Chapter 14
Insights into Aging of the Hippocampus: A View from the Topographic Differentiation

Shozo Jinno

Abstract More than fifty years ago, a number of studies reported the reduction of neuron numbers related to brain aging. However, later studies have concluded that the neuronal loss due to aging is limited to specific regions of the nervous system and its significance is irrelevant in both humans and non-human mammals. Instead, several other mechanisms that may underlie brain aging have attracted attention in the field of neuroscience research. Namely, some papers have indicated the relationship between memory impairment and decline in adult neurogenesis in the hippocampus during aging. It has also been reported that abnormalities of oligodendrogenesis in the mature brain may be involved in age-related cognitive decline. We herein briefly review recent findings on age-related changes in adult neurogenesis and oligodendrogenesis, and discuss their functional significance from the view point of topography of the hippocampus. Namely, the hippocampus has shown to be structurally and functionally differentiated along the longitudinal and transverse axes. In the rodent brain, the dorsal (septal) hippocampus is involved in cognition, learning, and memory, while the ventral (temporal) hippocampus contributes to regulation of emotion, mood, and anxiety. Nevertheless, the question of how topographic differentiation of the hippocampus might be affected by aging still remains largely unanswered. Our latest studies have shown that the waning of adult neurogenesis and oligodendrogenesis during aging is more relevant in the ventral hippocampus than in the dorsal hippocampus. We therefore hypothesize that the ventral-dominant decline in hippocampal neurogenesis and oligodendrogenesis may partly explain why major depression frequently precedes dementia in elderly people. These findings provide new insights into aging of the hippocampus.

Keywords Hippocampus • Differentiation • Topography • Aging • Adult neurogenesis • Oligodendrogenesis

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N. Mori, I. Mook-Jung (eds.), *Aging Mechanisms*,
DOI 10.1007/978-4-431-55763-0_14

14.1 Introduction

More than fifty years ago, much attention was given to changes in neuron numbers related to brain aging, and many papers reported the significant neuron loss occurred in the aged brain (Brody 1955). However, later studies have concluded that neuronal loss due to aging is limited to specific regions of the nervous system, and is irrelevant (probably no more than 10 %) in both humans and non-human animals (Curcio and Coleman 1982; Peters and Sethares 1993; Pakkenberg and Gundersen 1997). Considering that the variance of neuron numbers in humans with normal cognitive function is large, it is unlikely that a 10 % loss in neurons that is not ubiquitous is the significant factor causing various symptoms that often accompany normal aging (Pannese 2011). To date, several other mechanisms causing brain aging have attracted attention in the field of neuroscience research. For instance, there is a substantial amount of data showing that the rate of adult neurogenesis in the hippocampus radically wanes during aging (Merkley et al. 2014). It has also been suggested that age-related decline in adult neurogenesis is an important factor influencing cognitive performance (Artegiani and Calegari 2012). Similar to neurogenesis, oligodendrogenesis and white matter homeostasis might also be affected by aging (Sim et al. 2002; Miyamoto et al. 2013). We herein briefly review recent findings on age-related changes in adult neurogenesis and oligodendrogenesis, and discuss their functional significance from the view point of topography of the hippocampus.

14.2 Differentiation of the Hippocampus

The rodent hippocampus has an elongated shape with its major axis extending in a C-shaped fashion from the septal nuclei of the basal forebrain to the temporal lobe. Importantly, the structure and function of the rodent hippocampus is differentiated along the longitudinal (dorsoventral) and transverse axes (Fanselow and Dong 2010). Earlier anatomical studies have reported the topographic differentiation of the hippocampus along the dorsoventral axis (Gaarskjaer 1978). The dorsal hippocampus sends massive projections to the retrosplenial cortex and mammillary complex (Ishizuka 2001; van Groen and Wyss 2003). The ventral hippocampus has intimate reciprocal connections with the amygdala and strong projections to the nucleus accumbens (Pitkänen et al. 2000). The dorsal dentate gyrus (DG) receives afferents both from the lateral and medial area of the entorhinal cortex, whereas the ventral DG receives projections from the medial area of the entorhinal cortex (Witter et al. 1989). In a series of our studies, we have demonstrated the existence of dorsoventral differences in the cellular architecture of the mouse hippocampus (Jinno and Kosaka 2006, 2010). Functional differentiation along the dorsoventral axis has also been reported in the past two decades. Injuries to the dorsal hippocampus impair spatial learning (Moser et al. 1993), but lesions of the ventral

hippocampus affect anxiety-related behavior, and have no effect on spatial learning (Bannerman et al. 2003). Genes expressed in the dorsal hippocampus are associated with the brain regions related to cognitive information-processing, while genes expressed in the ventral hippocampus are associated with regions involved in emotional behaviors (Dong et al. 2009). To date, it has been widely accepted that the dorsal hippocampus plays a preferential role in cognition, learning and memory, while the ventral hippocampus is involved in regulation of emotion, mood, and anxiety. Interestingly, the differentiation of the hippocampus is evolutionarily conserved in rodents, monkeys (Colombo et al. 1998) and humans (Small et al. 2011).

14.3 Topography of Adult Hippocampal Neurogenesis

Throughout adulthood, new granule cells are continuously generated in the subgranular zone of the DG (Altman and Das 1967; Kaplan and Hinds 1977; Cameron et al. 1993). Recent studies indicated that adult neurogenesis is involved in various hippocampal functions (Balu and Lucki 2009). Drug-induced inhibition of cell proliferation impaired learning of a hippocampus-dependent spatial memory task (Shors et al. 2001). Addition and removal of adult-born granule cells in the DG might influence spatial learning and memory (Drapeau et al. 2003; Dupret et al. 2007; Farioli-Vecchioli et al. 2008).

In our recent study (Jinno 2011a), we examined the topography of adult neurogenesis along the longitudinal (dorsal vs. ventral) and transverse (suprapyramidal vs. infrapyramidal) axes of the DG of young adult mice using endogenous neurogenesis markers (Fig. 14.1): brain lipid binding protein (BLBP), doublecortin (DCX), calretinin (CR), proliferation cell nuclear antigen (PCNA) and Ki-67. BLBP belongs to the fatty acid binding protein family (Feng et al. 1994), and is expressed in radial-glia like progenitors and intermediate progenitors, i.e., neural stem cells (NSCs). DCX is a microtubule-associated phosphoprotein (Gleeson et al. 1999; Francis et al. 1999), which labels both lineage-restricted neuronal progenitors and immature granule cells, i.e., neural lineage cells (NLCs) (Brown et al. 2003; Rao and Shetty 2004). CR belongs to the EF-hand calcium-binding protein family, and is transiently expressed in granule cells at early postmitotic stage (Liu et al. 1996). PCNA (Celis and Celis 1985) and Ki-67 (Gerdes et al. 1984) can label dividing cells. Using combinations of these markers, the cells at specific stages of adult neurogenesis can be identified (Kempermann et al. 2004).

It was reported that adult neurogenesis may be more active in the dorsal hippocampus than in the ventral hippocampus (Snyder et al. 2009). In adult male gerbils, the number of 7-day-old bromodeoxyuridine (BrdU)-labeled granule cells was larger in the dorsal DG than in the ventral DG (Dawirs et al. 1998). Similarly, the number of 14-day-old BrdU-labeled granule cells was larger in the dorsal hippocampus than in the ventral hippocampus in adult male C57BL/6J mice (Ferland et al. 2002). In agreement with these studies, our recent study has shown

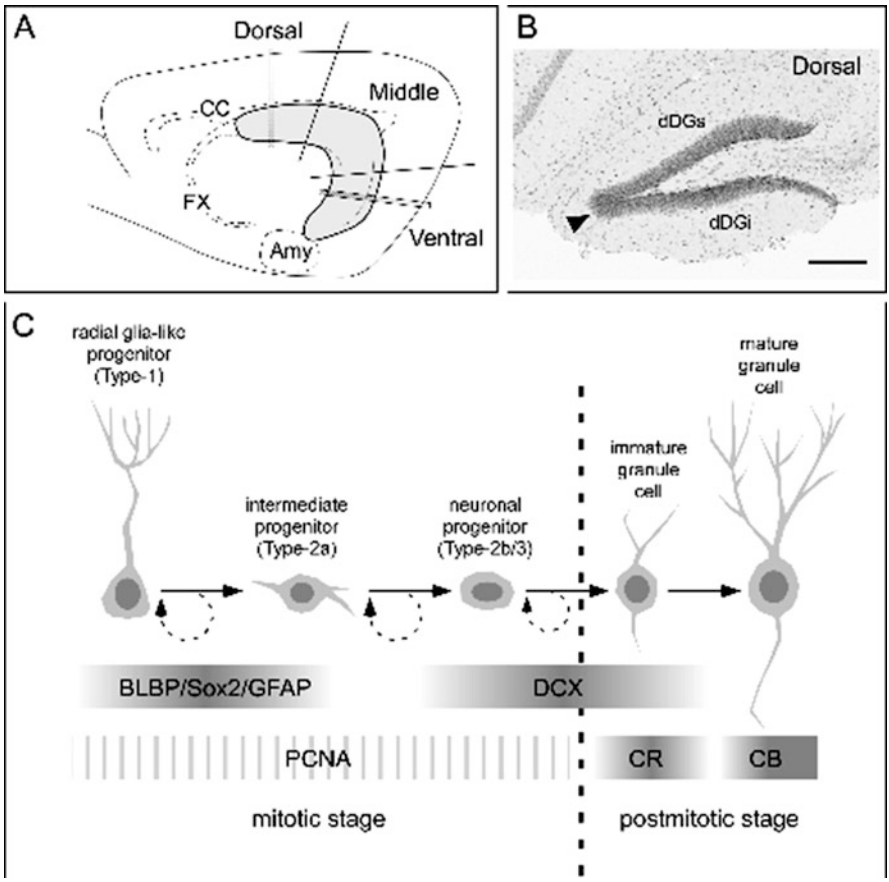

Fig. 14.1 Topography of the rodent hippocampus and endogenous markers of the adult neurogenesis. (**a**) The hippocampus (*shaded*) can be divided into the dorsal, middle and ventral regions according to the longitudinal axis. (**b**) Inverted image of 4′,6-Diamidino-2-phenylindole, dihydrochloride (DAPI)-stained transverse section of the dorsal DG. *Arrowhead* indicates the crescent. (**c**) Stages and endogenous markers of the adult neurogenesis in the hippocampus. *Scale bar* in **b** = 200 μm (applies to **b**). *Amy* amygdala, *CC* corpus callosum, *dDGi* infrapyramidal blade in dorsal DG, *dDGs* suprapyramidal blade in dorsal DG, *FX* fornix (Modified and reproduced from Jinno (2011a), with permission of the publisher)

that the numerical densities (NDs) of DCX+ NLCs and BLBP+ NSCs are significantly higher in the dorsal DG than in the ventral DG in young adult male C57BL/6J mice (Jinno 2011a). Considering the functional differentiation of the hippocampus, these results suggest that newly generated granule cells may play different roles in regulation of cognition (dorsal) and emotion (ventral).

Currently, functional dissociations along the transverse axis of the hippocampus are less intensively examined, but earlier studies reported some structural differences between two blades in the DG. For instance, the mossy fibers from the

suprapyramidal blade cross directly through the stratum radiatum to reach the distal part of the stratum lucidum, whereas those arising from the infrapyramidal blade travel through the hilus and contact the proximal part of CA3 area in the rat (Claiborne et al. 1986). With regard to the inter-blade differences in the adult neurogenesis, Ambrogini et al. (2000) showed that the number of 15-day-old BrdU+ granule cells was larger in the suprapyramidal blade than in the infrapyramidal blade in rats. Similarly, we have found that the NDs of DCX+ NLCs are relatively higher in the suprapyramidal blade in the dorsal DG (Jinno 2011a). Further research is necessary to tie these findings together and elucidate the functional significance of inter-blade difference in adult neurogenesis.

14.4 Age-Related Changes in Adult Neurogenesis

There is a substantial amount of data showing that the rate of new cell production in the hippocampus radically wanes during aging (Seki and Arai 1995; Cameron and McKay 1999). However, the mechanism underlying age-related decline in adult neurogenesis is still controversial. Namely, Alonso (2001) showed that the reduction of neurogenesis in aged rats was attributable to the decline in proliferation of primary progenitors. Hattiangady and Shetty (2008) also reported that aging did not alter the number of primary progenitors, and suggested that age-related decline might be an outcome of increased quiescence of progenitors in the neurogenic region of the rat hippocampus. By contrast, Olariu et al. (2007) claimed that the decreased neurogenesis in aged rats was attributable to loss of primary progenitor cells. Aizawa et al. (2011) reported that decline in primary progenitors defined by Sox2, GFAP, and BLBP expression was specific for aged primates, and there were no alterations in the number of these cells in aged (2-year-old) ICR mice. Walter et al. (2011) reported that age-related reduction in proliferation was not only caused by a general reduction in total number of progenitor subtypes but also by a subtype-specific alteration of the proliferation rate.

In our recent study (Jinno 2011b), we examined the age-related differences in adult neurogenesis between young adult (2-month-old) and middle-aged (10-month-old) mice using endogenous markers (see, Fig. 14.2). The age-related reductions in BLBP+ NSCs were significantly larger in the ventral DG (76 % decrease) than in the dorsal DG (56 % decrease). The age-related reductions in DCX+ NLCs were more drastic than those of NSCs accompanying with a similar dorsoventral gradient: the ventral DG (95 % decrease), dorsal DG (91 % decrease). In the field of geriatric psychiatry, major depressive disorder and dementia are common conditions in old age, and frequently occur concurrently (Korczyn and Halperin 2009). These two clinical entities have a very complicated relationship, and accurate mechanisms underlying their co-occurrence are largely unclear. Some studies hypothesize that depressive disorder is a risk factor for developing dementia (Kessing and Nilsson 2003; Ownby et al. 2006), and suggest that depression is an early prodromal phase of dementia state (Schweitzer et al. 2002). Our findings

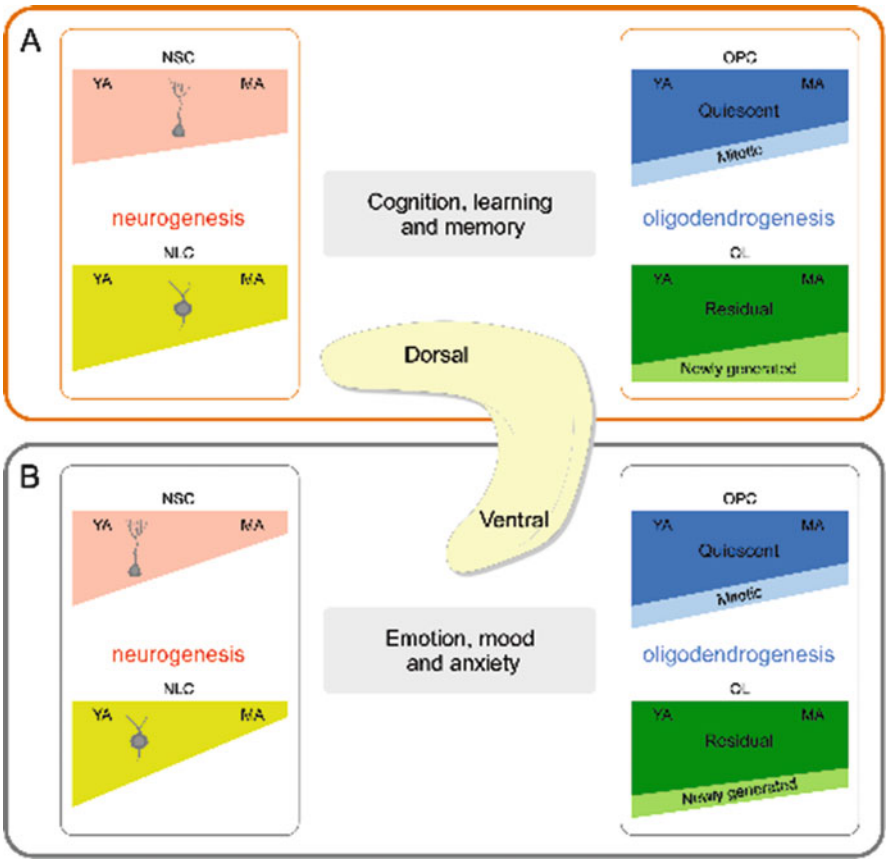

Fig. 14.2 Schematic illustration of the age-related changes in adult neurogenesis and oligodendrogenesis in the rodent hippocampus. (**a**) The dorsal hippocampus is mainly involved in cognition, learning and memory. In this region, the number of NSCs and NLCs halves from YA (young adult) to MA (middle-aged). The number of quiescent OPCs decline with age, and the fraction of mitotic OPCs remains invariant during aging. The number of residual OLs declines with age, while the fraction of newly generated OLs increases during aging. As a result, the number of OLs remain unchanged. (**b**) The hippocampus contributes to the regulation of emotion, mood and anxiety. The number of NSCs and NLCs drops sharply from YA to MA. The number of quiescent OPCs declines with age, and the fraction of mitotic OPCs remains invariant during aging. The number of residual OLs declines with age, and the fraction of newly generated OLs remains unchanged (Modified and reproduced from Jinno (2011b), with permission of the publisher)

indicate that hippocampal neurogenesis wanes faster in the ventral hippocampus than in the dorsal hippocampus during aging. Interestingly, exposure to chronic mild stress results in decreased cell proliferation in the ventral but not in the dorsal hippocampus (Jayatissa et al. 2006). Chronic treatment with agomelatin, an antidepressant, increases neurogenesis only in the ventral DG (Banasr et al. 2006). Together, these findings provide some key to understand why depression frequently precedes dementia in aged people. Future studies addressing this issue will inform

us on how age-related alterations in neurogenesis are involved in late onset depression and dementia.

At this time, only a few attempts have been made at the functional significance of age-related changes in transverse differentiation of the DG. In our study, we have reported that there were no inter-blade differences in neurogenesis in middle-aged (10-month-old) mice (Jinno 2011b), while the number of BLBP+ NLCs and DCX+ NLCs were significantly higher in the suprapyramidal blade than in infrapyramidal blade in young adult (2-month-old) mice (Jinno 2011a). In this regard, there is an interesting report showing that deposition and maturation of granule cells begin near the lateral tip of the suprapyramidal blade and proceed into the infrapyramidal blade, establishing the suprapyramidal to infrapyramidal morphogenic gradient in the DG (Angevine 1965). These results indicate that dentate neurogenesis might be more active in the suprapyramidal blade than in the infrapyramidal blade only during adolescence and young adulthood, and also suggest that larger number of new granule cells in the suprapyramidal blade could be involved in the higher cognitive performance of young animals.

14.5 Oligodendrogenesis and Myelin Homeostasis

Oligodendrocytes (OLs) synthesize myelin, which is required for fast saltatory conduction of nerve impulses. The majority of myelinating OLs are born in the early postnatal period by differentiation of oligodendrocyte precursor cells (OPCs). Recent evidence shows that impaired paranode structure and function can impact neural circuitry, leading to downstream effects related to emotion and potentially to mood regulation in human psychiatric disorders (Edgar and Sibille 2012). Histological analysis using Kluver–Barrera staining method revealed that the staining intensity of deep white matter in the dorsolateral prefrontal cortex was significantly less intense in subjects who suffered from major depression (Regenold et al. 2007). A decrease in OL density has been reported in the frontopolar cortex of major depressive disorder subjects (Hayashi et al. 2011).

In the healthy adult brain, OPCs continue to divide and generate new OLs (Richardson et al. 2011). It has been shown that OPCs express NG2 proteoglycan (so they are also known as NG2 cells) and the platelet-derived growth factor receptor-alpha (PDGFαR). NG2 and PDGFαR play a critical role in proliferation, migration and survival of OPCs (Noble et al. 1988; Barres et al. 1993; Hill et al. 2013; Binamé et al. 2013). Recent studies have indicated that OPCs are not just progenitors, but are also involved in regulation of neuronal circuits, because these cells receive synaptic inputs from neurons and respond to neurotransmitters released at synapses (Bergles et al. 2000; Wigley et al. 2007). Particularly, OPCs have AMPA-type glutamate receptors, which are activated by neural activity (Lin et al. 2005). In addition, OPCs sense fine changes in extracellular K^+ concentrations during physiological neuronal activity (Maldonado et al. 2013). The authors suggest that OPCs possibly remove the excess K^+ caused by neuronal K^+ efflux at

specific sites devoid of astrocytes via Kir4.1 channels. Moreover, OPCs are considered to release soluble factors, which promote neuronal survival, maintain axonal structure, and support synaptic plasticity (Wilkins et al. 2003; Sun et al. 2013). It is conceivable that OPCs sense the "state of health" of their partner neurons over the neuron-glial synapse and respond accordingly by release of neuroprotective substances (Sakry et al. 2011).

14.6 Topography of Age-Related Changes in Hippocampal Oligodendrogenesis

Until now, many papers reported the involvement of microglia and astrocytes in brain aging (Bronson et al. 1993; Sheng et al. 1996; Wu et al. 2005). Recently, age-related changes in OLs have also been well documented. For instance, several studies have shown that abnormalities of OLs and myelin may be involved in age-related cognitive decline (Peters and Kemper 2012; Kohama et al. 2012). The NDs of OLs in the rat hippocampus showed a significant aging-dependent reduction (Tanaka et al. 2005). The intensity of immunostaining for 2′,3′-cyclic nucleotide 3′-phosphodiesterase (a marker of OLs) in the rat hippocampus declined with age (Hayakawa et al. 2007). The number of OLs in the rat subcortical white matter also showed an aging-dependent reduction (Chen et al. 2011). Interestingly, the number of OLs in the mouse anterior commissure began to decline between 9 and 12 months and remained fairly low between 15 and 22 months, before rising sharply to above the 9 month level between 22 and 25 months and thereafter remaining constant (Sturrock 1987). In rhesus monkeys, the number of OLs in the optical nerve showed an age-dependent increase (Sandell and Peters 2002), while there were no significant age-related changes in the number of OLs in the occipital and prefrontal cortices (Peters and Sethares 2002).

In our recent study (Yamada and Jinno 2014), we estimated the age-related changes in oligodendrogenesis of young adult (2-month-old) and middle-aged (10-month-old) mouse hippocampi. To identify OPCs and OLs, we used a set of molecular markers, oligodendrocyte lineage transcription factor (Olig2) and PDGFαR. Intracellular dye injection shows that PDGFαR+/Olig2+ cells and PDGFαR-/Olig2+ cells can be defined as OPCs and OLs, respectively (Fig. 14.3). The quantitative analysis showed that the number of OLs declined with age in the ventral hippocampus, but they were not compromised in the dorsal hippocampus (Fig. 14.2). In this regard, it is necessary to consider two possibilities here. The first is the dorsoventral difference in death of OLs. The vulnerability of OLs increases with increasing age at differentiation as later-differentiating cells myelinate increasing the number of axonal segments (Bartzokis 2004). We thus hypothesized that mature OLs in the hippocampus might be more susceptible to aging in the ventral than the dorsal region. The second is the dorsoventral differences in production of OLs. Differently from neurogenesis, previous studies have shown

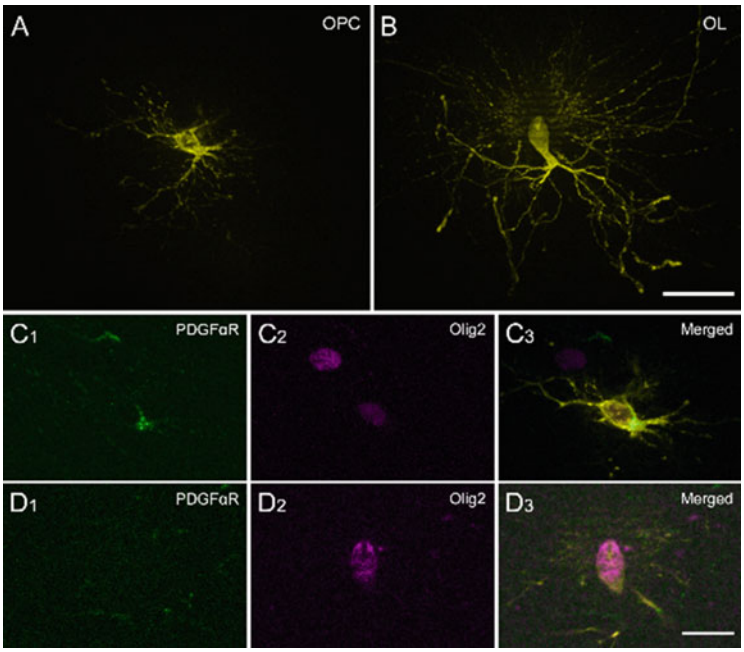

Fig. 14.3 Identification of OPCs and OLs by intracellular labeling and immunostaining for PDGFαR and Olig2 in the hippocampus. (**a**, **b**) Intracellular injection of lucifer yellow (LY) into OPC (**a**) and OL (**b**) in the mouse hippocampus. (**c**) An Olig2+/PDGFαR+ OPC shows short multi-branched processes. (**d**) An Olig2+/PDGFαR- OL shows long extended processes with ramified structure. *Scale bars* in **b** = 20 μm (applies to **a** and **b**), in $\mathbf{d}_3 = 10$ μm (applies to $\mathbf{c}_{1–3}$ and $\mathbf{d}_{1–3}$) (Modified and reproduced from Yamada and Jinno (2014), with permission of the publisher)

the rather controversial effects of aging on oligodendrogenesis. Namely, in the murine spinal cord, oligodendrogenesis was not only preserved, but it also increased during aging (Lasiene et al. 2009). In the rostral migratory stream of mice, the number of proliferative OPCs and new OLs remained unchanged during aging (Capilla-Gonzalez et al. 2013). Here we observed that the number of BrdU+ mitotic OPCs in the Ammon's horn were not compromised with age both in the dorsal and ventral hippocampus. It should also be noted that the number of BrdU+ newly generated OLs in the Ammon's horn significantly increased with age in the dorsal hippocampus, but remained unchanged in the ventral hippocampus. Together, these findings suggest that the number of OLs in the dorsal Ammon's horn may be compensatory maintained by increased generation of OLs.

14.7 Conclusion

Despite the increased number of publications in the field of gerontology, age-related changes in the topography of the hippocampus still remains largely unanswered. As this review summarizes here, the waning of adult neurogenesis and oligodendrogenesis during aging is more relevant in the ventral hippocampus than in the dorsal hippocampus. Because the ventral hippocampus mainly contributes to regulation of emotion, while the dorsal hippocampus has a preferential role in memory, these findings may provide some key to understanding various psychiatric problems seen in elderly people without dementia.

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