Microglia in the normally aged hippocampus

Jung Hoon Choi¹, Moo-Ho Won²*

¹Department of Anatomy, College of Veterinary Medicine, Kangwon National University, Chuncheon, Korea
²Department of Neurobiology, School of Medicine, Kangwon National University, Chuncheon, Korea

The hippocampus plays important roles in the regulation and combination of short and long term memory and spatial navigation with other brain centers. Aging is accompanied by a functional decline of the hippocampus and degenerative disease. Microglia are major immune cells in the central nervous system and response to degenerative changes in the aged brain. In this respect, functional and morphological changes of the hippocampus have been closely related to microglial changes during normal aging with or without disease. Therefore, in this review, we discuss morphological and functional changes of the hippocampus and microglia in the aging brain.

Key words: Aging, brain, memory, immune cells

Aging is accepted worldwide in social and political agendas as well as in research agendas. Functional declines in various organ systems including the central nervous system (CNS) are associated with normal aging processes. Aging in the brain is a major risk factor for increases in neurodegenerative diseases such as Alzheimer’s and Parkinson’s diseases [1,2]. Most functional changes in the CNS with normal aging are associated with a decline in learning and memory. It is well accepted that the hippocampus is a very important region related to learning and memory because the hippocampus is connected to other brain regions that are related to learning and memory [3-6]. The hippocampus is also known as the most vulnerable region affected by the internal and external changes of normal aging, and with strokes and other neurodegenerative diseases [7-10]. The functional decline of the CNS, including the hippocampus, with normal aging and degenerative processes is accompanied by changes in the number and function of neurons and glia, their volumes, and various factors such as neurotransmitters, hormones, oxidative stress and inflammation [2,11,12].

There is no doubt that microglial change in the CNS is associated primarily or secondarily with neurodegenerative diseases in the aged brain [13,14]. Microglia, which are immune cells, account for 5-20% of the total glial cell population in the CNS and are evenly distributed throughout the brain parenchyma. They respond rapidly to a variety of alterations in the microenvironment of the brain and act as a sensor for pathological events in the brain [15,16]. Numerous studies and reviews have reported that numerical, morphological and functional changes in microglia are apparently changed in the normal aging brain and in the aged brain with diseases [1,2,6,12,17-21]. In this review, we discuss the literature on age-related changes in microglia in the hippocampus.

Structure and Function of the Hippocampus

The hippocampus is one of the oldest brain regions phylogenetically. It consists of two major parts: the hippocampus proper (Ammon’s horn or cornu ammonis, CA) and the dentate gyrus (DG). The hippocampus proper contains three sub-regions (regions CA1-CA3), and each subregion consists of 3 distinct layers: stratum oriens (SO), stratum
pyramidale (SP) and stratum radiate (SR) (from the outermost to the innermost). Main excitatory output neurons referred to as pyramidal neurons are located in the SP [22]. The hippocampus is involved in various physiological functions such as olfaction, arousal, cognition, learning and memory [4,23,24].

Extensive work on hippocampal function associated with memory is still ongoing [25-28]. Although controversy on the exact functional role of the hippocampal sub-region is ongoing, the CA1 region appears to be related with the association and completion of temporal patterns as well as intermediate-term memory. The CA3 region mediates processes related with spatial pattern association and completion as well as short-term memory [4,26,28-31]. Although the DG is a main subregion of the hippocampus, its function also needs to be studied more; the DG is involved in metric spatial representation and spatial pattern separation [23,24,28].

Aging Hippocampus

Age-related losses of hippocampal volume and neuronal number in the aged hippocampus have been reported [7,18,32-35]. Early studies showed that a significant neuronal loss in the CA1 region is correlated with aging in the human hippocampus, not in other hippocampal regions [32,36]. In addition, pyramidal neurons are significantly decreased in the SP of the CA1 and CA3 regions of the hippocampus in both cognitively impaired and unimpaired rats [33]. Later, however, the same researchers and others reported that the number of hippocampal neurons with aging is relatively persistent in primates and rodents during normal aging using different methods [7,34,35]. These studies proposed that early studies, which showed that neuronal loss happens in the aged hippocampus, had some errors in their methods, sampling and pathological conditions. Many other researchers have confirmed that neuronal loss in the normally aged hippocampus is not characteristic of this brain region [5,37-39]. However, a marked neuronal loss in the aged hippocampus occurs in some degenerative conditions such as Alzheimer’s disease and experimental autoimmune encephalomyelitis [5,7,10,32,40].

On the other hand, a reduction in hippocampal volume with aging has been found in primates and rodents using histological studies [30,31,41]. Recently, many researchers have confirmed age-related decreases in the volume of the hippocampus using magnetic resonance imaging in primates and rodents [42-44]. Nowadays, therefore, it is well accepted that normal aging is accompanied by hippocampal shrinkage, and hippocampal shrinkage is closely related to functional decline in learning and memory in the aged brain. Various groups have tried to elucidate substrates of age-related hippocampal learning and memory deficits and have focused on neurobiological alterations as follows.

One of major finding in the literature is a change in synaptic plasticity of hippocampal neurons that present as long term potentiation and long term depression. It has been reported that no significant changes in dendritic regression are observed in the CA regions and subiculum, and, in the DG, dendritic extent is increased in the aged rat and human [45-47]. In addition, the spinal density of hippocampal neurons in the DG and CA1 region is not significantly changed in the aged human and rat [46,48,49]. Furthermore, biophysical properties of CA pyramidal cells or DG granule cells are mostly preserved in the normally aging hippocampus compared to those in the young hippocampus [6,18,50]. However, perforating synaptic contacts, especially presynaptic fibers, decrease in the DG of aged rats [51,52]. In addition, the density of fragmented axons, which project from various brain regions into the hippocampus, increases in the aged hippocampus [53].

On the other hand, there are many studies that show that noradrenergic, dopaminergic, serotonergic and cholinergic projecting fibers decrease in the aging hippocampus [29,54-56]. Other studies have focused on changes in the aged hippocampus in cellular substrates such as ions, hormones, neurotrophic factors and biomolecules. A role for glucocorticoids in neuronal aging in the hippocampus (the glucocorticoid cascade hypothesis) has been suggested by some researchers [9,57,58]. Starting with these studies, extensive studies have shown that, in the aging hippocampus, glucocorticoids and stress contribute to learning and memory function deficits in the aging hippocampus [19,21,59].

Many researchers have found correlations of hippocampal functional decline with changes in ions such as calcium, potassium and magnesium conductance in aged neurons [60,61]. For example, calcium conduction and the number of L-type calcium channels increase significantly in hippocampal CA1 and CA3 neurons of the aged rat and rabbit [62-65]. Other studies have reported that magnesium deficiency in the aged hippocampus impairs learning and memory function [66-68]. These studies suggest that the dysregulation of cation homeostasis might be a major cause of deficits in learning and memory in the aged hippocampus.

Brain-derived neurotrophic factor (BDNF) is implicated in age-related hippocampal function [69]. Many studies have reported that BDNF and the BDNF-TrkB system decrease with aging in human, monkey and rodent hippocampus [70-72]. The decline of BDNF levels in the hippocampus can cause an impairment in long-term potentiation in the aged
Microglia in the Aging Hippocampus

In the CNS, microglia are classified into ameboid, intermediate, ramified (resting), activated and phagocytic, depending on their morphology under normal and disease conditions [76-78]. During early postnatal development, ameboid microglia migrate and proliferate in the brain parenchyma, and are transformed into ramified microglia in the adult brain by transforming into intermediate microglia with elongated process or pseudopodia. Ramified microglia are known as resting microglia and have a small oval soma with numerous branched processes. These spread throughout the entire brain and play an important role in brain homeostasis under normal conditions. Ramified microglia are transformed into activated microglia and/or phagocytic microglia via reactive or primed microglia in response to certain pathological conditions such as traumatic injury, ischemia and Alzheimer’s disease (AD), which are accompanied by inflammation [8,13,77,79-82].

The hippocampus is one region of the brain where dense microglia present, like the olfactory bulb, telencephalon, basal ganglia and substantia nigra [15]. Studies on the regional distribution of microglia between various brain regions are limited, and results are controversial [15,83-88]. An early study reported that in the adult mouse hippocampus F4/80-immunoreactive microglia in the DG are more numerous than in Ammon’s horn [15]. Recently, the microglial distribution in the hippocampus has been reported using different stereological methods [83-86]. These studies show that microglial density in the CA1 region is higher than in the DG, although the total microgyc number is also different. Using immunohistochemistry with ionized calcium-binding adapter molecule 1, Jino et al (2007) found that in the mouse hippocampus microglial density in the CA3 region is lower than in the CA1 region and the DG, and the density of microglia in the CA1 is higher than in the DG [87]. They suggested that microglial density might be involved in site-specific vulnerability of the hippocampus, and that the heterogeneous distribution of microglia would participate in the modulation of hippocampal neuronal activity [88].

Microglia in the Aging Hippocampus

Only a small number of studies have focused on microglial distribution and total number in the hippocampus using stereological methods [89-92], although a large number of studies have been conducted in other brain regions under normal and abnormal conditions. No age-related differences in microglia were found in the aging hippocampus of male mice [89,90]. However, the same research team reported that the number of microglia is significantly increased in the hippocampus of the same mouse strain [90]. In contrast, some researchers found that the number of microglia is decreased in the aged hippocampal CA1 region of the ICR mouse [91,92]. This discrepancy may be due to different animals or strains, markers for microglia and stereological methods.

Although there is a lack of detailed studies on changes in microglial number with aging, the change must be related with functional changes with age. Actually, many studies show that morphology and/or antigen expression in microglia are changed in the aged hippocampus as well as in other brain regions [8,82,92-98]. It is well known that the resting form of microglia is transformed into the activated form of microglia with aging [96,97]. Many studies have shown that the activated form of microglia is increased in number in the aged monkey, dog and rodent hippocampus as well as in the human hippocampus [8,82,92-95]. These activated microglia show high elevations of various antigens such as major histocompatibility complex (MHC) antigens, interleukin-1α (IL-1α), MHC class II cell surface receptor, Iba-1 and lectin in the hippocampus [8,82,94,98,99].

Recently, a large number of studies on functional changes in adult and aged microglia have been conducted with primed microglia. The primed microglia, which was introduced by Perry, have shortened processes with surface antigens such as MHC II similar to those in activated microglia, and the primed microglia are devoid of the ability to secrete pro-inflammatory cytokines in the CNS [79-81]. Along with the primed microglia concept, it has been suggested that the functions of adult and aged microglia are different under normal and pathological conditions [17,20,79,100,101]. Microglia cultured from aged brains express high basal IL-6, and microglia more highly express IL-6 as well as IL-1β after lipopolysaccharide treatment compared to microglia cultured from adult brain [102,103]. In addition, aged microglia show an exaggerated response to systemic inflammation [79,100,101]: microglia in adult animal models of some types
of inflammation produce an increase in anti-inflammatory cytokines and fewer inflammatory cytokines. However, microglia in middle-aged animals show a reversed production of anti-inflammatory and inflammatory cytokines [103-105]. Consistent with these studies, emerging evidence suggests that hippocampal functions after systemic infection are accompanied by an increase in microglia activation, which are more easily disrupted in aged rodents [98,100,103,105, 106]. Nevertheless, many researchers agree we still need to examine further specific markers, methods and criteria to define primed microglia and activated microglia as well as resting microglia, because the morphology of primed microglia show some features similar to activated microglia. In addition, resting microglia and activated or phagocytic microglia also express MHC II and Iba-1 in normal and pathological conditions.

Microglial senescence represents a dystrophy with aging [107]. In an in vitro study, was reported that morphological degeneration of cultured microglia occurs after expose to amyloid beta protein [108]. Streit and his colleague reported that dystrophic microglia show a loss of fine branches (deramification), shortened tortuous processes or cytoplasmic fragmentation except for spheroid cytoplasm in the aged human brain. They suggested that microglial dystrophy is a sign of microglial senescence [107,109]. In addition, they suggested, based on their data, that neurodegeneration may occur secondarily after microglial senescence and that neurodegeneration is associated with a loss of microglial neuroprotective function. They also showed that dystrophic (senescent) microglia rather than activated microglia likely precede neurodegeneration in Alzheimer's disease [110]. In addition, abnormal and degenerating microglia are detected in other neurodegenerative diseases including amyotrophic lateral sclerosis, Creutzfeldt–Jakob disease, Huntington's disease and schizophrenia [111-113]. They also suggested that an increase in the number of activated microglia in the brain with aging and neurodegenerative disease must be reconsidered, because dystrophic microglia might have been misidentified as activated microglia in previous studies. Other groups have consistently provided evidence that microglial senescence produces a shortened telomere and a decrease in their activities in aging and neurodegenerative disease [114-117]. However, to the best of our knowledge, there is no study that has focused in detail on dystrophic changes of microglia in the hippocampal subregions with normal aging, although some studies have shown dystrophic changes in microglia in the parahippocampal cortex [107,110,115,117]. Further studies on the stereological classification of microglia combined with primed and dystrophic microglia could identify the region-specific functions of microglia in the aged hippocampus.

**Conclusion**

The most distinctive age-related change in the hippocampus is a decrease in its volume with a reduction in the number of projecting fibers from other related brain regions. No significant loss of hippocampal neurons occurs with aging. With the volume change, many cellular substrates also markedly change in the aging hippocampus. Stereological studies on the total or region-specific number of primed and dystrophic microglia should be done in the aged hippocampus. In addition, there are some controversies about on major microglial functions that are harmful or beneficial for the patient undergoing degenerative changes in the aged brain. However, in the aged hippocampus the majority of functional declines with aging are closely related to morphological and functional changes of microglia.

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**References**

1. Hamill RW, Caine E, Eskin T, Lapham L, Shoulson I, McNeill TH. Neurodegenerative disorders and aging. Alzheimer's disease and Parkinson's disease—common ground. Ann N Y Acad Sci 1988; 515: 411-420.
2. McGeer PL, McGeer EG. Inflammation and the degenerative diseases of aging. Ann N Y Acad Sci 2004; 1035: 104-116.
3. Vanguilder HD, Freeman WM. The hippocampal neuroproteome with aging and cognitive decline: past progress and future directions. Front Aging Neurosci 2011; 3: 8.
4. Sweatt JD. Hippocampal function in cognition. Psychopharmacology (Berl) 2004; 174(1): 99-110.
5. Rasmussen T, Schliemann T, Sorensen JC, Zimmer J, West MJ. Memory impaired aged rats: no loss of principal hippocampal and subicular neurons. Neurobiol Aging 1996; 17(1): 143-147.
6. Burke SN, Barnes CA. Neuronal plasticity in the ageing brain. Nat Rev Neurosci 2006; 7(1): 30-40.
7. West MJ, Coleman PD, Flood DG, Troncoso JC. Differences in the pattern of hippocampal neuronal loss in normal aging and Alzheimer's disease. Lancet 1994; 344(8925): 769-772.
8. Lee CH, Yoo KY, Choi JH, Park OK, Hwang IK, Kim SK, Kang JJ, Kim YM, Won MH. Neuronal damage is much delayed and microgliosis is more severe in the aged hippocampus induced by transient cerebral ischemia compared to the adult hippocampus. J Neurol Sci 2010; 294(1-2): 1-6.
9. Sapolsky RM, Krey LC, McEwen BS. Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. Proc Natl Acad Sci USA 1984; 81(19): 6174-6177.
10. Bobinski M, de Leon MJ, Tarnawski M, Węgieł J, Reisberg B, Miller DC, Wisniewski HM. Neuronal and volume loss in CA1 of the hippocampal formation uniquely predicts duration and severity of Alzheimer disease. Brain Res 1998; 805(1-2): 267-269.

11. Alabane PV, Hackenbaar FS, Medeiros TM, Mendes MF, Viaçaava PR, Schuller AK, Salomon TB, Ehrenbrink G, Brito MS. Oxidative stress in the brain of reproductive male rats during aging. Exp Gerontol 2011; 46(4): 241-248.

12. Tomasi D, Volkow ND. Aging and functional brain networks. Mol Psychiatry 2011; in press.

13. Perry VH, Nicoll JA, Holmes C. Microglia in neurodegenerative disease. Nat Rev Neurosci 2010; 6(4): 193-201.

14. Mrak RE, Griffin WS. Glia and their cytokines in progression of neurodegeneration. Neurobiol Aging 2005; 26(3): 349-354.

15. Lawton LJ, Perry VH, Dri P, Gordon S. Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. Neuroscience 1999; 39(1): 151-170.

16. Streit WJ. Microglia in the regenerating and degenerating central nervous system. Springer, New York, 2002; p 315.

17. Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J Leukoc Biol 2008; 84(4): 932-939.

18. Lister JP, Barnes CA. Neurobiological changes in the hippocampus during normative aging. Arch Neurol 2009; 66(7): 829-833.

19. McEwen BS. Stress and the aging hippocampus. Front Neuroendocrinol 1999; 20(1): 791-805.

20. Luo XG, Ding JQ, Chen SD. Microglia in the aging brain: relevance to neurodegeneration. Mol Neurodegener 2010; 5: 12.

21. Miller DB, O’Callaghan JP. Aging, stress and the hippocampus. Ageing Res Rev 2005; 4(2): 123-140.

22. Cross CG. Brain, vision, memory: tales in the history of neuroscience. MIT Press, Cambridge, 1998; p 273.

23. Kesner RP, Lee I, Gilbert P. A behavioral assessment of hippocampal function based on a subregional analysis. Rev Neurosci 2004; 15(5): 333-351.

24. Miyashita T, Williams CL. Peripheral arousal-related hormones modulate norepinephrine release in the hippocampus via influences on brainstem nuclei. Behav Brain Res 2004; 153(1): 87-95.

25. Koehl M, Abrous DN. A new chapter in the field of memory: adult hippocampal neurogenesis. Eur J Neurosci 2011; 33(6): 1101-1114.

26. Norman KA. How hippocampus and cortex contribute to recognition memory: revisiting the complementary learning systems model. Hippocampus 2010; 20(11): 1228-1227.

27. Brown MW, Warburton EC, Aggleton JP. Recognition memory: material, processes, and substrates. Hippocampus 2010; 20(11): 1228-1244.

28. Langston RF, Stevenson CH, Wilson CL, Saunders I, Wood ER. The role of hippocampal subregions in memory for stimulus associations. Behav Brain Res 2010; 215(2): 275-291.

29. Niewiadomska G, Bakalserska-Pazera M, Riedel G. The septo-hippocampal system, learning and recovery of function. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33(5): 791-805.

30. Shankaranarayana Rao BS, Govindailah, Laxmi TR, Meti BL, Raju TR. Subicular lesions cause dentritic atrophy in CA1 and CA3 pyramidal neurons of the rat hippocampus. Neuroscience 2001; 102(2): 319-327.

31. Bhattacharyya A. Synaptic atrophy in the senescent hippocampus. Mech Ageing Dev 1979; 9(1-2): 163-171.

32. Ball MJ. Neuronal loss, neurofibrillary tangles and granulovacular degeneration in the hippocampus with aging and dementia. A quantitative study. Acta Neuropathol 1977; 37(2): 111-118.

33. Isa AM, Rowe W, Gauthier S, Meaney MJ. Hypothalamic-pituitary-adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. J Neurosci 1990; 10(10): 3247-3254.

34. Rapp PR, Gallagher M. Preserved neuron number in the hippocampus of aged rats with spatial learning deficits. Proc Natl Acad Sci USA 1996; 93(18): 9926-9930.

35. Hof PR, Glaunakopoulos P, Bouras C. The neuropathological changes associated with normal brain aging. Histol Histopathol 1996; 11(4): 1075-1088.

36. West MJ, Cundersen H. Unbiased stereological estimation of the number of neurons in the human hippocampus. J Comp Neurol 1990; 296(1): 1-22.

37. Calhoun ME, Kurth D, Phinney AL, Long JM, Hengemihle J, Mouton PK, Ingram JK, Jackson M. Hippocampal neuron and synaptophysin-positive bouton number in ageing C57BL/6 mice. Neurobiol Aging 1998; 19(6): 599-606.

38. Keuker JJ, Luiten PG, Fuchs E. Preservation of hippocampal neuron numbers in aged rhesus monkeys. Neurobiol Aging 2003; 24(1): 157-165.

39. West MJ, Design-based stereological methods for counting neurons. Prog Brain Res 2002; 135: 43-51.

40. Ziehn MS, Avdessias AA, Tiwari-Woodruff S, Voskuhl RR. Hippocampal CA1 atrophy and synaptic loss during experimental autoimmune encephalomyelitis, EAE. Lab Invest 2010; 90(5): 774-786.

41. Paron D, Loewenstein DA, Potter E, Greig MT, Agron J, Greig MT. Neuroendocrinology of the brain. Springer, New York, 2002; p 315.

42. Malykhin NV, Bouchard TP, Camicioli R, Coupland NJ. Aging and senile dementia. Brain Res 1987; 402(2): 205-216.

43. Raz N, Ghisletta P, Rodrigue KM, Kennedy KM, Lindenberger U. Trajectories of brain aging in middle-aged and older adults: regional and individual differences. Neuroimage 2010; 51(2): 501-511.

44. Malychkin NV, Bouchard TR, Camicioli R, Coupland NJ. Aging hippocampus and amygdala. Neuroreport 2008; 19(5): 543-547.

45. Payapall GK, Turner DA. Increased dendritic extent in hippocampal CA1 neurons from aged F344 rats. Neurobiol Aging 1996; 17(4): 601-611.

46. Markham JA, McGan KP, Stroup TS, Juraska JM. Dendritic atrophy and senile dementia. Brain Res 1987; 402(2): 205-216.

47. Curcio CA, Hinds JW. Stability of synaptic density and spine number in aged rhesus monkeys. Neurobiol Aging 2000; 21(5): 613-620.
53. von Bohlen und Halbach O, Unsicker K. Morphological alterations in the amygdala and hippocampus of mice during ageing. Eur J Neurosci 2002; 16(12): 2434-2440.

54. von Bohlen und Halbach O, Unsicker K. Age-related decline in the tyrosine hydroxylase-immunoreactive innervation of the amygdala and dentate gyrus in mice. Cell Tissue Res 2003; 311(2): 139-143.

55. Nishimura A, Ueda S, Takeuchi Y, Sawada T, Kawata M. Age-related decrease of serotonergic fibres and S-100 beta immunoreactivity in the rat dentate gyrus. Neuroreport 1995; 6(10): 1445-1448.

56. Ypsilanti AR, Girao da Cruz MT, Burgess A, Aubert I. The length of hippocampal cholinergic fibers is reduced in the aging brain. Neurobiol Aging 2008; 29(11): 1666-1679.

57. Sapolsky RM, Krey LC, McEwen BS. Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. J Neurosci 1985; 5(5): 1222-1227.

58. Landfield PW, Widdire JC, Lynch G. Hippocampal aging and adrenocorticoids: quantitative correlations. Science 1978; 202(4372): 1098-1102.

59. Brenner JD, Narayan M. The effects of stress on memory and the hippocampus throughout the life cycle: implications for childhood development and aging. Dev Psychopathol 1998; 10(4): 871-885.

60. Kumar A, Bodhithathan K, Foster TC. Susceptibility to Calcium Dysregulation during Brain Aging. Front Aging Neurosci 2009; 1: 2. doi:10.3389/neuro.24.002.2009.

61. Foster TC, Kumar A. Calcium dysregulation in the aging brain. Neuroscientist 2002; 8(4): 297-301.

62. Disterhoft JF, Kronfort-Williams M, Oh MM, Power JM, Preston AR, Weiss C. Cholinergic facilitation of trace eyeblink conditioning in aging rabbits. Life Sci 1999; 64(6-7): 541-548.

63. Landfield PW, Pitter TA. Prolonged Ca2+ dependent afterhyperpolarizations in hippocampal neurons of aged rats. Science 1984; 226(4678): 1089-1092.

64. Moyer JR Jr., Disterhoft JF. Nimodipine decreases calcium action potentials in rabbit hippocampal CA1 neurons in an age-dependent and concentration-dependent manner. Hippocampus 1994; 4(1): 11-17.

65. Thibault O, Landfield PW. Increase in single L-type calcium channels in hippocampal neurons during aging. Science 1996; 272(5264): 1017-1020.

66. Billard JM. Ageing, hippocampal synaptic activity and magnesium. Magnes Res 2006; 19(3): 199-215.

67. Bardgett ME, Schultheis PJ, McGill DL, Richardson RE, Wagge JR. Magnesium deficiency impairs fear conditioning in mice. Brain Res 2005; 1038(1): 100-106.

68. Slusky I, Abumaria N, Wu LJ, Huang C, Zhang L, Li B, Zhao X, Govindarajan A, Zhao MG, Tonegawa S, Liu G. Enhancement of learning and memory by elevating brain magnesium. Neuron 2010; 65(2): 165-177.

69. von Bohlen und Halbach O. Involvement of BDNF in age-dependent alterations in the hippocampus. Front Aging Neurosci 2010; 2: 36.

70. Hayashi M, Mistry and Fohira K. Shimizu K. Changes in BDNF-immunoreactive structures in the hippocampus of the aged macaque monkey. Brain Res 2001; 918(1-2): 191-196.

71. Webster MJ, Herman MM, Kleinman JE, Shannon Weickert C. BDNF and iba1 mRNA expression in the hippocampus and temporal cortex during the human lifespan. Gene Expr Patterns 2006; 6(8): 941-951.

72. Silhol M, Bonnichon V, Raje F, Tapia-Aracibia L. Age-related changes in brain-derived neurotrophic factor and tyrosine kinase receptor isoforms in the hippocampus and hypothalamus in male rats. Neuroscience 2003; 132(3): 613-624.

73. Gooney M, Messaoudi E, Maher FO, Bramham CR, Lynch MA. BDNF-induced LTP in dentate gyrus is impaired with age: analysis of changes in cell signaling events. Neurobiol Aging 2004; 25(10): 1323-1331.

74. VanGuilker HD, Yan H, Falby JA, Sonntag WE, Freeman WM. Aging alters the expression of neurotransmission-regulating proteins in the hippocampal synaptotrope. J Neurochem 2010; 113(6): 1577-1586.

75. Freeman WM, VanGuilker HD, Bennett C, Sonntag WE. Cognitive performance and age-related changes in the hippocampal proteome. Neuroscience 2009; 159(1): 183-195.

76. Davis EJ, Foster TD, Thomas WE. Cellular forms and functions of brain microglia. Brain Res Bull 1994; 34(1): 73-78.

77. Perry VH, Andersson PB, Gordon S. Macrophages and inflammation in the central nervous system. Trends Neurosci 1993; 16(7): 268-273.

78. Streit WJ, Graeber MB, Kreutzberg GW. Functional plasticity of microglia: a review. Glia 1988; 1(5): 301-307.

79. Perry VH. The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. Brain Behav Immun 2004; 18(5): 407-413.

80. Perry VH, Matsuzak MK, Fearn S. Altered antigen expression of microglia in the aged rodent CNS. Glia 1993; 7(1): 60-67.

81. Perry VH, Newman TA, Cunningham C. The impact of systemic infection on the progression of neurodegenerative disease. Nat Rev Neurosci 2003; 4(2): 103-112.

82. Choi JH, Lee CH, Hwang IK, Won MH, Seong JK, Youn YS, Lee HS, Lee IS. Age-related changes in ionized calcium-binding adapter molecule 1 immunoreactivity and protein level in the gerbil hippocampal CA1 region. J Vet Med Sci 2007; 69(11): 1131-1136.

83. Wiernekeld M, Dalmau I, Finsen B. Estimation of absolute microglial cell numbers in mouse fascia dentata using unbiased and efficient stereological cell counting principles. Glia 2003; 44(2): 129-139.

84. Vanderwolf CH. Hippocampal activity, olfaction, and sniffing: an olfactory input to the dentate gyrus. Brain Res 1992; 593(2): 197-208.

85. Long JM, Kalehua AN, Muth NJ, Hengemihle JM, Jucker M, Calhoun ME, Ingram DK, Mouton PR. Stereological estimation of total microglia number in mouse hippocampus. J Neurosci Methods 1998; 84(1-2): 101-108.

86. Savchenko VL, McKanna JA, Nikonenko IR, Skibo GG. Microglia and astrocytes in the adult rat brain: comparative immunocytochemical analysis demonstrates the efficacy of lipoic and lipoic acid on the progression of microglial activation. Neuroscience 2000; 96(1): 195-203.

87. Imai Y, Ibata I, Itou D, Ohsawa K, Koshaka S. A novel gene iba1 in the major histocompatibility complex class III region encoding an EF hand protein expressed in a monocytic lineage. Biochem Biophys Res Commun 1996; 224(3): 855-862.

88. Jinno S, Fleischer F, Eckel S, Schmidt V, Kosaka T. Spatial distribution of microglia and macrophages in the mouse hippocampus: a stereological study in comparison with astrocytes. Glia 2007; 55(13): 1334-1347.

89. Long JM, Kalehua AN, Muth NJ, Calhoun ME, Jucker M, Hengemihle JM, Ingram DK, Mouton PR. Stereological analysis of astrocyte and microglia in aging mouse hippocampus. Neurobiol Aging 1998; 19(5): 497-503.

90. Mouton PR, Long JM, Lei DL, Howard V, Jucker M, Calhoun ME, Ingram DK. Age and gender effects on microglia and astrocyte numbers in brains of mice. Brain Res 2002; 956(1): 30-35.

91. Hayakawa N, Kato H, Araki T. Age-related changes of microglial cells and microglial microglial cells and microglial cells in the mouse hippocampal CA1 sector. Mech Ageing Dev 2007; 128(4):
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92. Adachi M, Abe M, Sasaki T, Kato H, Kasahara J, Araki T. Role of inducible or neuronal nitric oxide synthase in neurogenesis of the dentate gyrus in aged mice. Metab Brain Dis 2010; 25(4): 419-424.

93. Park JH, Yoo KY, Lee CH, Kim JH, Shin BN, Choi JH, Hwang IK, Won MH. Comparison of glucocorticoid receptor and ionized calcium-binding adapter molecule 1 immunoreactivity in the adult and aged gerbil hippocampus following repeated restraint stress. Neurochem Res 2011; 36(6): 1037-1045.

94. Hwang IK, Lee CH, Li H, Yoo KY, Choi JH, Kim DW, Suh HW, Won MH. Comparison of ionized calcium-binding adapter molecule 1 immunoreactivity of the hippocampal dentate gyrus and CA1 region in adult and aged dogs. Neurochem Res 2008; 33(7): 1309-1315.

95. Nicolle MM, González J, Sugaya K, Baskerville KA, Bryan D, Lund K, Gallagher M, McKinney M. Signatures of hippocampal oxidative stress in aged spatial learning-impaired rodents. Neuroscience 2001; 107(3): 415-431.

96. Finch CE. Neurons, glia, and plasticity in normal brain aging. Neurobiol Aging 2003; 24 Suppl 1: S123-S127.

97. Finch CE. Neurons, glia, and plasticity in normal brain aging. Adv Gerontol 2002; 10: 35-39.

98. Chen J, Buchanan JB, Sparkman NL, Godbout JP, Freund GG, Johnson RW. Neuroinflammation and disruption in working memory in aged mice after acute stimulation of the peripheral innate immune system. Brain Behav Immun 2008; 22(3): 301-311.

99. Sheng JC, Mrak RE, Griffin WS. Enlarged and phagocytic, but not primed, interleukin-1 alpha-immunoreactive microglia increase with age in normal human brain. Acta Neuropathol 1998; 95(3): 229-234.

100. Godbout JP, Chen J, Abraham J, Richwine AF, Berg BM, Kelley KW, Johnson RW. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. FASEB J 2005; 19(10): 1329-1331.

101. Sierra A, Gottfried-Blackmore AC, McEwen BS, Bulloch K. Microglia derived from aging mice exhibit an altered inflammatory profile. Glia 2007; 55(4): 412-424.

102. Ye SM, Johnson RW. Increased interleukin-6 expression by microglia from brain of aged mice. J Neuroimmunol 1999; 93(1-2): 139-148.

103. Sparkman NL, Johnson RW. Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. Neuroimmunomodulation 2008; 15(4-6): 323-330.

104. Wu Z, Tokuda Y, Zhang XW, Nakashita H. Age-dependent responses of glial cells and leptomeninges during systemic inflammation. Neurobiol Dis 2008; 32(3): 543-551.

105. Barrientos RM, Higgins EA, Biedenkapp JC, Sprunger DB, Wright-Hardesty KL, Watkins LR, Rudy JW, Maier SE. Peripheral infection and aging interact to impair hippocampal memory consolidation. Neurobiol Aging 2006; 27(5): 723-732.

106. Wynn AM, Henry CJ. Godbout JP. Immune and behavioral consequences of microglial reactivity in the aged brain. Integr Comp Biol 2009; 49(3): 254-266.

107. Streit WJ, Sammons NW, Kuhns AJ, Sparks DL. Dystrophic microglia in the aging human brain. Glia 2004; 45(2): 208-212.

108. Korotzer AR, Pike CJ, Cotman CW. Beta-Amyloid peptides induce degeneration of cultured rat microglia. Brain Res 1993; 624(1-2): 121-125.

109. Godbout JP, Chen J, Abraham J, Richwine AF, Berg BM, Kelley KW, Johnson RW. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. FASEB J 2005; 19(10): 1329-1331.

110. Sierra A, Gottfried-Blackmore AC, McEwen BS, Bulloch K. Microglia derived from aging mice exhibit an altered inflammatory profile. Glia 2007; 55(4): 412-424.

111. Miller KR, Streit WJ. The effects of aging, injury and disease on microglial senescence: a case for cellular senescence. Neuron Glia Biol 2007; 3(3): 245-253.

112. Flanary SE, Xue QS, Streit WJ. Formation of multinucleated giant cells and microglial degeneration in rats expressing a mutant Cu/Zn superoxide dismutase gene. J Neuroinflammation 2007; 4: 9.

113. Simmons DA, Casale M, Alcon B, Pharm N, Narayan N, Lynch G. Ferritin accumulation in dystrophic microglia is an early event in the development of Huntington's disease. Glia 2007; 55(10): 1074-1084.

114. Miller KR, Streit WJ. The effects of aging, injury and disease on microglial function: a case for cellular senescence. Neuron Glia Biol 2007; 3(3): 245-253.

115. Flanary SE, Xue QS, Streit WJ. The effects of aging, injury and disease on microglial function: a case for cellular senescence. Neuron Glia Biol 2007; 3(3): 245-253.

116. Flanary SE, Sammons NW, Nguyen C, Walker D, Streit WJ. Evidence that aging and amyloid promote microglial cell senescence. Rejuvenation Res 2007; 10(1): 61-74.

117. Miller KR, Streit WJ. Microglial senescence: does the brain's immune system have an expiration date? Trends Neurosci 2006; 29(9): 506-510.

118. Flanary SE, Xue QS, Streit WJ. The role of microglial cellular senescence in the aging and Alzheimer diseased brain. Rejuvenation Res 2005; 8(2): 82-85.