas, 2010). In addition, the neurotransmitter γ-aminobutyric acid (GABA) has a fundamental role during adult neurogenesis. At early stages, precursor cells are activated by ambient GABA through nonsynaptic mechanisms before showing any spontaneous or evoked postsynaptic currents, and later on, during their maturation, newborn neurons subsequently receive GABA synaptic inputs (Ge et al., 2007). Whereas GABA functions as an inhibitory neurotransmitter in mature neurons, it acts as an excitatory signal in neural progenitors and immature neurons. The GABA-mediated depolarization of newborn neurons has shown to be relevant for synapse formation and dendritic development (Ge et al., 2006).

More recently, intrinsic factors regulating adult neurogenesis have been uncovered. The transcription factor Sox2 is important for the maintenance of NSC and is downregulated during differentiation (Suh et al., 2007). On the other hand, the transcription factor NeuroD1 is required for the survival and differentiation of adult-born GCs and is also involved in the migration and maturation of OB neurons (Gao et al., 2009). Interestingly, this relevant factor is one of the targets of the Wnt signaling activation which may control NeuroD1 expression by using dual regulatory elements in the promoter of the NeuroD1 gene that could potentially bind both Sox2 and downstream transcription factors of the Wnt pathway (Kuwabara et al., 2009).

Adult neurogenesis is also regulated by neuronal activity. In the OB, integration of adult-born neurons is influenced by odor experiences (reviewed in Ma et al., 2009b), while neurogenesis in the SGZ is affected by different stimuli such as enriched environment and voluntary running (Kempermann et al., 1997; Kempermann and Gage, 1999; van Praag et al., 1999). On the other hand, stress and depression have a negative effect on adult hippocampal neurogenesis while antidepressant treatment increases neurogenesis (Malberg et al., 2000; Perera et al., 2007; Sahay and Hen, 2007).

In brief, adult neurogenesis is a highly regulated physiological pro-

Figure 1. Adult neurogenesis in the SGZ of the hippocampal dentate gyrus. (A) Schematic representation of the generation of new granular cells in the dentate gyrus (DG). Neurogenesis occurs in different stages. First, the progenitors, type 1, divide asymmetrically and give rise to transient amplifying type 2 cells. Then, these cells differentiate into type 3 cells or neuroblasts, which are already committed to become neurons and start to migrate through the granular cell layer (GL). Finally, neuroblasts mature into granular cells, projecting their axons into the hilus (H) toward the CA3 region of the hippocampus and extend their dendrites into the granule cell layer and molecular layer (ML). (B) Immunostaining of BrdU-positive cells in the DG of a 2-month-old mouse hippocampus (our unpublished data). New neurons stained for BrdU (red) are detected in the SGZ of the DG. Mature neurons were stained for NeuN (green) to identify the GL. Inset shows a higher magnification of the BrdU-positive cells in the SGZ.
cess that can be influenced by different stimuli. In the present review, we attempt to summarize the findings that link adult neurogenesis, mainly in the SGZ, to normal brain function, and also to discuss the evidence of altered neurogenesis during aging and disease, particularly in Alzheimer’s disease (AD).

**PHYSIOLOGICAL IMPLICATIONS OF ADULT NEUROGENESIS**

If newborn neurons generated in the adult brain are recruited into preexisting networks in an active way, and whether they play functional roles in the discrete regions where they are generated, are some of the questions that emerged with the discovery of adult neurogenesis.

The first question, whether new neurons are active and functional, was answered by electrophysiological approaches using retroviral hippocampal injection for the identification of new neurons. Gage and Schinder groups (Laplagne et al., 2006, 2007; Mongiat et al., 2009) demonstrated that these new neurons were integrated in a preexisting network and have the same electrical characteristics as GCs generated during hippocampal development. However, the exact roles that new neurons play in adult hippocampal function is unclear. It is known that in newborn neurons, the threshold for the induction of long-term potentiation, which is the enhancement of the transmission between neurons, is lower than that in mature GC (Snyder et al., 2001), and it has been proposed that this phenomenon could increase the plasticity of the hippocampus and the acquisition of new memories (Kempermann, 2008).

The hippocampus has different functions. The dorsal leaf is related to learning and memory, and the ventral leaf to affective behaviors (Bannerman et al., 2004). So, it is likely that changes in the rate of neurogenesis in one of these regions may differentially
TABLE 2. Factors that Regulate Adult Neurogenesis

<table>
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<th>Effect on neurogenesis</th>
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<td>Positive regulator of proliferation</td>
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<td>FGF-2</td>
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<td>Sex hormones</td>
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<td>Positive effect on proliferation and negative effect for fate commitment</td>
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<td>EGF</td>
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<td>Positive regulator of fate commitment</td>
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<td>Wnt ligands</td>
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<td>GABA</td>
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<td>Negative regulator of proliferation</td>
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<td>TGF-β1</td>
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<td>Glucocorticoids</td>
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<td>Mineralocorticoids</td>
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<td>Positive regulator of proliferation and fate commitment</td>
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<td>Voluntary wheel running</td>
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<td>IGF-1</td>
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<td>Positive regulator for fate commitment and for survival</td>
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<td>Neuro D</td>
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<td>Antidepressants</td>
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<tr>
<td>BMP</td>
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<td>Negative effect on fate commitment</td>
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</table>

affect hippocampal function. Those functions are affected in aging and AD, and its alteration may be directly or indirectly related to the levels of neurogenesis. It is believed that neurogenesis has an important role in affective behaviors, since antidepressants promote an increase in hippocampal neurogenesis (Malberg et al., 2000), and mood regulation by antidepressants requires a basal unaffected level of neurogenesis (Santarelli et al., 2003). And, as previously mentioned, stress has a negative effect in the neurogenesis rate (Zhao et al., 2008).

Also, there is evidence that supports that newborn GC also play a pivotal role in the cognitive function of the hippocampus. It is known that several factors can enhance neurogenesis, such as exercise, adrenalectomy, and environmental enrichment (Montaron et al., 1999; van Praag et al., 1999; Brown et al., 2003). An increase in the proliferation and integration of newborn GC in adult mice, generated using each of these approaches, is transduced in a better performance in the spatial memory test of the Morris water maze. On the other hand, ablation of neurogenesis in rats produced by low-dose X-irradiation generates a diminished performance in a spatial long-term memory test (Snyder et al., 2005).

These findings were interpreted in the sense that adult neurogenesis plays a key role in almost all of the hippocampal-dependent cognitive functions. Nevertheless, using new techniques to ablate neurogenesis including transgenic mice, and using different tests to measure some hippocampal-related functions, inconsistent results have been generated (Deng et al., 2010). For example, for fear conditioning, single trial test results suggest that this kind of memory depends on neurogenesis; however, the multiple trial test results indicate the opposite (Drew et al., 2010). Another function is working memory, which is associated with logic thought and intelligence. When exposed to the radial arm maze test, rodents in which hippocampal neurogenesis is ablated have better performance, suggesting a negative relationship between neurogenesis and this kind of memory (Saxe et al., 2007). On the other hand, Wino and coworkers (2006), using the same behavioral task with variations in the experimental protocol, observed a deficit in the working memory in mice with ablated neurogenesis. However, there is also a study in which no effect in this kind of memory was observed when neurogenesis was affected (Hernandez-Rabaza et al., 2009).

Another example of controversy is the role of hippocampal neurogenesis in the place recognition memory. Different times after an irradiation protocol to ablate neurogenesis generate distinct effects in the T-maze behavioral task, observing significant differences in the first weeks (Madsen et al., 2003), but not after the seventh week of irradiation (Madsen et al., 2003; Rola et al., 2004; Saxe et al., 2007).

Different studies that measure other kinds of hippocampal functions, such as pattern separation, object recognition, long term spatial memory, among others, predict important roles of adult neurogenesis. As previously mentioned, Wnt signaling has been described as a pivotal modulator of the neurogenesis in the SGZ (Lie et al., 2005). Downregulation of the Wnt signaling, used to ablate neurogenesis in mice, revealed in behavioral spatial tests that adult hippocampal neurogenesis have functions in the spatial pattern separation, that is the recognition of two overlapped objects in the same time or in the same place (Clelland et al., 2009). The approach of using a dominant-negative Wnt has also been used to demonstrate the importance of neurogenesis in the object recognition test (Jessberger et al., 2009).

In birds, LaDage et al. (2011) observed that neurogenesis is increased in sparrow after migratory periods, correlating neurogenesis with the migratory conductance. This evidence highlights the ecological role of adult neurogenesis (LaDage et al., 2010).
Also there are computational predictions that suggest that adult neurogenesis might be relevant in episodic memory and temporal encoding events in humans (Aimone et al., 2006). Other roles described for human neurogenesis is the relationship between memory and proliferation in patients who underwent epileptic surgery (Coras et al., 2010). After a memory test, samples were extracted, and hippocampal cells were cultured and evaluated in their capacity to assess proliferation and differentiation. Results suggest a correlation between the cognitive abilities of the patient thrown by the test and the proliferation and differentiation of neuronal cultures (Coras et al., 2010).

NEUROGENESIS IN AGING: FACTORS REGULATING THE DECLINE OF NEUROGENESIS

A negative relationship between aging and neurogenesis exists (Kuhn et al., 1996; Luo et al., 2006; Olariu et al., 2007). A reduction in neurogenesis with increasing age has been reported under laboratory conditions in rats (Kuhn et al., 1996; Olariu et al., 2007), canines (Siwak-Tapp et al., 2007), marmoset primates (Leuner et al., 2007), and also in free-living animals (Barker et al., 2005). It has been reported that old DG neurogenesis is more than 80% less than in young adults (Kuhn et al., 1996; Cameron and McKay, 1999; Olariu et al., 2007). Although a gradual decrease in the birth and differentiation of new GC is observed, most of the new cells in old rats are arranged in clusters along the SGZ, in the same pattern observed in the young ones (Kuhn et al., 1996).

The decrease in neurogenesis with age is dependent on species and living conditions. In housed species like marmoset, the decrease of neurogenesis is lineal (Leuner et al., 2007), but in free-living rodents the relationship is more complex and the decrease is hyperbolical, with a strong decline in the first years of life and a low, but persistent reduction in the rest of the life span (Barker et al., 2005). There is also a difference between free-living animals; in adult squirrels there is a decrease in proliferating cells but not in new neurons and, on the contrary, in adult chipmunks, the decrease is in the density of young neurons. These differences might be occurring because of the use of distinct memories in the survival strategies of these species, that is, squirrels use more the spatial memory, because they have multiple food storage sites (Barker et al., 2005).

It is unclear why this decline in neurogenesis occurs, but different studies suggest that a loss of precursor cells or a slowing in the cell cycle progression may contribute to the reduction in neurogenesis in aging SGZ. Olariu et al. (2007) observed a decline in dividing precursors and no change in the duration of the cell cycle of the dividing cells in the DG. On the other hand, Luo et al. (2006) observed an age-dependent decrease in cells positive for BrdU, and a decrease in the ratio of BrdU-positive cells in S phase to the total number of cycling cells, as shown by the general S phase marker Ki67. The authors discussed that the second observation can be either due to an increase in the cell cycle length of the precursor cells or a reduced number of cells in S phase, because of an augment in cell death.

In the lateral ventricles, a thinning of the SVZ has been observed in aging compared to young and juvenile mice (Luo et al., 2006). This thinning might be due to a decrease in the number of SVZ neurons and/or a decrease in the birth of new neurons. Different groups have described that there is more than a 50% decrease in SVZ neurogenesis in old compared with young adult animals (Tropepe et al., 1997; Maslov et al., 2004; Luo et al., 2006). Luo et al. (2006) observed a reduction in cell proliferation, an increased number of astrocytes, and that neuroblasts and neurogenesis in general has become restricted to the anterior dorsolateral horn of the SVZ (Luo et al., 2006). This observation contradicts the findings of Kuhn et al. (1996) showing that the age-related attenuation of proliferation is specific for the SGZ.

In both neurogenic systems the loss of precursors might be occurring because of cell death, symmetric cell division (Olariu et al., 2007), or decline in telomerase activity (Luo et al., 2006). The last possibility is characterized by a shortening in telomeres and a loss of chromosome protection, which is translated in replicative senescence and eventually in genetic instability with loss of cell viability (Lee et al., 1998; Blackburn, 2001). Sarin et al. (2005) provided more evidence for the role of telomeres in the proliferation of stem cells, showing proliferation of latent stem cells through overexpression of the telomerase reverse transcriptase.

In addition, several secreted factors could be related to the decreased neurogenesis observed during aging (Fig. 2). The adrenal hormones are involved in cell birth, survival, migration, and cell death. Increased levels of these hormones result in a decrease in both cell death and birth in the DG during development (Gould et al., 1992). Aging is characterized by an increase in the basal levels of corticosteroids (Gould et al., 1992; Cameron and McKay, 1999; Montaron et al., 1999), and also the glucocorticoid and mineralocorticoid receptors on type-1 and type-2 precursor cells and postmitotic neurons, which result in an augmented steroid sensitivity (Garcia et al., 2004). There is evidence supporting the idea that these high levels of hormones and sensitivity are responsible for the age-related decline in hippocampal neurogenesis. Elderly humans with similar levels of corticosteroid as young people show no evidence of structural changes in the hippocampus; on the other hand, humans with higher levels of the hormone have impaired hippo-
campal-dependent memory and a reduction in hippocampal volume (Lupien et al., 1994, 1998). Suppression of corticosterone levels by adrenalectomy results in an increase in degenerating neurons and glia, and also in an increase of newborn GC (Gould et al., 1992). This increase in neurogenesis was accompanied by an increase in the neural cell adhesion molecule, polysialated neural cell adhesion molecule (PSA-NCAM), which is necessary for the migration of the new neurons (Montaron et al., 1999), and all these new cells were capable of survival and differentiation into normal GC (Cameron and McKay, 1999). It is important to mention that all these findings with different concentrations of adrenal hormones were only observed in the DG. In fact, in the SVZ, the proliferation was not influenced by corticosterone (Montaron et al., 1999).

It is known that stressful experiences result in a diminished proliferation of GC precursors (Gould et al., 1998) and a decreased survival rate of newly generated cells. Simon et al. (2005) demonstrate that older animals are more vulnerable to chronic stress than their younger counterparts (Simon et al., 2005). This augmented vulnerability to stress might be due to the increased glucocorticoid and mineralocorticoid receptors (Garcia et al., 2004) and the stress-related increase in levels of corticosteroids (Tanapat et al., 1998).

Sex hormones, both male and female, can also influence neurogenesis during aging, as gonadal hormones diminish in menopause and andropause (Lamberts et al., 1997). In fact, the number of BrdU-labeled cells is greater during the estrous cycle, when estrogen levels are higher, suggesting an estrogen-dependent increase in precursor cell proliferation in female rats (Tanapat et al., 1999). Different studies suggest a neuroprotective function for estrogen and that this effect can be mediated by a cross-talk between insulin-like growth factor (IGF-I) and the estrogen receptors (Garcia-Segura et al., 2000), or alternatively, independent of the activation of estrogen receptors (Behl et al., 1997). Diminished estrogen during menopause is associated with cognitive dysfunction, and this may be caused by a deficiency in the neuroprotective effect of estrogen and a decreased proliferation of neural precursors. Rasika et al. (1994) observed that exogenous administration of testosterone generates an increase in the volume of the high vocal center of female canaries. This effect is not because of an augment in the generation of new neurons (Goldman and Nottebohm, 1983), but rather because of an increased recruitment and/or survival of the new cells (Rasika et al., 1994). A proposed model for the testosterone-dependent recruitment of neurons suggests that this hormone augments angiogenesis and vascular permeability through upregulation of vascular endothelial growth factor and its receptor (Louissaint et al., 2002). So, diminished testosterone during andropause could be related to a decrease in the survival of new neurons, at least in the SVZ.

Growth factors such as fibroblast growth factor-2 (FGF-2), IGF-1, and vascular endothelial growth factor are considered like stem/progenitor cell proliferation factors, as they induce the survival and proliferation of these cells in a dose-dependent manner (Ray et al., 1993). The hippocampal concentration of all of them decline with age, and the major decline occurs between young and middle aged adults (Shetty et al., 2005). It is known that IGF-1 plays a role during development. Mice lacking IGF-1 presented an augmented population of newborn cells in the SGZ but reduced brain weights and diminished volume of the granular cell layer of the DG (Beck et al., 1995; Cheng et al., 2001). Interestingly, restoring its levels in senescent rats resulted in increased neurogenesis (Lichtenwalner et al., 2001). This evidence and the fact that IGF-1 can attenuate N-methyl-D-aspartate (NMDA) antagonist-induced apoptosis (Takadera et al., 1999) suggest that the role of IGF-1 might promote the survival of new cells. FGF-2 is expressed in the SVZ and SGZ of adult rodent (Yazaki et al., 1994), and the intracerebroventricular infusion of FGF-2 in senescent mice results in an augment of BrdU-positive cells in both neurogenic niches (Jin et al., 2003). The expression of epidermal growth factor (EGF) also diminished with

age, and young mice with low levels of EGF show the same phenotype as old mice with fewer interneurons in the SVZ (Enwere et al., 2004). On the other hand, there is an age-related enhancement in other growth factors like transforming growth factor-β1 (TGF-β1) which is a cell cycle regulator. Studies using chronic overproduction of transforming growth factor-β1 resulted in a complete blockage in the generation of new neurons in aged mice by inhibiting neural progenitor proliferation (Buckwalter et al., 2006). The same was observed in neural crest cultures (Zhang et al., 1997). These findings suggest that the change in the concentration of growth factors during aging might induce a decrease in neurogenesis (Fig. 2).

The cyclic adenosine monophosphate (cAMP) responsive element binding protein (CREB) plays an important role in neurogenesis. Nakagawa et al. (2002b) chemically activated the cAMP cascade and observed an increase in the proliferation of cells in the mouse hippocampus. The same group later observed that it also regulates the survival and probably the differentiation and function of the new neurons (Nakagawa et al., 2002a). In the hippocampus, p-CREB diminished with age especially between middle and old age (Hattinghady et al., 2005), which may have contributed to the observed decrease in neurogenesis.

NEUROGENESIS IN ALZHEIMER’S DISEASE MODELS

Alzheimer’s disease, one of the big ills of the 21st century, is a neurodegenerative disease that involves the loss of the superior capacities of the central nervous system, including severe cognitive alterations, like learning and memory dysfunction, by widespread neurodegeneration in the limbic system and associative cortex (Dickson, 1997). One of the neuropathological hallmarks of AD includes the formation of neurofibrillary tangles inside the neuron, corresponding to paired filaments mainly composed of tau, a microtubule-associated protein (Grundke-Iqbal et al., 1986). In AD, tau protein is amended by hyperphosphorylation, leading to a negative interaction of tau protein with microtubules and destabilizing them, bringing with it a neuronal branching retraction. Another feature of AD is the formation of senile plaques, the most specific neuropathological feature of the disease (Morgan et al., 2004). These consist of an extracellular material with a dense appearance, mainly composed by β-amyloid peptide (Aβ), generated by the proteolytic processing of the amyloid precursor protein (APP) (Jarrett et al., 1993; Soto et al., 1994; Selkoe, 2001; Perl, 2010). Familial AD (FAD) is caused by mutations in APP (Goate et al., 1991), presenilin 1 (PS1) (Schellenberg et al., 1992), and PS2 (Levy-Lahad et al., 1995), PS being a central player as a catalytic core in the function of γ-secretase complex. This enzyme cleaves APP, producing the Aβ peptide (LaFerla et al., 2007).

As described above, an important factor related to diminished adult neurogenesis is aging, which is strongly related to AD. A useful approach to study neurogenesis in AD brains has been the use of animal models of the disease. FAD cause three major lines of mutations to mimic the pathology: APP mutations (Jin et al., 2004a; Donovan et al., 2006; Wolf et al., 2006; Taniuchi et al., 2007; Zhang et al., 2007; Yu et al., 2009), PS1 mutations (Wen et al., 2004; Zhang et al., 2007; Choi et al., 2008; Rodriguez et al., 2008), PS2 mutations (Janicki and Monteiro, 1999; Hwang et al., 2002), and the combination of them as APP mutations effects are accelerated by PS mutations.

In vivo models based on APP mutations overexpress mutated APP generating Aβ plaques, hippocampal pathology, and cognitive impairments (Games et al., 1995; Ashe, 2001). In these models, there is still discrepancy about what occurs with neurogenesis (Table 3). As an example, Zhang et al. (2007) used APP, PS1, and both APP-PS1 mutants, and only observed diminished neurogenesis in the double knock-in mice. On the other hand, Jin et al. (2004a) observed an increased neurogenesis in platelet-derived growth factor-APP(5W,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 increased neurogenesis in AD mice, suggesting that it could be a compensatory mechanism in the pathology.

Animal models based on PS FAD mutations, which have been generated under a variety of promoters (Elder et al., 2010), show elevated generation of Aβ42. In these models, there is no agreement about what occurs to hippocampal neurogenesis (Table 3). 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 survive after 4 weeks. In a different study, Wang et al. (2004), in the PS1M146V knock-in mice, observed that neurogenesis was decreased. They determined decreased proliferation, differentiation, and survival of precursors.

Despite the importance of animal AD models, the main goal in this area must be to determine the state of neurogenesis in AD human patients. However, findings in patients have never found an agreement in the results obtained, which could be a consequence of the variability in the methodologies used in different labs (Table 3). In a classic study, Braak and Braak (1991) described different stages in the progression of AD obtained from brains of human patients. The stages are divided in two groups, one for the classification of Aβ progression, that is, stage A: initial deposits can be found in basal portions of isocortex; stage B: Aβ in all isocortical association areas, and partially in the hippocampal formation; and stage C: Aβ is present in all areas of isocortex, including sensory and
motor, and another one for the neurofibrillary changes, which can be summarized as follows: stages I and II, presence in transentorhinal region; stages III and IV, presence in limbic areas; and stages V and VI, massive presence in isocortical areas (Braak and Braak, 1991). Thus, to finally answer the question whether neurogenesis is elevated or diminished in human patients, it would be necessary to evaluate neurogenesis according to the different Braak’s stages of the disease, as a technical standardization. As an example, Boekhoorn et al. (2006) studied proliferation of neural progenitors in presenile AD brains, and showed increased proliferation but low neurogenesis levels in the hippocampus, arguing that this proliferation goes to gliogenesis and vasculature changes (Boekhoorn et al., 2006). A similar study by Ziabreva et al. (2006), focused on the SVZ neurogenesis. In this work, the authors determined a significant reduction in NSC proliferation in AD patients compared with age-matched controls (Ziabreva et al., 2006). It has also been suggested that AD patients show increased proliferation, but low rates of survival of new neurons (Shruster et al., 2010), which actually is the most accepted hypothesis according to what is observed in patients and animal models of AD. This affirmation could be explained by aberrations in the cell cycle, which could carry the new neuron to degeneration (Bonda et al., 2010).

Several pathways involved in adult neurogenesis have also been associated to the molecular neuropathology of AD. sAPP, which is secreted by α-secretases during APP cleavage and decreased in AD, regulates the proliferation of neural progenitors in the SVZ modulated by EGF, meaning that, under AD pathology, adult neuro-

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<th>Model</th>
<th>Mutation</th>
<th>Results</th>
<th>Author</th>
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<tr>
<td>AD patients</td>
<td>nd</td>
<td>Increased proliferation in hippocampus, measured by Ki67 marker</td>
<td>Nagy et al. (1997)</td>
</tr>
<tr>
<td>Human</td>
<td>nd</td>
<td>Increased proliferation; the differentiation was reported to be mostly to neuron.</td>
<td>Jin et al. (2004b)</td>
</tr>
<tr>
<td>nd</td>
<td>Reduced proliferation rate in SVZ</td>
<td>high proliferation, but mostly differentiated in glia in presenile AD</td>
<td>Ziabreva et al. (2006)</td>
</tr>
<tr>
<td>nd</td>
<td>High proliferation</td>
<td>Glial differentiation in glia in presenile AD</td>
<td>Boekhoorn et al. (2006)</td>
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### Table 3. Discrepancies in Adult Neurogenesis Observations Taken from Different Strategies and Models

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<th>Model</th>
<th>Mutation</th>
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<tr>
<td>Animal model</td>
<td>PS1 P117L mice</td>
<td>Neural progenitor proliferation was unaffected, but new cells are unable to survive.</td>
<td>Wen et al. (2004)</td>
</tr>
<tr>
<td></td>
<td>PS1 A246E mice</td>
<td>Increased proliferation, but low rate of survival in new cells</td>
<td>Chevallier et al (2005)</td>
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<td>PS1 M146V</td>
<td>Reduced NG in the dentate gyrus in tg mice</td>
<td>Wang et al. (2004)</td>
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<td></td>
<td>PDAPP mice</td>
<td>Age-dependant decrease in SGZ proliferation in tg mice</td>
<td>Donovan et al. (2006)</td>
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<td></td>
<td>PDGF-APP_swe_ind</td>
<td>Increased proliferation and neuronal commitment in tg mice</td>
<td>Jin et al. (2004a)</td>
</tr>
<tr>
<td></td>
<td>APPswe/PS1ΔE9 mice</td>
<td>Reduced proliferating cells in tg mice, and this can be rescued with enriched environment</td>
<td>Hu et al. (2010)</td>
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<td></td>
<td>APP257L/PS1M146L</td>
<td>Increased survival in adult-generated neurons after Aβ immunotherapy</td>
<td>Biscaro et al. (2009)</td>
</tr>
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<td></td>
<td>APPswe/PS1ΔE9 mice</td>
<td>AD-degree dependant decreased NG in tg mice, no gender difference</td>
<td>Taniuchi et al. (2007)</td>
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<td>APP_K670N/M671N/PS1M146L</td>
<td>Increased proliferation, but the differentiation ratio in glia and neurons was similar in tg mice</td>
<td>Yu et al. (2009)</td>
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<td></td>
<td>APP-PS1; PS1;APP</td>
<td>Diminished NG in double knock-in tg, no effects on each mutation alone</td>
<td>Zhang et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>APPswe/PS1M146V/tau301L</td>
<td>Impaired ability to generate new neurons, and this increases with age</td>
<td>Rodriguez et al. (2008)</td>
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</table>

AD, Alzheimer’s disease; NG, adult neurogenesis; tg, transgenic.
 genesis must be decreased (Caille et al., 2004). Another possible cause of neurogenesis decrement is the upregulation of FGF-2 observed in the limbic areas of AD patient’s brains, especially in the hippocampus (Cummings et al., 1993). FGF-2 is a powerful mitogenic factor, promotes proliferation, and maintains the neural precursors in an immature state (Johe et al., 1996). In addition, FGF-2 regulates tau expression and phosphorylation, and this process is mediated by glycogen synthase kinase-3β (GSK-3β) (Tatebayashi et al., 1999). This FGF-2-mediated inhibition of adult neurogenesis can be recovered in vitro by trophic factors, like ciliary neurotrophic factor, and glial-derived neurotrophic factor (Chen et al., 2007).

As previously mentioned, the Wnt signaling pathway is highly involved in adult neurogenesis. It has been documented that the activation of β-catenin drives the neural progenitor proliferation pool, and also the inhibition of GSK-3β induces new cells’ differentiation into neurons (reviewed in Inestrosa and Arenas, 2010). This molecular process would be impaired in AD patients, where the Wnt signaling pathway is affected (De Ferrari and Inestrosa, 2000; Inestrosa and Toledo, 2008). In human AD brains, β-catenin is diminished which is explained by the high levels of GSK-3β activity and elevated β-catenin phosphorylation (He and Shen, 2009). Dickkopf-1, a negative modulator of the canonical Wnt signaling, is also upregulated in brains of AD patients. Dickkopf-1 upregulates tau phosphorylation by increasing GSK-3β expression, indicating that it is associated with neuronal degeneration (Caricasole et al., 2004). GSK-3β is one of the most relevant kinases having a role in tau phosphorylation in AD brains (Lovestone et al., 2007).

The relationship between adult neurogenesis and GABAergic transmission in a transgenic mouse model of AD based on mutated hAPP has been studied (Sun et al., 2009). Sun et al. (2009) observed in this transgenic model that newborn cells shows GABA Cl− currents reversal potentials (EGABA) more hyperpolarized, at 14 to 18 and 21 days (new cell age) than controls, which was depolarizing at these stages as previously described (Ge et al., 2006; Zhao et al., 2006), indicating a faster developmental transition in this mouse model. This correlates with their observation about morphological and functional acceleration during the first 3 weeks of newborn neurons, after which there are progressive morphological impairments as Aβ1-42 accumulates with age (Sun et al., 2009). Interestingly, if GABA A receptors are inhibited during the first 7 days after birth, these impairments are ameliorated. These results indicate that the high levels of GABAergic signaling in hAPP mice have deleterious effects to newborn cell maturation (Sun et al., 2009).

GABAergic signaling in AD has also been studied in a mouse model of sporadic AD carrying a mutation in apolipoprotein E4 (apoE4), a major risk factor for developing AD in humans. By proteolytic cleavage, neuronal apoE can generate neurotoxic fragments, apoE4 being more susceptible to this modification. ApoE4 fragments can increase tau phosphorylation (Tanzi and Bertram, 2001). In the mouse model of sporadic AD carrying a mutation in apoE4, increased proliferation of NSC but a decreased maturation of newborn neurons was observed (Li et al., 2009). After a month of birth, new neurons have much less arborization than in control animals, which is explained by the authors as a consequence of a decreased number of GABAergic interneurons in the hilus. In addition, they describe that new neurons in apoE4 transgenic mice have higher input resistance than controls, suggesting a delayed maturation in those cells, along with a significant reduction in functional GABAergic inputs in newborn neurons. Based on this observation, the authors potentiate GABA A receptor, and interestingly they were able to restore neurogenesis and also to improve dendritic development in apoE4 transgenic mice (Li et al., 2009). From these studies, we can conclude that a deregulation in GABAergic transmission can decrease adult neurogenesis in AD models, negatively affecting the new neuron morphology and functionality.

Inflammatory processes might also be relevant for neurogenesis in AD brains. Inflammation is present in AD pathology triggered by microglia which increase around senile plaques generating positive staining for proinflammatory mediators like cyclooxygenase 2 (Cox-2), interleukin-1 (IL-1) and IL-6, and elevated levels of cytokines and chemokines (Nelson et al., 2002; Liu and Hong, 2003; Glass et al., 2010), which at the same time, are harmful for the adult neurogenic process (Ekdahl et al., 2003, 2009; Das and Basu, 2008; Ghosal et al., 2010). Therefore, it is thought that anti-inflammatory therapy could be appropriate to restore the levels of neurogenesis in AD brains.

**CONCLUDING REMARKS**

Throughout this review we have seen that adult hippocampal neurogenesis is a highly regulated physiological process in which newborn neurons are integrated in preexisting circuits. Different approaches have permitted to study the morphology, integration and plasticity of these new neurons in the brain. Behavioral tests have shown that adult neurogenesis is important for some hippocampal functions and that it could affect the plasticity of the hippocampus and the acquisition of new memories, which is one of the most appealing physiological roles of adult neurogenesis in the SGZ.

During aging, a decrease in hippocampal neurogenesis is well established. As discussed, the age-related reduction in neurogenesis is regulated by a great number of different factors. The finding that restoring levels of different growth factors and hormones can generate an increase in neurogenesis in old mice, and that this increase restores the levels found in young adults, suggests that the basic components of neurogenesis are maintained through life, and opens the possibility that modulating neu-
Hippocampal neurogenesis could help to prevent the cognitive deficit that may be associated to neurogenesis loss. Such a scenario presents opportunities for the treatment of neurodegenerative diseases, such as AD, in which there is an important neuronal loss and as previously discussed, hippocampal neurogenesis is diminished. Although there has been some controversy, findings lead us to assume that in AD there is an increased proliferation of neural precursors, but at the end newborn neurons will not be able to mature and to be fully integrated in the hippocampal circuitry. Future studies should focus on the different stimuli and factors that could potentiate the development, integration, and function of newborn neurons under pathological conditions. These studies will help to elucidate whether stimulating neurogenesis is therapeutically relevant to prevent or treat cognitive deficits associated to neurodegenerative diseases and aging.

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