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Review Article

The effects of aging in the hippocampus and cognitive decline

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ABSTRACT

Aging is a natural process that is associated with cognitive decline as well as functional and social impairments. One structure of particular interest when considering aging and cognitive decline is the hippocampus, a brain region known to play an important role in learning and memory consolidation as well as in affective behaviours and mood regulation, and where both functional and structural plasticity (e.g., neurogenesis) occur well into adulthood. Neurobiological alterations seen in the aging hippocampus including increased oxidative stress and neuroinflammation, altered intracellular signalling and gene expression, as well as reduced neurogenesis and synaptic plasticity, are thought to be associated with age-related cognitive decline. Non-invasive strategies such as caloric restriction, physical exercise, and environmental enrichment have been shown to counteract many of the age-induced alterations in hippocampal signalling, structure, and function. Thus, such approaches may have therapeutic value in counteracting the deleterious effects of aging and protecting the brain against age-associated neurodegenerative processes.

1. Introduction

Aging is a natural biological process that is associated with physiological decline – both physically and cognitively. Cognitive decline, in particular, can impair one's quality of life and is shown to occur both in normal aging and pathological conditions, such as neurodegenerative diseases. With normal aging, cognitive decline can present as deficits in certain domains including episodic (or declarative) memory, spatial learning, working memory, and attention (Kausler, 1994). However, there are substantial differences between individuals in the manifestation of this decline due to variability in resilience and cognitive reserve. This includes factors such as education, intelligence, and mental stimulation, which allow the brain to adapt to pathological damage and maintain cognitive function. Aging is also associated with various debilitating neurodegenerative conditions, the most common being Alzheimer's Disease (AD). Due to advances in health care and the resulting increase in life expectancy of the population as well as the lack of an effective treatment, the prevalence of neurodegenerative diseases is increasing and imposing a significant burden on the population.

The hippocampus is found deep within the medial temporal lobe of the brain, being part of the limbic system. Its main roles include consolidation of declarative (episodic) memories and context-dependent spatial learning, as well as the regulation of emotional behaviors (El-Falougy and Benuska, 2006). Of note, some *in vivo* studies have demonstrated functional localization along the longitudinal axis of the rodent hippocampus, where lesions to the anterior hippocampus impair spatial learning, while lesions to the posterior aspect of this structure impair fear-conditioning and anxiety-related behaviors (Bannerman et al., 2002). The structural and functional integrity of the hippocampus is crucial for normal learning and memory consolidation, and this structure is particularly vulnerable to the aging process (Geinisman et al., 1995). Previous research has also demonstrated that structural

Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPK, AMP-activated kinase; APOE, apolipoprotein; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CA, Cornu Ammonis; CNS, central nervous system; CR, calorie restriction; CRM, calorie restriction mimetics; DCX, doublecortin; DG, dentate gyrus; ECM, extracellular matrix; Egr1, early growth response 1; FGF-2, fibroblast growth factor-2; FOXO, forkhead box O; GR, glucocorticoid receptor; HPA, hypothalamus-pituitary-adrenal; IEG, immediate-early gene; IF, intermittent fasting; IGF-1, insulin growth factor-1; IL-1β, interleukin-1β; IL-6, interleukin-6; LTD, long-term depression; LTP, long-term potentiation; MR, mineralocorticoid receptor; MRI, magnetic resonance imaging; NAD^+, nicotinamide adenine dinucleotide; NF-κB, nuclear factor-kappa B; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; NSC, neural stem cell; pRB, retinoblastoma protein; PSD-95, postsynaptic density protein 95; RNS, reactive nitrogen species; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SC, senescent cell; SGZ, subgranular zone; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor

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and functional changes to the hippocampus are related to the severity and development of neurodegenerative disorders associated with cognitive decline. In fact, many of the cognitive deficits seen with aging can be mirrored in animal models that have bilateral hippocampal damage (Geinisman et al., 1995), which further supports the key role of the hippocampus in aging and cognition. The present review summarizes the most relevant mechanisms contributing to age-related hippocampal dysfunction and cognitive decline, and discusses possible interventions that can be employed to delay the onset of hippocampal dysfunction.

2. Alterations in hippocampal volume with age

The hippocampus undergoes several structural changes both grossly and at the cellular level with aging, and these have been correlated with cognitive decline in both animals and humans. In support of this idea, a correlation between age-related decline in hippocampal-dependent learning and memory and a reduction in hippocampal volume has been observed in female rats (Driscoll et al., 2006). In this study, young-adult (3 months of age), middle-aged (12 months of age), and old (24 months of age) female rats were tested for hippocampal-dependent memory (assessed with the Morris water maze and the transverse pattern learning tests), as well as hippocampal-independent memory (assessed with a visual discrimination task). As expected, an age-dependent deficit in spatial memory formation and overall hippocampal-dependent memory was found, with deficits in these cognitive functions being specifically observed in both middle-aged and old rats. Furthermore, an overall decrease in hippocampal volume was found in the 24-month old age group, further supporting the putative relationship between hippocampal volume and hippocampal-dependent cognitive functioning. However, contradictory findings have also been reported. For example, a longitudinal study failed to detect significant changes in hippocampal size with magnetic resonance imaging (MRI) in wild-type mice from 6 to 14 months of age (Maheswaran et al., 2009). Although the results from this study do not exclude the possibility that changes in hippocampal volume could still be detected in mice older than 14 months of age, a different study that compared 8- and 21–26-month old male mice observed only a small but insignificant decrease in hippocampal volume with age, although an increase in axonal degeneration in the hippocampus was noted with age (Von Bohlen und Halbach and Unsicker, 2002). Although the reasons for the discrepancies regarding changes in hippocampal volume with age that have been reported in the literature are still not fully understood, they may be related, at least in part, with differences between species (rats versus mice) and age windows investigated, as well as with variability in hippocampal sizes between samples and heterogeneity of age-related changes in various hippocampal sub-regions (Driscoll et al., 2006).

Contradictory results have also been found in human studies. For example, hippocampal-dependent memory and learning deficits (as assessed with hippocampal-dependent tasks such as the virtual water maze test and the transverse pattern discrimination task) have been specifically detected in elderly subjects when compared with their young counterparts and appear to be correlated with a bilateral reduction in hippocampal volume in the elderly (as assessed by MRI) (Driscoll et al., 2003). In agreement, a longitudinal study has shown that an age-related reduction in hippocampal volume and activity (demonstrated by structural and functional MRI) were correlated with decreased performance in episodic memory tasks over a course of two decades (Persson et al., 2012). However, it is also possible that this reduction in hippocampal activity with age may actually be associated with the fact that older adults may rely less in spatial strategies (and therefore the hippocampus) to solve these tasks, and instead utilize other brain structures, as noted by an increase in the activity of the caudate nucleus with age (Konishi et al., 2013).

Of note, while several cross-sectional studies further support this age-related hippocampal atrophy (Mu et al., 1999; Raz et al., 2004a; Schuff et al., 1999; Walhovd et al., 2005), some have found no significant changes in hippocampal volume with age (Du et al., 2006; Sullivan et al., 1995), and one study only observed a significant reduction in men (Pruessner et al., 2001). Other reports have also failed to demonstrate a clear association between structural and functional hippocampal changes and memory decline with age (Persson et al., 2012; Spreng et al., 2010). As cross-sectional studies are associated with several confounding variables such as heterogeneity of early-life hippocampal volume, greater reliability and consistency of results can be attained using longitudinal studies. In a five-year longitudinal study, where MRIs were conducted on individuals ranging from 26 to 82 years of age, a modest reduction in hippocampal volume was noted in individuals under 50 years of age, whereas as a dramatic volume loss of approximately 1.2% per year was found in individuals over the age of 50 (Raz et al., 2004b). In a different longitudinal study, a non-linear and accelerated shrinkage of the various hippocampal subregions including the *Cornu Ammonis* (CA) 1–4, subiculum, and dentate gyrus (DG) was found to occur in participants older than 49 years of age over a period of 30 months (Raz et al., 2010).

Interestingly, there is also some controversy with regards to the portion of the hippocampus (anterior versus posterior) that is mostly affected with age. Thus, while Driscoll et al. (2003) has shown that the anterior hippocampus was significantly larger than the posterior hippocampus, postulating that the anterior hippocampus may be more resilient to the effects of aging, in a more recent study, a greater age-related decline in hippocampal volume was seen in the anterior part (i.e., the head and body of the hippocampus), when compared with the posterior tail of this structure (Gordon et al., 2013). These authors proposed that the observed age-related atrophy of the anterior hippocampus may be a result of the anterior hippocampus having more connectivity to the subcortical and hypothalamic nuclei, thus being subjected to the effects of stress hormones and alterations of the hypothalamic-pituitary axis (Gordon et al., 2013).

3. Structural changes in the hippocampus with age

One of the reasons underlying the age-related decrease in hippocampal volume may be the neuronal loss that occurs in this brain structure during the aging process. In agreement with the idea of hippocampal atrophy with age, a significant decrease in the numbers of both NeuN-positive neurons and non-neuronal cells was found in the hippocampus of 25-month old female mice when compared with their 7-month old counterparts (Fu et al., 2015). Similarly, in humans an age-related reduction in the hippocampal levels of the neuronal metabolite *N*-acetylaspartate (NAA) was seen (Driscoll et al., 2003; Schuff et al., 1999), being suggestive of hippocampal neuronal loss in the elderly.

An alternate or complementary process that may contribute to the age-related decrease in hippocampal volume is a potential decrease in neuronal production or neurogenesis with age. Indeed, the sub-granular zone (SGZ) of the hippocampal DG is one of the two regions in the adult brain that retains the capacity to produce neurons throughout adulthood (for review see Lie et al., 2004). These newborn neurons are generated in the SGZ and migrate to the DG granule cell layer, where they undergo dendritic arborization and integrate into existing neuronal circuitries, thus contributing to the functioning of the hippocampus (Bruel-Jungerman et al., 2007; Cameron et al., 1993). The occurrence of adult neurogenesis in the human DG was first confirmed by a study that used *post-mortem* tissue obtained from cancer patients that had received 5-bromo-2′-deoxyuridine (BrdU; a synthetic thymidine analogue that incorporates into the DNA of dividing cells) for diagnostic purposes (Eriksson et al., 1998). More recently, a study that investigated individuals that had been exposed to elevated atmospheric levels of the radioactive carbon-14 isotope (^{14}C) provided further evidence for a high turn-over of neurons in the human hippocampus (Spalding et al., 2013). The results from this study demonstrated that the adult human hippocampus is able to generate approximately 700 new neurons/day