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APOPTOSIS IN THE AGING BRAIN

Neurogenesis in the aged and neurodegenerative brain

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Abstract It has been well established that adult neurogenesis occurs throughout life in the subventricular (SVZ) and subgranular (SGZ) zones. However, the exact role of this type of brain plasticity is not yet clear. Many studies have shown that neurogenesis is involved in learning and memory. This has led to a hypothesis which suggests that impairment in memory during aging and neurodegenerative diseases such as Alzheimer's disease (AD) may involve abnormal neurogenesis. Indeed, during aging, there is an age-related decline in adult neurogenesis. This decline is mostly related to decreased proliferation, associated to decreased stimulation to proliferate in an aging brain. In AD, there is also evidence for decreased neurogenesis, that accompanies the neuronal loss characteristic of the disease. Interestingly in AD, there is increased proliferation, that may be caused by increasing amounts of soluble amyloid ß42-protein ($A\beta_{42}$). However, most of these new neurons die, and fibrillar $A\beta_{42}$ seems to be involved in generating an inappropriate environment for these neurons to mature. These findings open prospects for new strategies that can increase neurogenesis in normal or pathological processes in the aging brain, and by that decrease memory deficits.

Keywords Neurogenesis · Aging · Alzheimer's disease · Learning and memory · Neural stem cells · Brain · Plasticity

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Introduction

Most of the cells in an adult brain are generated during the embryonic and post-natal periods. However, recent research has shown that neurogenesis occurs throughout the adult lifespan (adult neurogenesis) in two distinct neurogenic regions of the brain; the subventricular zone (SVZ) lining the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampal formation [1].

The process of adult neurogenesis begins with proliferation of neuronal stem cells and progenitor cells. Neuronal stem cells exhibit low proliferation, self-renewing qualities and multipotentiality to the different neuroectodermal lineages, while progenitor cells exhibit high proliferation, limited self-renewal and multipotentiality. While multipotent progenitors can differentiate into at least two different cell lineages, lineage specific progenitors are restricted to one distinct lineage. Neural stem cells and progenitor cells are defined together as neural precursor cells (NPCs). The proliferation of progenitor cells gives rise to immature neurons that are able to differentiate to neurons or glial cells. Many immature neurons do not survive the differentiation process. A problem occurring at any stage will results in unsuccessful neurogenesis [2] (Fig. 1a).

In the DG, newborn cells are generated from cells in SGZ and migrate a short distance to the granule cell layer (GCL). In the GCL, the cells mature to granule cells, send dendrites to the molecular layer (ML) and axons to CA3 regions and become part of the hippocampal circuitry. In the SVZ, newborn cells migrate up the rostral migratory system (RMS) towards the olfactory bulb (OB). In the OB, they differentiate to granule cells in the GCL and periglomerular neurons in the glomerular layer (GL) [2].

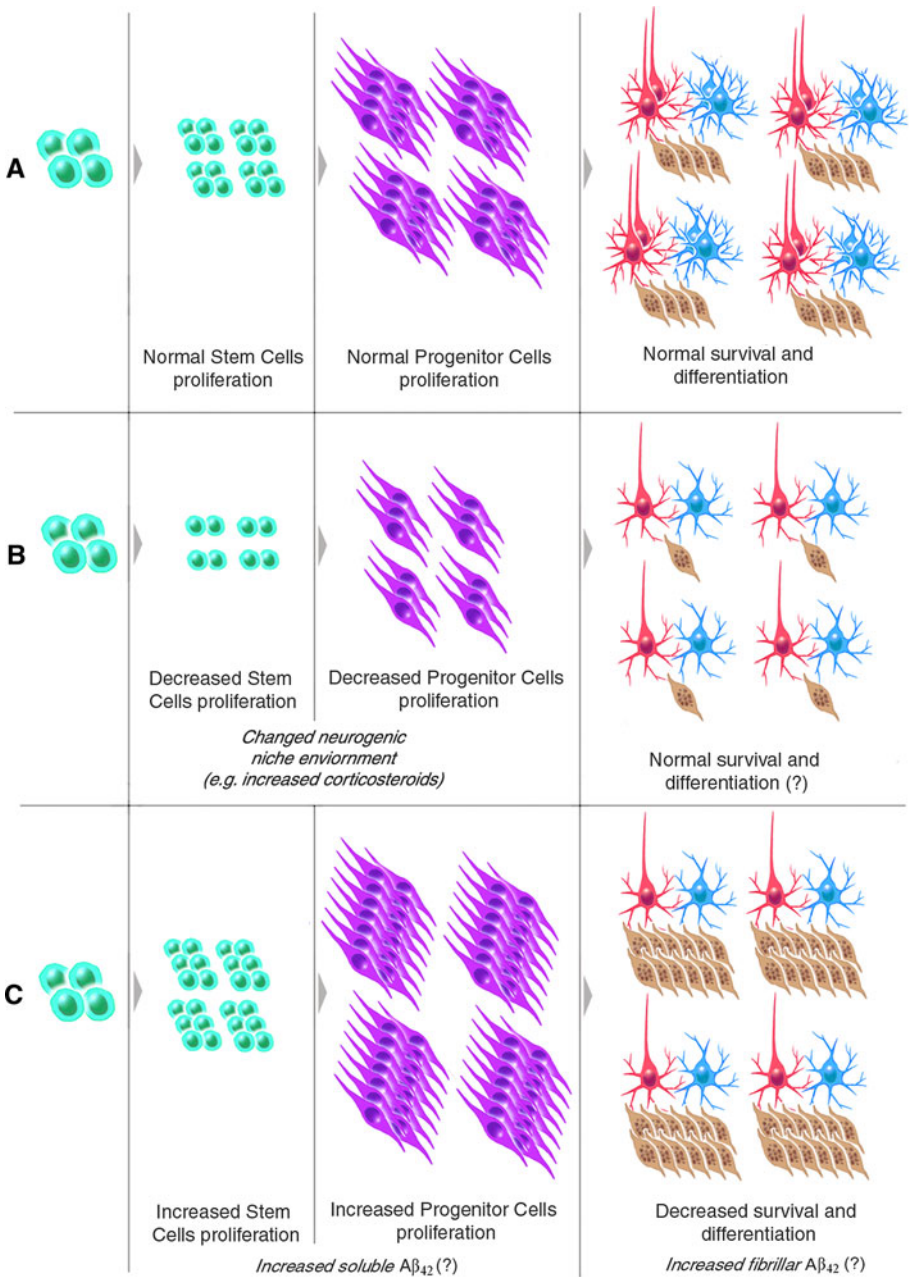

Fig. 1 Different stages of adult neurogenesis in young normal brain and their changes in aged or neurodegenerative brain. Neurogenesis in young adult (**a**) starts with precursor cells (*round cells*) proliferation, which generates immature cells (*spindle-like cells*) that differentiate into neurons or glial cells. A large portion of the cells do not survive and die (*dotted cells*). In the aged brain (**b**), there is an apparent reduced proliferation of precursor cells. In the AD brain (**c**), in spite of increased proliferation of precursor cells, only a small fraction of cells survives and reaches maturity

The importance of adult neurogenesis in the normal brain is still being studied. The involvement of the hippocampus in learning and memory [3] has led to the hypothesis that adult hippocampal neurogenesis plays an important part in learning and memory processes. Moreover, it has been hypothesized, whether the memory deficits seen during normal aging or pathological aging may be linked to alterations in adult neurogenesis.

The goal of this review is to discuss the importance of neurogenesis in the memory process and review the changes in neurogenesis during normal and pathological aging seen in neurodegenerative diseases such as Alzheimer's disease (AD).

Adult neurogenesis and memory

The role of adult neurogenesis had been investigated for many years. One of the main aims of this research was to examine the role of adult neurogenesis in the process of learning and memory. A correlation between neurogenesis and learning can be evaluated by applying one identical physiological change, and examining its influence on both those systems. Some reports show a positive correlation between learning and neurogenesis [4–8]. Enriched environmental and physical activity increased neurogenesis in the GCL of mice, and improved performance in the Morris water maze test [9, 10]. In addition, prenatal stress induced

a reduction of proliferation in the DG of rats and impaired Morris water maze performance [11]. Other studies found a negative correlation between neurogenesis and learning and memory [12, 13]. Chronic stress in tree shrews enhanced learning in hippocampal-dependent tasks, despite elevated cortisol levels, and reduced DG proliferation [14]. However, it is not entirely clear whether there is a connection between adult neurogenesis and learning, since these two processes may be regulated independently.

The effect of learning tasks on adult neurogenesis is as yet unidentified. Learning tasks have been found to increase adult neurogenesis in some studies [15–17] while in other the neurogenesis decreases or does not change [18, 19]. Hippocampal-dependent learning tasks (trace eye blink conditioning and Morris water maze) increased neurogenesis in the rat DG while hippocampal-independent learning tasks (delay eye blink conditioning and cue maze training) did not [20]. Social transmission of food preference task, which can be used to asses associative learning in rodents, caused complex alterations in adult neurogenesis in the DG. While 1 day of training increased survival of 8 day newborn cells, 2 day training decreased it [21]. In contrast to some other studies, Morris water maze learning was found to decrease the survival of 7–9 day newborn cells [22]. In addition, fear learning caused a decrease in proliferation in the DG but no change in the neurogenesis [23].

In order to explore whether adult neurogenesis is critical for the learning process, several studies have used the method of reducing neurogenesis with a toxin for proliferating cells, i.e., methylazoxymethanol acetate (MAM), or radiation. The results were, once more, controversial. Rats treated with MAM showed decreased proliferation in the DG and substantial decrease in trace hippocampal-dependent trace eye blink conditioning, but not in hippocampal-independent delay eye blink conditioning [24]. In another study in rats, MAM reduced trace fear conditioning, but not contextual fear conditioning or Morris water maze [25]. These results imply that adult neurogenesis may be critical for only some hippocampal learning tasks. Moreover, in irradiated rats, neurogenesis was found to be non-critical for Morris water maze learning, but rather important for long-term spatial memory [19].

To date, the connection between neurogenesis and leaning is controversial. In spite of that, there is enough evidence that suggests the importance of neurogenesis in learning and memory.

Neurogenesis in the aging brain

Many studies have shown that adult neurogenesis is reduced in the aging brain. The reason for the reduced numbers of new neurons can be attributed to a lowering in the number of NPCs, reduced proliferation of NPCs or reduction in the survival and differentiation of newborn neurons.

No change in the number of NPCs in the SGZ was found during aging in rats [26]. However, in another study, a decrease in the number of NPCs in the SGZ was observed in primates but not in mice, suggesting different properties of NPCs in rodents versus primates [27].

The proliferation of precursor cells was studied extensively by labeling dividing cells by BrdU. Cell proliferation can also be assessed by labeling for proliferation markers such as Ki67 and NH3. All these studies show a decrease in proliferation during aging in the DG of rodents [9, 11, 28–31]. In contrast to studies in rodents, the reduction in the number of mature neurons in the SGZ of primates has been attributed to reduced number of NPCs, and not to decreased proliferation [27]. In the SVZ, findings differ: whereas in mice there was a decrease in proliferation of NPCs with aging [30, 32], in rats there was no change in proliferation of NPCs between the age of 6–21 months [33]. Once more, species variation might be responsible for these contradictive results.

The extent of survival and differentiation of newborn neurons, i.e., "neurogenesis" is mostly based on labeling with an immature neuronal markers, such as doublecortin (DCX), PSA-NCAM or beta-III-tubulin for short-term survival, and co-localization of BrdU with a marker of mature neuronal cells such as NeuN and MAP2, for long-term survival. Survival and differentiation of newborn cells seem to be unaffected by aging [28, 34, 35]. It has been shown, that although there is decreased proliferation of NPCs in the GCL and Hilus of the DG of mice with aging, there is no reduction in the survival rate of these cells in the 4 weeks that follow birth, thus suggesting that the total reduction after 4 weeks is can be solely attributed to decreased proliferation [29]. It has also been observed that the survival of immature neurons in the DG decreases 10 days after their birth, but there was no difference in the survival rate during aging. Indeed, 5 months after injection of BrdU, the survival of mature neurons labeled with BrdU/NeuN was similar to controls [28]. In contrast to this finding, most studies show a reduction in the number of mature cells during aging [32, 36–38]. Four weeks after injection of BrdU, there are more mature neurons labeled with BrdU/NeuN in the DG of 6 month-old mice, than in 18-month old animals [39].

In summary, it seems, that the most notable reason for reduced adult neurogenesis in the SGZ and SVZ of rodents is the reduction of proliferation of NPCs (Fig. 1b). In primates, there may be a different mechanism that needs further investigation.

The reason for decreased proliferation during aging may be related to an intrinsic inability to respond to the proliferative stimulation in the neurogenic niche. It may also be the outcome of a change in the neurogenic niche that cannot issue the appropriate signal. It has been shown that by increasing pro-neurogenic factors or decreasing anti-neurogenic factors, it is possible to change the number of proliferating NPCs, suggesting that the impaired proliferation in the aged brain results from changes in the neurogenic niche [34, 40].

The anti-neurogenic factor which is mostly correlated with reduced neurogenesis in the aged brain is corticosteroids. 10-week-old rats that were subjected to chronic stress was manifested decreased proliferation of NPCs in the SGZ. After 3 weeks of recovery, there was an increase in proliferation, but it was still less than that present in the control group [41]. These findings, together with the fact that there is an age-dependent increase in the level of corticosteroids [42], led to investigation of the effect of adrenolectomy on neurogenesis. In adrenolectomised rats, there was an increase in proliferation of NPCs in the DG compared to controls [43], suggesting that NPCs may be more quiescent in the aged brain, because they lack the right stimulation to proliferate.

Neurogenesis in the neurodegenerative brain

In this chapter, we shall discuss the emerging approach of associating several human neurodegenerative diseases with abnormal adult neurogenesis, as exemplified in Alzheimer's disease (AD). AD is a progressive neurodegenerative disease that affects 5% of the population over 65. AD is characterized by a wide range of cognitive impairments, the most prominent and early deficit being the inability to recall recent activities. Although cognitive impairment is the hallmark of AD, functional and behavioral problems are also hallmarks of the disease [44]. AD histopathology is characterized by amyloid plaques and neurofibrially tangles. Amyloid plaques are spherical extracellular deposits, composed predominantly of the amyloid ß-protein (Aß). Neurofibrially tangles are intraneuronal aggregates of abnormally phosphorylated tau protein. Aß is produced by the cleavage of amyloid precursor protein (APP) at the N-Terminal by the ß-secretase and at the C-terminal by γ-secretase, that cleaves mostly after 40 or 42 amino acids, thus creating $A\beta_{40}$ and $A\beta_{42}$, respectively. Since Aß and especially $A\beta_{42}$ seem to initiate a cascade of degeneration, most of the studies on AD and specifically on neurogenesis in AD focus on $A\beta_{42}$ [45]. Data on the potential role of neurogenesis in AD is compiled from three resources: post-mortem brain tissue form AD patients, mouse models of AD, and studies in tissue culture.

Evidence from AD patients

The extent of neurogenesis has been studied on post-mortem tissues from AD patients. Firstly, the number of NPCs in an AD brain was examined. A nine-fold reduction in the number of NPCs was found in the SVZ of patients with AD, compared to controls [46]. In a study of cultured NPCs from AD patients, significantly fewer viable NPCs were observed in the hippocampus of AD patients as compared to controls. The same study also revealed decreased proliferation of NPCs, reflected by the number of NPCs from the AD patients, which increased by 8.6-fold and reached senescence after 2 weeks, while those from controls, continued to proliferate for 5 weeks, and their number increased by 40-fold [47]. It has also been reported, that the proliferation of NPCs is increased in the hippocampus of AD patients [48]. In another study, that used tissues from pre-senile AD patients, a significant increased proliferation in all hippocampal sub-regions was observed, mainly in the CA1-3 region. However, in the DG, there was no difference in the number of immature neurons between control and pre-senile AD patients. The authors suggest that the high proliferation rate is due to glial lineage proliferation [49]. Other studies explored the extent of neuronal differentiation and survival. A significant increase in nestin, a neuronal precursor marker, immunoreactivity was found in the SVZ from patients with AD, without a significant increase in GFAP immunoreactivity [46]. This increase in immature neurons in an AD brain was also found in the hippocampus of severely affected AD patients. However, the expression of the mature neuronal marker NeuN did not increase [50]. This inability of newborn neurons to mature was also found when the expression of mature neuronal marker MAP2 a and b decreased in DG of AD patients. The total MAP2, that includes isoform c, a marker for immature neuronal cells, slightly decreased, implying that MAP2c levels do not change or even decrease [51].

From these post-mortem studies, we can conclude that in AD patients the overall NPCs proliferation is increased, while however, the immature neurons are not able to mature.

Evidence from animal models of AD

Another tool to study the role of neurogenesis in AD is by using AD mice models. In parallel with the post-mortem study on brain tissue from AD patients, where increased neurogenesis was found [50], similar results, i.e., increased proliferation and neurogenesis were also obtained in mice models of AD. Transgenic mice over-expressing both the Swedish and Indiana mutations (APPswe,ind) showed the same tendency of increase in proliferation and neurogenesis in all the studies. In one such model, increased

proliferation in the DG of 3 and 12-month-old mice and in the SVZ of 12-month-old mice, was reported. In addition, the number of immature neurons were increased in the DG of the 3- and 12-month-old mice, and SVZ of 12-month-old mice [52]. In another APPswe, ind model (J20), increased proliferation and neurogenesis were observed in 3-month-old mice, but this was not found with aging. Interestingly, this increase was found to correlate with levels of oligomeric Aβ [53]. It should be noted that the long-term survival of newborn neurons was not examined in these studies.

Various AD models studies revealed a different tendency. A study on transgenic mice over-expressing the Indiana mutation (PDAPP) found decreased proliferation in the SGZ of 1-year-old PDAPP mice, compared to controls. However, no correlation between Aβ plaque load and proliferation rate in the SGZ was observed. In addition, there were significantly fewer immature neurons in the SGZ of PDAPP mice compared to controls. On the other hand, there was an increase in the number of immature neurons in the outer granule cell layer (oGCL) of PDAPP mice, compared to controls. There was no difference in the number of cells expressing BrdU/NeuN between PDAPP and wild type (WT) mice 4 weeks after BrdU injection in the SGZ and oGCL. However, BrdU-positive cells in the PDAPP mice matured abnormally, relative to WT [54]. This is a good example of the importance of subdividing the DG into different areas of function, and examining the proliferation rate and neurogenesis in each area separately. In APP transgenic mice with the Swedish mutation, decreased proliferation in the DG was seen in 1-year-old mice compared to WT. BrdU/N-CAM immunoreactive cells were decreased in the DG of APP mutant mice compared to control [55].

Although there was no apparent change of proliferation rate of NPCs in the DG of 2-month-old PS1 transgene mice P117L, there was a reduction in the survival rate of these cells 1 month later in the PS1-mice compared to WT. Furthermore, the number of immature and mature neurons decreased in the DG of this model [56]. Decreased proliferation was also found in the DG of PS1 M146V/-KI model. This decrease was followed by a reduction in the number of BrdU/NeuN positive cells [57].

In a 6-month-old APPswe/PS1dE9 mouse model, there was no change in the proliferation of NPCs in the SGZ. There was also no change in the short-term survival of these cells in the SGZ compared to WT. However, 1 month later, there was a decrease in the survival of these cells in APP/PS1 mice compared to WT. More importantly, BrdU/NeuN-positive cells were fewer in the APP/PS1 model compared to controls [58]. In another APP/PS1 model, there was a decrease in proliferation of NPCs, and in the number of immature neurons in the DG of 8–9- and 18–24-month-old APP/PS1 mice [59]. In contrast to the latter APP/PS1 models, 9-month-old $APP_{k670/M671N}/PS1_{M146L}$ mice showed increased proliferation in the hippocampus compared to WT. Also, the numbers of immature and mature neurons were higher in APP/PS1 mice than controls [60]. Decreased proliferation in the DG and GCL of 3xTg and WT mice with age was noted. This decrease in the 3xTg mice was 60–90% greater than that of the WT mice. Similar results were found in SVZ of these 3xTg mice [61].

In a conditional PS1/PS2KO mouse, a model for early stages of neurodegeneration (ESND) with no formation of plaques or tangles (7–9-month-old mice), a higher proliferation rate was noted in the DG of PS1/PS2KO mice as compared to controls. The increase was not as large in the late stages of neurodegeneration (LSND) (18–20-month-old mice). There were also a raised number of immature and mature neurons labeled by BrdU/NeuN 2 weeks later in the DG in both ESND and LSND. Four weeks later, there were more BrdU/NeuN cells in the DG in ESDN, but no difference between PS1/PS2KO and WT in LSND was reported [62].

The results from the AD models are confusing. However, most studies reveal a tendency for reduced proliferation and neurogenesis. The diverse results reported here probably reflect not only the outcome of different models, but also the different protocol regimens. The age of the animal, the BrdU injection protocol and the markers used are all factors that may affect the observations.

Evidence from cell culture models

Several studies on neurogenesis in AD have been performed on NPCs in culture. One study examined the effect of $A\beta_{42}$ on the amount of survival and differentiation of cultured NPCs from the striatum and hippocampus of normal rats. A significant increase in the number of immature neurons was found at cultured cells treated on days 0 and 7 with aggregated $A\beta_{42}$ for 24 h. The effect was stronger on cells maintained for a longer time period in culture before the treatment. There was no effect on proliferation of NPCs. Moreover, fresh $A\beta_{42}$ or $A\beta_{40}$ (fresh or aggregated) did not affect neurogenesis [63].

Although amyloid plaques are one of the main pathology of AD, there is no correlation between the amount of plaques and the severity of neurodegeneration in AD. The question then arises, how do the different form of Aβ affect NPCs. When NPCs were treated with monomeric, oligomeric or fibrillar $A\beta_{42}$ during proliferation, it was found that the oligomeric form of $A\beta_{42}$ increased the number of NPCs in culture. When cells were exposed to $A\beta_{42}$ for 24 h, after 2 days of differentiation, oligomeric $A\beta_{42}$ increased the number of immature neurons [64]. Another study tested the affect of Aβ on NPCs differentiation. $A\beta_{40}$

increased the number of neurons in culture, while $A\beta_{42}$ increased the number of astrocytes. Both $A\beta_{42}$ and $A\beta_{40}$ increased proliferation of NPCs after treatment for 24 h. Soluble $A\beta_{42}$ also increased the number of neurons [65].

Cell culture studies facilitate the characterization of the elements influencing neurogenesis in AD. It seems that soluble $A\beta_{42}$ has a proliferative effect, while fibrillar $A\beta_{42}$ reduces or does not affect neurogenesis (Fig. 1c). This may correspond to the pathogenesis of AD where, at early stages, there is mostly diffuse $A\beta_{42}$, while later on, there is a shift to plaques comprising mostly the fibrillar state of $A\beta_{42}$. Furthermore, the increased ratio between $A\beta_{42}$ and $A\beta_{40}$ as the disease progresses may also exacerbate the disease process, since the neurogenic effect of $A\beta_{40}$ is then diminished.

Conclusions

There is accumulating evidence that associates adult neurogenesis with both aging and AD. Studies in aging and AD indicate that neuronal stem cell therapy should focus on providing the appropriate conditions for proliferation and neurogenesis. The goal of such therapies would be to deliver the required agents to the neuronal stem cells, stimulate proliferation and allow differentiation and survival of newborn neurons. Further investigation to better elucidate the neurogenesis process, and development of the right regimens of therapeutic agents to enhance this process should be encouraged.

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