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SPECIAL ISSUE

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Adult hippocampal neurogenesis and aging

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Abstract The demographic changes in the foreseeable future stress the need for research on successful cognitive aging. Advancing age constitutes a primary risk factor for disease of the central nervous system most notably neurodegenerative disorders. The hippocampus is one of the brain regions that is prominently affected by neurodegeneration and functional decline even in what is still considered "normal aging". Plasticity is the basis for how the brain adapts to changes over time. The discovery of adult hippocampal neurogenesis has added a whole new dimension to research on structural plasticity in the adult and aging hippocampus. In this article, we briefly summarize and discuss recent findings on the regulation of adult neurogenesis with relevance to aging. Aging is an important co-variable for many regulatory mechanisms affecting adult neurogenesis but so far, only few studies have specifically addressed this interaction. We hypothesize that adult neurogenesis contributes to a neural reserve, i.e. the maintained potential for structural plasticity that allows compensation in situations of functional losses with aging. As such we propose that adult neurogenesis might contribute to the structural correlates of successful aging.

Key words environmental enrichment · physical activity · depression · dentate gyrus · stem cell · precursor cell

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Introduction

Aging is a fundamental determinant of life and as such a parameter that cuts across all disciplines of research that deal with living things. The essence of aging is difficult to grasp, because it is a variable like no other. In some sense, aging can only be addressed in an interdisciplinary approach, especially if the consequences of aging on complex cognitive functions with implications in many domains are to be studied. We here take a reductionism approach and equal "aging" largely with the biology of very long time-scales. Implicit in this understanding is that age-dependent changes essentially reflect an unidirectional development. In the course of aging, everything builds upon what has happened before.

The biology of aging has so far largely been focused on the molecular and cellular level of analysis, or has looked at entire organisms, for example, if the determinants of longevity were studied. In vivo studies have mostly been cross-sectional and cohort analyses as we know them from developmental and lifespan psychology are hardly ever found in biology. Consequently, our knowledge about the neurobiology of aging is still limited. In the context of adult neurogenesis, only one truly multi-level analysis has been published to date, and even there, only three time-points could be investigated [33]. Ultimately, a theory of adult neurogenesis in particular and cellular plasticity in general will require close reference to concepts on other levels of research, including systems biology, behavioral and cognitive neuroscience, and developmental and cognitive psychology.

Recent years have brought fundamentally new insight in how brain function and structure are linked. This mutual interaction is called "plasticity". The term remains rather elusive and runs the danger to become a mere label. But the concept is important. It essentially states that one cannot see cognitive function independent of the underlying

structure (and also vice versa). In this context, adult neurogenesis has become a topic of particular attraction.

Stem cell biology has raised new hopes for Regenerative Medicine, especially with respect to aging-related disorders, because stem cells embody the potential for regeneration [107]. There is, however, only limited evidence that adult neurogenesis would primarily contribute to regeneration, although adult neurogenesis responds to a wide range of pathologies (reviewed in [29]). Rather, we propose that it is the physiological function of the new neurons that might be impaired by aging and that, if adequately preserved, might contribute to the compensation of age-related losses. From this hypothesis the focus of the present review can be deduced. Key findings from the field are summarized in Table 1.

Age-related changes in adult neurogenesis

The discovery that in the adult brain neurons are continuously generated opens a novel perspective on the neurobiology of aging. Adult neurogenesis is a complex process, starting with the division of a precursor cell and leading to the functional integration of newly born neurons into a pre-existing circuitry. Adult neurogenesis occurs in two brain structures throughout life, the olfactory bulb and the hippocampus.

In the olfactory bulb two types of interneurons are generated from a dividing precursor cell population in the subventricular zone (SVZ) [3, 5, 25, 92, 138]. The continuous addition of interneurons, which modulate spatial and temporal coding of olfactory information, might provide a substrate for adapting to environmental changes [21, 31].

In the dentate gyrus of the hippocampus, new granule cells are continuously generated from precursor cells in the subgranular zone [4, 18, 68, 83]. Hippocampal neurogenesis includes different steps from a presumably bipotent radial glia-like stem cell with astrocytic properties [46, 116] to transiently amplifying lineage-determined progenitor cells to early postmitotic and mature neurons [73]. Newly generated cells mature into functional neurons, which are structurally integrated into a pre-existing network; they receive synaptic input from local interneurons and from the entorhinal cortex and extend axons to target cells in the CA3 region (for review see for example: [1, 2, 31]). Structural integration of neurons generated in the adult brain is the prerequisite for functional synaptic integration [20, 114, 126, 131, 134].

Across the lifespan, a progressive reduction of adult hippocampal neurogenesis occurs. With growing age, there is a decline in precursor cell proliferation and net neurogenesis [83]. This reduction takes place in the context of other structural changes [34, 110]. Similar observations have been made for neurogenesis in the aging olfactory bulb [14, 43, 91]. Aged mice show olfactory discrimination deficits, attributed to a decline in olfactory neurogenesis [43]. In the remainder of this review we focus on adult hippocampal neurogenesis.

Aging has sometimes been designated as a strong (or even the strongest) negative regulator of adult hippocampal neurogenesis. Although it is undisputed that neurogenesis decreases with age and in old age lingers at a few percent of the value in early adulthood, the term "regulator" appears problematic. The decline does not seem to be "regulated" but rather to be the by-product of age-related changes of other sorts. A few of these have been identified: Maintenance of the youthfully low levels of corticosteroids into older age, for example, prevented the age-related decrease in neurogenesis [17]. In general it seems that aging is one of the global key determinants that (in concert with numerous specific regulators) can influence both the baseline level and the regulation of adult neurogenesis. Because of its strong influence on the net effects and its interaction with many regulatory principles, aging is a variable that generally should be taken into account in the consideration of adult neurogenesis. Numbers alone might be deceiving. For example, even if the baseline level of adult neurogenesis is very low in oldest age, the relative regulation that is possible from this baseline might be much larger than early in life [76].

Functional relevance and activity-dependent regulation of adult hippocampal neurogenesis

Although aging is not a disease, it is characterized by cognitive impairments, often independent of neurodegeneration, which in the hippocampus might involve the loss of neurons or degradation of circuits and synapses as well as changes in adult neurogenesis [34, 110]. It should be noted though that in humans, stereological analysis revealed that cell loss in the aging hippocampus was sub-region dependent and could not be detected in the dentate gyrus [136]. This might be indicative of the ongoing neurogenesis in the dentate gyrus but it might also simply mean that only few granule cells die.

Plasticity of the hippocampal circuits provides the structural foundation for the functioning of the hippocampus in learning and memory processes. Cellular plasticity is an aspect of structural plasticity that goes beyond synapses and circuits. We hypothesize that adult hippocampal neurogenesis contributes to hippocampal function by allowing a demand-driven optimization of the mossy fiber connection between the dentate gyrus and CA3 according to the levels of complexity and novelty experienced by the individual [72, 77, 140]. This hypothesis involves the assumption that adult neurogenesis could make a contribution to

Table 1 Overview over key studies on adult hippocampal neurogenesis and aging

Adult neurogenesis in old age			
Kuhn et al. 1996 [83]	Rats (Fisher 344)	21 months	First report on age-related changes in adult neurogenesis in rats. Decrease in mitotic activity of neuronal precursor cells in the dentate gyrus resulting in reduced net neurogenesis
Kempermann et al. 1998 [76]	Mice (C57BL/6)	6, 18 months	First report on age-related decrease of adult neurogenesis in mice
Eriksson et al. 1998 [4]	Humans	up to 72 years	First report on adult neurogenesis in humans
Gould et al. 1999 [5]	Macaque monkeys	up to 23 years	First report on age-related decline in adult dentate neurogenesis in non-human primates
Barker et al. 2005[8]	Wild living squirrels and chipmunks	up to 8 years	Age-related decline in adult hippocampal neurogenesis is species dependent
Rao et al. 2005 [108]	Rat (Fisher 344)	4, 12, 24 months	Normal but slowed development of new neurons in the aged hippocampus
Simon et al. 2005 [121]	Tree shrews	19, 20, 30 months	Older animals were significantly more vulnerable to the adverse effect of stress on dentate cell proliferation
Regulation of neurogenesis in the aging hippocampus			
Kempermann et al. 1998 [76]	Mice (C57BL/6)	6, 18 months	Adult neurogenesis persists in old mice and can be induced by environmental stimuli. The relative net effect is larger than in younger mice
Cameron et al. 1999 [17]	Rats (Sprague Dawley)	5, 25 months	The age-related decrease in adult hippocampal neurogenesis can be prevented by adrenalectomy, which removes the source for elevated corticosterone levels in the aging animals
Lichtenwalner et al. 2001 [87]	Rats (BnxF)	5, 18, 28 months	Restoration of decreased insulin like growth factor 1 (IGF1) levels in old rats increased hippocampal neurogenesis
Kempermann et al. 2002 [72]	Mice (C57BL/6)	20 months	Exposure to an enriched environment from age 10 months to 20 months maintained adult neurogenesis at an elevated level
Jin et al. 2003 [66]	Mice (CD1)	3, 20 months	Relative effect of intracerebroventricular infusion of fibroblast growth factor 2 and heparin binding epidermal growth factor (HB-EGF) on precursor cell proliferation was up to 10-fold larger in aged than in young-adult mice
Heine et al. 2004 [57]	Rats (Wistar)	6 weeks, 6, 24 months	Neurogenesis decreases with age but in contrast to (17) no age-related increase in corticosterone levels are found
Darsalia et al. 2005 [27]	Rats (Wistar)	15 months	Normal and ischemia-induced reactive neurogenesis are reduced in the aged hippocampus
Wati et al. 2006 [135]	Rats (Sprague Dawley)	4, 30 months	Aging reduces survival of newborn neurons both under baseline conditions and after the survival-promoting stimulus of contextual fear conditioning
Kronenberg et al. 2006 [80]	Mice (C57BL/6)	3, 9, 12, 24 months	Physical exercise prevents the strong decrease in cell proliferation between 3 and 9 months of age and acutely up-regulates adult neurogenesis even at 12, 24 months
Darnaudery et al. 2006 [26]	Rats (Sprague Dawley)	2, 24 months	Chronic IGF-1 treatment restores the spatial learning abilities, reduces HPA axis dysfunction and increases plasma estradiol levels as well as cell proliferation in the dentate gyrus in prenatally stressed rats
Age-related decrease in neurogenesis in relation to hippocampal function			
Bizon et al. 2004 [11]	Rats (Long Evans)	7, 25 months	No strict correlation between water maze performance and the rate of adult hippocampal neurogenesis in aged rats
Kempermann et al. 1998 [76]	Mice (C57BL/6)	6, 18 months	Increased neurogenesis in response to environmental enrichment is associated with increased water maze performance
Drapeau et al. 2003 [32]	Rats (Sprague Dawley)	3, 20 months	The level of adult hippocampal neurogenesis in individual aged rats is to some degree predictive of water maze performance
Montaron et al. 2006 [102]	Rats (Sprague Dawley)		Manipulation of corticosterone levels reveals correlation between glucocorticoid secretion, adult neurogenesis and water maze performance in aged rats
Driscoll et al. 2006 [33]	Rats (FBNF1)	3, 12, 24 months	Unusual multi-level analysis that relates decreased neurogenesis to reduced water maze performance and numerous other parameters
Van Praag et al. 2005 [132]	Mice (C57BL/6)	3, 19 months	Physical activity in old age increases neurogenesis and water maze performance

network plasticity that could not be similarly obtained by other means, that is on the synaptic level. A number of other hypotheses have been proposed [2, 9, 23, 28, 86].

In humans, both participation in moderately challenging cognitive tasks as well as in moderate physical activity reduce the risk of developing dementias in older age and thus contribute to

"successful aging" [24, 137]. In suggestive analogy (the truth of which of course remains to be tested) adult neurogenesis is promoted by both cognitive activity, which might be associated with some but not all types of hippocampal-dependent learning and memory [30, 119, 120], and experience-dependent activation of the hippocampus [75, 81, 128]. The survival of adult-generated granule cells can be enhanced in response to conditioning tasks [119] and spatial learning such as in the water maze task [120]. However, the data remain somewhat ambiguous, since exposure to the test might also result in a robust decrease of precursor cell proliferation and in a reduced number of calretinin-positive immature neurons [42]. The calretinin-positive neurons likely represent the phase of greatest synaptic plasticity in the course of neuronal development in the adult dentate gyrus [12, 73, 105, 114]. The discrepancy might be explainable by species differences, physical activity, and stress related to the task. The result shows, however, that variability in the response exists. Aging has not yet been investigated as potentially confounding variable here.

An enriched environment is characterized by varying sensory stimulation, social interaction, and cognitive challenges [130]. It provides learning stimuli albeit in a less focused way than in the above-mentioned experiments with specific learning tasks. One of the classical theories of the 1970s and 1980s, on how environmental enrichment exerts its effect on the brain has been the "learning and memory theory" (reviewed in [111]).

Living in enriched housing conditions promoted the survival of newly born cells in the dentate gyrus of aged mice [69]. The experience-dependent regulation of adult neurogenesis appears to be primarily a survival-promoting effect on postmitotic cells that are committed to a neuronal lineage [12]. However, there is an additional effect on the precursor cells themselves. In studies with a sustained exposure to the beneficial stimulus, increased adult hippocampal neurogenesis did not reflect an acute response to a novel stimulus, but rather a persistently elevated baseline [71, 72]. By these means, "enrichment" might maintain a potential for cellular plasticity in the aging brain. A similar observation has been made with respect to physical activity.

Physical activity, e.g. voluntary wheel running in animal models, has an acute up-regulating effect on precursor cell proliferation and neurogenesis, which however wears off with continued exercise [80, 103, 129]. It has been suggested that the stimulatory effects of running were mediated by vascular endothelial growth factor (VEGF) [45] or insulin-like growth factor 1 (IGF1) [127]. IGF1, coincidentally also decreases with age and restoration of IGF1 levels corresponding to a younger age strongly up-regulated neurogenesis [87] and attenuated learning deficits in aged rats [26]. Voluntary wheel running also improved hippocampal learning, increased hippocampal longterm potentiation [128], and induced hippocampal neurogenesis in adult and aged mice [80, 132].

Physical activity not only acutely promoted neurogenesis in aged animals. If applied over longer periods, it also prevented the dramatic age-dependent decrease in precursor cell proliferation in the hippocampus that occurs during the first months of life in a rodent [80]. However, presumably in the absence of additional cognitive stimuli this maintained potential was not translated into an increased level of net neurogenesis. Consequently, both might be needed to achieve sustained neurogenesis: physical and cognitive stimulation.

From these animal data one is tempted to propose that learning and memory, knowledge and experience, intellectual stimulation, regular physical activity, social behavior and interaction promote successful aging by preserving cognitive function in association with a higher level of adult neurogenesis. Conversely, increasing age-related difficulties to learn and to adopt complex and novel situations might at least in part be due to an exhaustion of adult neurogenesis. This hypothesis remains to be tested in detail in the future.

The neurogenic niche differently influences neurogenesis in aging

The reduction of neurogenesis in the aged brain might be due to both a loss of extrinsic signals and a reduced responsiveness of the aging precursor cells to normal signaling. Senescence of precursor cells in the neurogenic zones of the adult brain has so far only been directly addressed in one study: an increase of p16INK4a, a cyclin dependent kinase inhibitor linked to senescence mechanisms, was found to be associated with the age-related loss of precursor cells in the SVZ/olfactory bulb system but not in the dentate gyrus [101].

One hallmark of stem cells is the expression of telomerase that prevents telomere shortening in proliferative cells [85]. Telomere shortening occurs in aging but is difficult to study in rodents who generally have long telomeres. Telomerase activity has been brought into connection with the regulation of adult neurogenesis but no study focusing specifically on age effects has been published [19].

Adult neurogenesis requires a specific molecular and cellular microenvironment, which is able to provide the necessary signals to sustain and regulate the proliferation and differentiation of the adult stem cell population [99, 106, 115]. The neurogenic niche consists of the precursor cells and their progeny, additional glia cells, endothelial cells and a presumably specific extra cellular matrix surrounded by a shared basal membrane. Within this niche, specific

cell–cell contacts, likely involving gap junctions, paracrine effects of neurotransmitters, neurotrophic factors and growth factors as well as synaptic contacts control sequential steps in neurogenesis. Precursor cells and their niche form a functional unit that shows high similarity in tissues as diverse as testis, bone marrow, olfactory epithelium and brain. As an extreme position it has been proposed that the decline in precursor cell activity in the aging hippocampus is the result of increased quiescence and not reduced precursor cell numbers—presumably inflicted by changing niche properties [55].

Growth factors play a prominent role in controlling precursor cell proliferation and neuronal differentiation and thus might be important mediators of cellular plasticity in aging [16, 54, 84, 118]. Alterations in growth factor expression levels might thus underlie changes in neurogenesis as consequence of disease or aging. Neurotrophic factors, growth factors and their receptors are abundant during development and decline with age [22, 118, 139]. However, the aged mouse brain retains the capacity to respond to the neurogenesis-stimulating effects of growth factors [66, 87, 123]. While some factors decrease with age, others such as cell cycle regulator transforming growth factor β1 (TGFβ1) might increase. Over expression of TGFβ1 in old mice inhibited the proliferation of early precursor cells [15].

To date our insight is rather limited into the possible mechanisms underlying the age-related decline in adult neurogenesis and the possible factors that might help to prevent it. Few "usual suspects" (corticosterone, IGF1, etc.) dominate the discussion. For example, the cAMP response element-binding protein (CREB) is a key mediator of stimulus-induced nuclear responses that underlie survival, memory and plasticity in the nervous system and its hippocampal expression decreases with age (at least in CA1) [82]. However, intracellular signaling from numerous pathways converges on or affects pCREB, placing pCREB in larger networks of regulatory mechanisms. More comprehensive models of hippocampal transcriptional mechanisms that distinguish successful from unsuccessful aging have been proposed [90]. They remain to be applied to adult neurogenesis. Changes in the expression of transcription factors linked to aging could potentially be identified. Gene–gene and gene-environment interactions still need to be investigated. There is a large natural variation in the individual sensitivity to aging effects as well as polygenic disease processes. Similarly, adult neurogenesis shows large natural variations [70]. Age-related changes in neurogenesis and numerous other parameters will show this variation as well. Ultimately, molecular, genetic and environmental factors, which favor successful aging, could provide a useful framework for interventions to reduce aging-associated diseases including loss of cognitive capabilities.

The relationship between pathological aging and adult hippocampal neurogenesis

Pathological aging is an aging process, during which changes to cognitive functions exceed the level that is considered to be normal. This functional definition is usually complemented by the condition that concrete pathological events can be detected. Neurodegenerative disease is defined by an age-dependent progressive loss of neurons based on the accumulation of misfolded proteins, e.g. alpha synuclein in Parkinson disease, huntingtin in Huntington disease, and amyloid beta in Alzheimer disease. In a wider sense, neurodegenerative disorders include secondary degeneration such as in inflammatory disorders or ischemia.

Adult neurogenesis shows a dual relationship to neurodegenerative disorders. First, neural precursor cells and their progeny might be directly affected by the pathology. The consequences of failing adult neurogenesis might thus contribute to the clinical picture. Second, adult neurogenesis might provide some means of compensatory or even regenerative capacity in the affected aging brain. In line with the results discussed in the previous paragraphs we have argued that adult hippocampal neurogenesis might thereby contribute to a structural or neural reserve that if appropriately trained early in life might provide a compensatory buffer of brain plasticity in the face of increasing neurodegeneration.

We recently reviewed the current state of knowledge about adult neurogenesis and neurodegenerative disease and refer to that text for more detailed information [122].

Hormonal regulation of adult neurogenesis in the aging hippocampus

Estrogen has neuroprotective properties and estrogen deficiency during menopause can be associated with cognitive dysfunction. Estrogen substitution therapy in postmenopausal women might have a positive effect on these problems, but no consistent link between hormone replacement therapy and cognitive performance could be found [60, 88].

Cell genesis in the adult dentate gyrus is also influenced by various hormonal stimuli and sex hormones, both male and female, can influence adult neurogenesis [47]. In the female rodent hippocampus cell proliferation peaks during estrogen-high proestrous [124]. However, exogenous application of estradiol led only to a transient increase in cell proliferation, presumably because of compensating feedback mechanisms [104].

In addition, estrogen and IGF1 interact in the promotion of neuronal survival and neuroprotection [49], which might be related to increased hippocam-

pal synaptic plasticity in aging. Furthermore, estrogen might act through a serotonin-mediated pathway to stimulate precursor cell proliferation in the adult dentate gyrus [6]. A study that specifically addresses estrogen effects on adult neurogenesis in aging, however, does not yet exist.

More information is available on the effects of glucocorticoids. Acute stress reduces precursor cell proliferation in the adult brain and presumably does so—at least in rodents—through the action of stress hormone corticosterone [100]. Stressful experiences, which elevate the levels of glucocorticoids and stimulate hippocampal glutamate release, inhibit precursor cell proliferation in the dentate gyrus [50, 52]. In humans, effects of glucocorticoids, produced by the stress-responsive hypothalamic-pituitary-adrenal (HPA) system, have been linked to several age-related problems [56, 93]. But in animal models, the effects of chronic stress and chronically elevated corticosterone levels on adult neurogenesis have been more difficult to assess. Overall, the data remain somewhat controversial. Many models of chronic stress did not show changes in adult neurogenesis [57, 58]. Also, experimental situations associated with increased neurogenesis such as voluntary wheel running frequently come along with higher not lower plasma levels of corticosterone [128]. However, neurogenesis in tree shrews was more vulnerable to chronic psychosocial stress in old than in younger age [121].

Reduced neurogenesis during aging and age-related memory decline might be due to chronically increased glucocorticoid levels even in the absence of stressful experience. In aging, a dysregulation of the HPA system might be found that leads to elevated levels of circulating corticosteroids [79, 113]. The age-related reduction in adult neurogenesis might also be a result of increased corticosteroid levels in older age, although some conflicting data exist [57]. But corticosteroid receptor expression increases on precursor cells in older age, possibly making them more sensitive to corticosterone action [48]. Even a short treatment with mifepristone, a glucocorticoid receptor antagonist, upregulated hippocampal neurogenesis and improved cognitive function in old rats [97]. Prevention of glucocorticoid-mediated effects in aging rats maintained increased neurogenesis levels [17, 102].

Adult hippocampal neurogenesis and depression in aging

Aging is also a risk factor for depression [98]. Although major affective disorders are rare in old age [10], there are a number of diseases such as stroke or Parkinson disease, which have an ethiological link to (late-life) depression. A much-debated hypothesis has linked failing adult hippocampal neurogenesis with the pathogenesis of major depression [35, 38, 64, 65, 74]. Animal studies showed that a decreased birth of new neurons might contribute to reduced hippocampal plasticity—an effect that could be reversed by antidepressant treatment [37, 39]. The observation that major depression is less frequent in older subjects in according to the level of symptoms seems to be in line with the hypothesis that plasticity earlier in life determines the ability of the hippocampus to cope with complexity and novelty. In old age, when neurogenesis is low, the chances of accumulating as the consequences of reduced cellular plasticity for the first time would be actually lower [74]. Low neurogenesis in old individuals would primarily become an issue (and lead to decompensation and depression), when plasticity had already been reduced before. Physical activity might prevent this loss of plasticity (e.g. [53]) and thereby reduce depressive episodes. This idea is again in line with a "reserve" hypothesis but still remains largely speculative albeit based on evidence from the animal research discussed here.

The neurotrophic hypothesis of depression and antidepressant action in the hippocampus fits into this picture. It proposes that chronic stress causes a decrease of BDNF and other growth factors, which cause the symptoms. Antidepressants reverse this effect [40]. In contrast, however, no change in neurogenesis was found in certain animal models of depression and after the effective treatment of the depression-like state, suggesting that neurogenesis is not the primary etiological, but rather an epiphenomenal factor in depression [59].

The general reasoning in favor of these ideas is based on two main observations. First, unipolar depression is associated with hippocampal volume loss [117, 133]. This observation is generally consistent with reduced levels of adult neurogenesis. However, the total volume that adult neurogenesis might contribute to the volume of the entire hippocampus is minute and below the threshold of detection by imaging techniques. Other factors such as loss of existing neurons, changes in synaptic bulk and in dendritic arborization that are equally sensitive to stress and steroid exposure might also contribute to hippocampal atrophy [89]. On the other hand, aging possibly influences the balance between neurogenesis and apoptosis, neuronal migration and maturation, and might thus have considerable consequences for the connectivity of the hippocampal circuitry [57].

The neurogenesis hypothesis of depression is secondly supported by the general observation that essentially all known antidepressant drugs increase adult hippocampal neurogenesis (reviewed in [96]; see also Czéh and Lucassen and Vollmayr et al., this issue). In this context, serotonin (5-HT) plays a particularly important role, because changes in the serotonergic system are often found in depression. Studies in humans and animals point to a deficit in serotonergic neurotransmission that correlates with increased anxiety [61, 63, 109].

Lesions of the serotonergic input decreased adult neurogenesis [13]. Several studies addressed the action of agents that facilitate or inhibit serotonin reuptake, and discovered that the chronic administration of antidepressants up-regulated adult neurogenesis [41, 95]. Chronic treatment with selective serotonin reuptake inhibitor fluoxetine reversed the decrease in proliferation and in adult neurogenesis, and enhances the number of BrdU-positive cells in the dentate gyrus [94]. The 5-HT_{1A} receptor contributes to the action of antidepressants, and might be the mediator of at least some of the effects of serotonin in this context [112, 141]. In addition, 5-HT_{1A} receptors regulate normal development of spine density and synapse formation of pyramidal and granule cell dendrites, and elicit long-term plastic changes that decrease anxiety-like behavior [7, 125].

Serotonergic innervation changes over the course of the life span as illustrated by a partial depletion of 5-HT in the hippocampal formation with age [78]. Aging was also associated with a neuronal loss of cells in the dorsal raphe nucleus and in the hippocampus in a genetic rat model of depression [62]. Furthermore, age-dependent changes of the serotonin transporter (SERT) occur, following denervation of serotonergic afferents. After lesioning serotonergic neurons with 5,7-dihydroxytryptamine older animals did not show recovery of hippocampal SERT expression, whereas after a certain time younger animals did [36, 67].

Conclusions

Aging is a major cofactor in the control of adult hippocampal neurogenesis. From the factors that cause the progressive decline in precursor cell proliferation and neurogenesis in the aging dentate gyrus to date primarily cell-extrinsic cues are known. For example, modified expression of neurotrophic factors, growth factors, changed neurotransmitter release, as well as increased glucocorticoid levels contribute to the effect of aging on adult neurogenesis. In the future we will certainly learn more about cell intrinsic determinants and the impact of precursor cell senescence on neurogenesis in aging.

Our general hypothesis is that adult neurogenesis is one of the key mechanisms of structural plasticity in the hippocampus. As such it will be of relevance to many age-related changes that affect the hippocampus, be it in normal cognitive aging, in neurodegenerative disease, in major depression, and in attempts to improve cognitive abilities in old age. We propose that across the lifespan adult neurogenesis contributes to the neural reserve that is here the potential for structural plasticity that allows compensation in the face of age- or disease-related cognitive decline. As outlined in this brief review, age is a co-variable that affects all other regulatory mechanisms. As such it is difficult to study it independently. Our knowledge about age-related factors in a stricter sense, such as senescence of stem cells, etc., is still rather limited. But in addition, we also lack detailed cohort studies and longitudinal studies of age-related changes to cellular plasticity in the hippocampus. We propose that given the very general impact of the variable "age" on all aspects of plasticity, more and more studies should include the consideration of long time scales as a co-variable.

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