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Aging affects new cell production in the adult hippocampus: A quantitative anatomic review

Shozo Jinno *

Department of Anatomy and Neuroscience, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

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ABSTRACT

In the last century, cognitive impairment in elderly people was considered as the consequence of neuronal death. However, later analyses indicated that age-related reduction in neuron number was limited to specific regions of the central nervous system, and was irrelevant to brain dysfunction in both humans and non-human animals. Recent studies have indicated that progressive diminution of neural plasticity across an individual's life span may underlie age-related brain dysfunction. To date, various factors have been shown to contribute to neural plasticity. In particular, substantial data supports the importance of production of new cells in the adult brain: the rate of hippocampal neurogenesis wanes radically during aging; similarly, white matter homeostasis via oligodendrogenesis is also affected by aging. This review briefly summarizes quantitative studies on adult hippocampal neurogenesis and oligodendrogenesis. Although the hippocampus is traditionally recognized as the memory center of the brain, it has started to emerge as an integrator of cognition and emotion. One of the current research highlights is that diverse functions of the hippocampus are topographically embedded along its longitudinal and transverse axes. Here we discuss alterations in adult neurogenesis and oligodendrogenesis during aging from a topographic view point. The quantitative anatomic approach to age-related alterations in production of new cells in the hippocampus may give a novel insight into how brain functions suffer from aging.

1. Introduction

In the last century, irreversible reduction in the number of neurons during aging was investigated intensely, and numerous studies reported significant neuronal loss in various regions of the aged brain (Brody, 1955). At that time, cognitive impairment in elderly people was considered as the consequence of neuronal death. However, recent studies indicated that neurodegeneration related to healthy aging is limited to specific regions of the aged brain, and the rate of neuronal loss is insignificant (probably no more than 10%) in both humans and non-human mammals (Curcio and Coleman, 1982; Pakkenberg and Gundersen, 1997; Peters and Sethares, 1993). Considering that the variance of neuron numbers in humans with normal cognitive functions is quite large, a non-ubiquitous 10% loss in neurons may not be a significant factor causing cognitive dysfunction in older people (Pannese, 2011).

Recent studies have indicated that progressive diminution in neural plasticity across an individual's life span may underlie cognitive decline in elderly people (Freitas et al., 2013). Although various factors are involved in regulation of neural plasticity, this review will focus on new cell production in the hippocampus. Substantial data shows that the number of adult-born granule cells in the hippocampus wanes radically during aging (Merkley et al., 2014). It has been suggested that age-related decline in adult neurogenesis is involved in downstream cognitive processes during aging (Artegiani and Calegari, 2012). Oligodendrogenesis is also affected by aging, and white matter lesion observed in aging is considered to be one of the main causes for cognitive impairment (Miyamoto et al., 2013; Shibata et al., 2004; Sim et al., 2002).

Although the hippocampus is traditionally recognized as the memory center of the brain, it has started to emerge as an integrator of cognition and emotion (Femenia et al., 2012; Small et al., 2011). One of the current research highlights is that diverse functions of the hippocampus are topographically embedded along its longitudinal (dorsoventral) and transverse axes (Strange et al., 2014). Here we briefly summarize quantitative and anatomic studies on the neurogenesis and oligodendrogenesis of the hippocampus, and then discuss how alterations in new cell production may cause age-related brain deterioration.

* Corresponding author. Tel.: +81 92 642 6051; fax: +81 92 642 6202.
E-mail address: sjnno@med.kyushu-u.ac.jp

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2. Topographic differentiation of the hippocampus

The rodent hippocampus extends in a C-shaped fashion from the septal nuclei of the basal forebrain to the amygdalar region. Importantly, the structure and function of the hippocampus are divided along its longitudinal and transverse axes (Fanselow and Dong, 2010; Strange et al., 2014). In the early 1970s, Andersen and colleagues proposed that the principal excitatory pathway of the hippocampal formation is organized along the transverse axis in a lamellar fashion (Andersen et al., 1971). The trisynaptic circuit from the entorhinal cortex, through the dentate gyrus (DG) and CA3 area to CA1 area, has long been assumed, often tacitly, to be the major information-processing route in the hippocampus (Bliss and Lomo, 1973; Malenka and Nicoll, 1999). The functional differentiation of the hippocampus along the transverse axis has been well described: the DG has a role in pattern separation, the CA1 area is important in input integration, and the CA3 area is crucial for pattern completion (Small et al., 2011).

The longitudinal axis of the rodent hippocampus is often referred to as the dorsoventral (or septotemporal) axis, which is analogous to the primate anteroposterior axis. Anatomical differentiation of the rodent hippocampus along the dorsoventral axis has been reported since the 1970s (Gaarskjaer, 1978). The dorsal DG receives afferents from both the lateral and medial entorhinal cortex, whereas the ventral DG receives projections from the medial entorhinal cortex (Witter et al., 1989). Massive projections are sent from the dorsal hippocampus to the retrosplenial cortex and mammillary complex (Ishizuka, 2001; Van Groen and Wyss, 2003). There are intimate connections between the ventral hippocampus and the amygdala, medial prefrontal cortex, nucleus accumbens, and hypothalamus (Arszovszki et al., 2014; Chiba, 2000; Fanselow and Dong, 2010; Hoover and Vertes, 2007; Pitkanen et al., 2000). In a series of our quantitative anatomic studies, we have reported various dorsoventral gradients in the numerical density (ND) of eight subtypes of chemically defined GABAergic neurons in the hippocampus of C57BL/6J mice (Jinno et al., 1999; Jinno and Kosaka, 2000, 2002, 2003, 2006). Briefly, the ND of GABAergic neurons was generally higher in the ventral region than in the dorsal regions. Significant dorsoventral differences were seen in GABAergic neurons labeled by calretinin (CR), calbindin D28K (CB), somatostatin, cholecystokinin, vasoactive intestinal protein, and nitric oxide synthase. We also examined the dorsoventral differences in the ND of glutamatergic neurons in the hippocampus C57BL/6J mice (Jinno and Kosaka, 2010). In the CA1 area, the ND pyramidal neurons was almost three times higher in the dorsal region than in the ventral region, In the CA3 area, there were no significant dorsoventral differences in the ND of pyramidal neurons. In the dentate gyrus, the ND of granule cells was significantly higher in the dorsal region than in the ventral region. These results provide an essential anatomic basis for elucidating mechanisms of distinct neural circuits underlying various hippocampal functions.

It has also been shown that the hippocampus is functionally differentiated along its longitudinal axis. For instance, injuries in the dorsal hippocampus impair spatial learning (Moser et al., 1993), while lesions of the ventral hippocampus affect the anxiety-related behavior, and have no effect on spatial learning (Bannerman et al., 2003). Genes expressed in the dorsal and ventral hippocampus are associated with the brain regions involved in cognitive information processing and emotional behaviors, respectively (Dong et al., 2009). Together, the dorsal hippocampus plays a preferential role in cognition and memory (Cholvin et al., 2014), and the ventral hippocampus regulates emotion (Schoenfeld et al., 2014). Additionally, differentiation of the hippocampus is evolutionarily conserved in rodents, monkeys (Colombo et al., 1998), and humans (Small et al., 2011).

3. Stereological estimation of the cytoarchitecture of the hippocampus

Since 1998, we have reported the ND of various neurons and glial cells in the mouse hippocampus using the optical disector, an unbiased stereological sampling method. Originally, the term "stereology" was coined to describe a set of methods that provide a three-dimensional interpretation of the structure based on two-dimensional sections (Haug, 1986). As reported previously, the chief problem of a conventional quantitative approach is that the detection efficiency of objects is related to their size, shape and spatial orientations (Sterio, 1984). For instance, larger objects are potentially counted more frequently than smaller ones, and such sampling biases are usually uncorrectable. However, the use of the optical disector enables an accurate sampling that will not be biased by differences in shape, size and spatial orientations of the objects (Mayhew and Gundersen, 1996). Because the ND is affected by the tissue shrinkage, all ND data shown in our papers are carefully corrected by estimating the volume of samples before and after the immunoprocessing (Jinno et al., 1998; Schmitz and Hof, 2005).

It has been repeatedly emphasized that estimation of the ND of synapses and neurons does not make sense for evaluation of the differences that are related to development, aging, stress, trauma, etc (West et al., 1991). The reason is that the ND is affected by potential volume changes that are often accompanied by such events. Instead of the ND, estimation of the total number of structural entities is recommended in such cases. However, the aim of our studies is to evaluate the potential dorsoventral and transverse differences in the cytoarchitecture of the hippocampus, which cannot be deduced from the total numbers of various types of cells in the hippocampus. Therefore, we consider that estimation of the ND of neurons and glias gives meaningful results.

In the field of neuroscience, 300–400-μm-thick transverse hippocampal slices are widely used to obtain physiological data, because they are considered to preserve the normal lamellar organization of the hippocampus to some extent. To help interpretation of the modern multidisciplinary studies using hippocampal slices, we have calculated the numbers of GABAergic and glutamatergic neurons in a 300-μm-thick virtual hippocampal slice (Jinno and Kosaka, 2006, 2010). In addition, potential age-related anatomic changes of the brain e.g., shrinkage, hypertrophy, transformation (Long et al., 1999), can be reflected in the virtual hippocampal slice to a certain degree. Therefore, we assume that the cell numbers in a virtual hippocampal slice will be helpful for evaluating age-related alterations in neurogenesis and oligodendrogenesis (Jinno, 2011b; Yamada and Jinno, 2014).

4. Age-related alterations in the adult hippocampal neurogenesis

4.1. Topography of the hippocampal neurogenesis

Throughout adulthood, production of new granule cells continues in the subgranular zone of the DG (Altman and Das, 1967; Cameron et al., 1993; Kaplan and Hinds, 1977). Recent studies indicated that adult-born granule cells contribute to various hippocampal functions (Balu and Lucki, 2009). Inhibition of proliferation impairs the learning of hippocampus-dependent spatial memory tasks (Shors et al., 2001). Addition and removal of granule cells in the DG influence spatial learning and memory (Drapeau et al., 2003; Dupret et al., 2007; Farioli-Vecchioli et al., 2008; Richetin et al., 2015). Experience-induced alterations in production of new granule cells may fine-tune the hippocampus to a predicted environment (Opendak and Gould, 2015).

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