Brain Aging: Rejuvenation & Regeneration

Beyin Yaşlanması: Yenilenme ve Gençleşme

İhsan KARA[a]

[a]İstanbul Üniversitesi
Deneysel Tıp Araştırma Enstitüsü,
İSTANBUL

Yazışma Adresi/*Correspondence:*
İhsan KARA
İstanbul Üniversitesi
Deneysel Tıp Araştırma Enstitüsü,
İSTANBUL
sankara@istanbul.edu.tr

ABSTRACT Ageing especially appears in slowing down of cognitive functions and motor activity. These changes can be the result of decreasing ATP production and of functional cell number in the brain. This process is observed as progressive and cumulative phenomenon. Researchers generally accepted causes of the ageing is that oxidative damage is accumulated in cell structures and this cause the apoptosis of the cell. And also researchers suggested that main cause of changes as seen in naturally ageing brains can be uncovered misbalancing of neurogenesis/apoptosis equilibrium. Mitochondria especially have active roles in apoptosis. Also mitochondria are the main source of cellular energy and of oxidative stressors generation. Due to these reasons mitochondria can be taken part of the etiology of ageing. Apoptosis inducing factors can released by due to the accumulation of oxidative damage of cellular structures and degradation of mitochondrial functions and morphology. Main reasons of ageing can be counted as losing of the functional cells by apoptosis, weakening of synaptic connections between neurons and decreasing the rate of neurogenesis. Nowadays, this variational process can be slowing down with exogen antioxidant supplements.

Key Words: Brain ageing, neurogenesis, apoptosis, mitochondrion

ÖZET Yaşlanma özellikle kognitif fonksiyonlarda ve motor aktivitelerdeki yavaşlamalarla kendini göstermektedir. Yaşlanma sürecinde görülen bu değişimlerin hücresel temelde ATP üretim sürecindeki azalmaya ve fonksiyonel hücre kayıplarının bu değişimlere neden olduğu düşünülmektedir. Bu süreç progresif ve kümülatif olarak gerçekleşmektedir. Bunun nedenleri arasında özellikle oksidatif stresin neden olduğu hücresel hasarların zaman içerisinde birikerek hücrelerin apoptozla kaybedilmesinden kaynaklandığı düşüncesi yaygın olarak bilim dünyasında kabul görmektedir. Doğal yaşlanma sürecinde beyinde gözlenen bu değişimlerin ana nedeni, zamanla apoptoz sürecinin hızlanarak, nörogenez-apoptoz arasındaki dengenin bozulmasından kaynaklanabileceği görüşü literatürde öne sürülmektedir. Apoptoz sürecinde özellikle mitokondri etkin bir rol üstlenmektedir. Ayrıca mitokondrinin hücresel enerji üretiminin ve de oksidatif stresörlerinde ana üretim merkezi olması nedeniyle yaşlanmanın etiyolojisinde anahtar bir rol üstlendiği düşünülmektedir. Biriken oksidatif hasar, mitokondriyal fonksiyonların ve morfolojinin bozulmasına neden olarak, apoptoz başlatıcı faktörlerin hücre içerisine salınmasına neden olmaktadır. Apoptozla kaybedilen hücreler, zaman içerisinde zayıflayan sinaptik bağlantılar ve nörogenezin azalması yaşlanmada görülen değişimlerin temel nedenidir. Bu değişimsel sürecin yavaşlatılması eksojen antioksidan takviyelerle günümüzde gerçekleştirilmektedir.

Anahtar Kelimeler: Beyin yaşlanması, nörogenez, apoptoz, mitokondri

Turkiye Klinikleri J Med Sci 2009;29(Suppl):S63-S67

BRAIN ATROPHY

With age, the brain undergoes structural and functional deterioration, which is thought to be responsible for the reported cognitive decline. Overall, the literature consistently reports global brain atrophy in normal adults, generally more pronounced in frontal areas, often followed by parietal, temporal and insular gray matter (GM) loss1. As a result of different methodologies and inclusion criteria, other brain areas have been the matter of conflicting findings, notably the hippocampus. The "region of interest" procedure (ROI), which consists in selecting specific brain regions to address specific hypotheses, sometimes showed the hippocampus to undergo structural deterioration2,3. However sometimes revealed no significant correlation between hippocampal volume and age, suggesting that this structure may be relatively preserved in normal aging4.Recently, structural brain changes have been investigated using the 'optimized voxel-based morphometry procedure' (VBM), which makes it possible to assess the whole brain without postulating prior hypotheses about specific regions of the brain. Authors have systematically reported GM loss in the frontal lobe with aging1,5 also affecting the insula, Heschl gyrus, anterior cingulate cortex, sensorimotor areas and cerebellum. These authors, using ROI analyses (including frontal lobe, hippocampal and parahippocampal areas) by decades, found that the frontal cortex volume declined linearly and had the strongest age association, whereas the hippocampal volume remained steady until about 60 years of age, while thereafter its volume began to rapidly decline. A few longitudinal studies have also been performed to address the issue of age-related GM volume time course. Most have revealed prominent GM loss in prefrontal regions6,7 with smaller but significant decline in other regions, notably in mesial temporal areas. Overall, hippocampal atrophy has been often reported in the available longitudinal studies, but it appears to occur late in life, and even then to be relatively modest.

NEUROGENESIS

Until recently, a central assumption in neuroscience had been that new neurons do not arise in the adult mammalian brain. In the last few years, however, this belief has been challenged by numerous studies that demonstrated that certain areas of the brain retain pluripotent precursors with the capacity of self-renew and differentiation into new neural lineages in adult mammals such as rodents8, non-human primates9 and humans10. In rodents, it was shown that undifferentiated neural stem/progenitor cells (NSCs) are concentrated in the subventricular zone (SVZ) of the lateral ventricle wall8 and the subgranular zone (SGZ) of the dentate gyrus of the hippocampus11. Cells born in the rodent SVZ during adult life travel anteriorly through the rostral migratory stream into the olfactory bulb (OB), where they differentiate into interneurons12. Cells born in the SGZ of the dentate gyrus migrate a short distance to integrate in the granular layer. That NSCs also exist in adult primate and human brain has now been well established9 for the subependymal zone13, for the hippocampus14 and very recently for the human olfactory bulb15. The dentate gyrus and the hilus in cornus ammonis 4 (CA4) region of the human hippocampus are, however, the most active areas of NSC proliferation in adult non-human primates16 and humans17. The neurogenicity of SVZ and SGZ NSCs in the young adult mammalian brain is restricted by signals from their local environment. Not surprisingly, developmental signal molecules and morphogens such as Notch18, bone morphogenetic proteins, Noggin and sonic hedgehog19, have been implicated in the maintenance of adult neurogenic microenvironments20 containing glial and endothelial cells21. The activation of neurogenic processes as a response to chronic damage is much less well documented, although some22 but not all23 studies have supported the hypothesis that slow neurodegenerative damage may also induce NSC proliferation. The evidence for de novo neurogenesis induced by chronic injury, however, is far from being definitive. Although neurogenesis continues throughout life, its rate declines with increasing age in rodents24 and non-human primates25. In aged rats, the proliferation rate of NSCs in the SGZ of the dentate gyrus is reduced by 80%26. The age-associated reduction in adult neurogenesis may be due to an intrinsic decline in NSC responsiveness to stimulating environmental cues, to a decrease in or disappearance of these environmental cues, or to the appearance or accumulation of inhibitory factors. Supporting a role for environmental cues in the age-associated decline in neurogenesis, it was shown that exogenous addition of growth factors such as insulin-like growth factor I (IGF-I)27, epidermal growth factor (EGF) and fibroblast growth factor (FGF-2) or a reduction of corticosteroid levels by adrenalectomy28 can, at least partially, negate the effects of age in the rate of NSC proliferation. The observed increase in adult born neurons in older animals were at the expense of newly generated astrocytes, argu-

ing that the effects of environmental enrichment affect the fate choice of proliferating multipotent progenitors or alternatively, specifically promote survival of newly born neurons. Environmental conditions may therefore have a crucial role in the modulation of neurogenesis during aging in rodents since like in young rodents experience, the stimulation of neurogenesis and improved functional outcomes may be causally linked in aged brains as well. Age-associated memory deficits are broadly similar to those induced by damage to the hippocampus, which is one of several limbic structures implicated in the pathophysiology of mood disorders. It was recently shown that stress29 and depression30 lead to hippocampal atrophy, while chronic antidepressant treatments result in an increase in hippocampal neurogenesis. Antidepressant action may require neurogenesis in mice31, although hippocampal neurogenesis was not required for the anxiolytic effects of environmental enrichment32. It has been proposed that the age-related decline in neurogenesis may underlie age-associated learning and memory declines and may contribute to pathological conditions such as Alzheimer's disease33. Although neurogenesis may contribute to function in the adult human CNS, the process does not suffice to preserve function during normal aging, or when injury or degenerative processes have ensued. However, that stimulation of NSC proliferation and possibly survival may be enhanced by growth factors or behavioral interventions even in older rodents34 suggests that the endogenous neurogenic response could be modulated exogenously. The human RMS was finally demonstrated around a lateral ventricular extension reaching the OB, the ventriculo-olfactory neurogenic system (VONS) which, in contrast to the rodent brain, takes a caudal path en route from the SVZ to the olfactory cortex as a consequence of the pronounced enlargement of the frontal cortex in the human forebrain that places the rostral caudate, SVZ and frontal cortex rostral to the olfactory tubercle16. In contrast, the dentate gyrus and the hilus in CA4 region of the human hippocampus, which were detected earlier, are possibly the most active areas of progenitor proliferation in adult primates9 and humans18. Endogenous augmentation of trophic factor expression (such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and FGF-2) in brains of laboratory animals has been achieved by behavioral interventions35 such as enriched experience, voluntary exercise36 and training/learning37. Both enriched housing and training have been shown to increase synaptogenesis38 and neurogenesis39 as well. IGF-I has neuroprotective and neurogenic effects40 and it has been shown that peripheral infusion of IGF-I can increase NSC proliferation, selectively induce neurogenesis41 and ameliorate the age-related decline in hippocampal neurogenesis in rats42.The protective effects of physical exercise were shown to be mediated by circulating IGF-I31. The discovery of neurogenesis and its role in the adult mammalian brain opened up exciting possibilities for the development of therapeutic interventions that might mitigate age-related learning and memory declines, and mood disorders. . Behavioral interventions such as the diffusion of information required for lifestyle choices, the socialization of institutions providing access to continuing education, creative occupation, physical activity and the enjoyment of the arts may help societies increase their overall "cognitive reserve" and reduce the human, economic and social burden associated with increased numbers of cognitively impaired elderly in developed societies with high life expectancy.

APOPTOSIS, "PROGRAMMED CELL DEATH"

In the days following the birth, 50% of the neurons in the central and peripheral nervous systems are disappeared by apoptosis. During the development phase and in the adulthood, physiological apoptosis "physiological cell death" is occurred continually by the rule. Apoptosis occurs as the result of the activation of different molecular pathways in the cell. As is known, caspases are proteins possessing the protease activity. Caspases are a group of enzymes present in the cytoplasm as zymogens (active precursor) and called as cystein proteases since they possess cystein in their active centers43. Until know 14 of them are defined and most of them play a role in the apoptosis. Caspases cause a proteolytic cascade by activating each other. While some (Caspase 2, 8, 9, 10) are known as inducing caspases, some (Caspase 3, 6, 7) are known as affector caspases. Inducing caspases transfer the death signals induced by apoptotic warning to affector caspases. And the affector caspases cause apoptotic cell morphology by degrading relevant proteins (e.g. cell skeleton proteins actin or fodrin, nuclear membrane protein lamin A, poly (ADP-ribose) polymerase (PARP) playing a role in DNA repair). The first defined enzyme is ICE (interleukin 1-β converting enzyme) and is known as procaspase 1. The caspase cascade can be activated by the activation of procaspase 9 by cytochrome c release to cytoplasm, as well as, the caspases may cause the release of cytochrome c. IAP ("inhibitors of apoptosis"), a caspase inhibitor family, selectively inhibit caspases and

thus they stop the apoptotic mechanism44. According to a recent thought on apoptosis is not only occurring in a caspase-dependent manner but there is also a caspase-indepedent pathway. This molecular cascade called "caspase-independent apoptosis mechanism" is thought to be an apoptotic process induced by proteins activated by the damage free radicals caused to cellular structures (nucleic acids, proteins, membranes). Especially, the Apoptosis Inducing Factor – AIF leaked from the mitochondria to the cytosol during ischemia/reperfusion is believed to be the main element in this mechanism. The AIF protein in known to reach directly to the nucleus and to cause DNA fragmentation and chromatin condensation. Unless this nuclear DNA damage is fixed by the DNA repair mechanisms the apoptosis signal will be distributed in the cell and the death of the cell will occur in a caspase-independent way. Another protein present in the caspase-independent pathway are the calpain proteins. Calpain proteins are proteins with cystine-protease activity. Calpain proteins are activated when intra-cellular calcium concentration is increased. In this case, calpains cause the proteins in contact with calpains to degrade and irreversible tissue damage to occur. Over-activated calpains induce the apoptosis in the cell by damaging especially the proteins in the cellular skeleton structure (e.g. neurofilaments, spectrin, and microtubule subunits). The apoptosis induced by caspase-independently is still not clarified. Neurogenesis and apoptosis are not in equilibrium in post-mitotic neurons. As the course of natural aging, accompanying the acceleration of the apoptosis in some locations of the brain tissue, dysfunction of that tissue will occur. On the basis of the neurodegenerative diseases the same mechanism is present along with the slowing down and declining of the cognitive functions, slowing down of motor functions and imbalance appears.

REFERENCES

1. Abe O, Yamasue H, Aoki S, Suga M, Yamada H, Kasai K, Masutani Y et al. Aging in the CNS: comparison of gray/white matter volume and diffusion tensor data, Neurobiol. Aging. 2008; 29(1):102-16.
2. Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Akcer JD. Aging sexuel dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences involumes, Neurobiol.Aging 2004; 25.
3. Raz N, Rodrigue KM, Head D, Kennedy KM, Acker JD. Differential aging of the medial temporal lobe: a study of a five-year change, Neurology 2004; 62.
4. Bigler ED, Blatter DD, Anderson CV, Johnson SC, Gale SD, Hopkins RO, Burnett B.Hippocampal volume in normal aging and traumatic brain injury, Am. J. Neuroradiol. 1997; 18.
5. Yanase D, Matsunari I, Yajima K, Chen W, Fujikawa A, Nishimura S, Matsuda H, Yamada M. Brain FDG PET study of normal aging in Japanese: effect of atrophy correction, Eur. J. Nucl. Med. Mol. Imaging 2005; 32.
6. Rettmann ME, Kraut MA, Prince JL, Resnick SM. Cross-sectional and longitudinal analyses of anatomical sulcal changes associated with aging, Cereb. Cortex 2006; 16:1584–1594.
7. Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging, Arch. Neurol. 2003; 60: 989–994.
8. Maslov AY, Barone TA, Plunkett RJ, Pruitt SC. Neural stem cell detection, characterization, and age-related changes in the subventricular zone of mice. J Neurosci. 2004; 24:1726–33.
9. Pencea V, Bingaman KD, Freedman LJ, Luskin MB. Neurogenesis in the subventricular zone and rostral migratory stream of the neonatal and adult primate forebrain. Exp Neurol. 2001;172:1–16.
10. Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. Neurogenesis in the adult human hippocampus. Nat Med. 1998; 4:1313–7.
11. Gage FH. Mammalian neural stem cells. Science. 2000; 287:1433–8.
12. Alvarez-Buylla A, Lim DA. For the long run: maintaining germinal niches in the adult brain. Neuron. 2004; 41:683–6.
13. Bedard A, Parent A. Evidence of newly generated neurons in the human olfactory bulb. Brain Res Dev Brain Res. 2004; 151:159–68.
14. Roy NS, Benraiss A, Wang S, Fraser RA, Goodman R, Couldwell WT, Nedergaard M, et al. Promoter-targeted selection and isolation of neural progenitor cells from the adult human ventricular zone. J Neurosci Res. 2000; 59:321–31.
15. Roy NS, Wang S, Jiang L, Kang J, Benraiss A, Harrison-Restelli C, et al. In vitro neurogenesis by progenitor cells isolated from the adult human hippocampus. Nat Med. 2000; 6:271–7.
16. Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, Wikkelso C, Holtås S, et al. Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. Science. 2007;315:1243–9.
17. Kornack DR, Rakic P. Continuation of neurogenesis in the hippocampus of the adult macaque monkey. PNAS. 1999; 96:5768–73.
18. Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. Neurogenesis in the adult human hippocampus. Nat Med. 1998; 4:1313–725.
19. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: cell fate control and signal integration in development. Science. 1999; 284:770–6.
20. Pozniak CD, Pleasure SJ. A tale of two signals: Wnt and Hedgehog in dentate neurogenesis. Sci STKE. 2006; 5.
21. Lim DA, Tramontin AD, Trevejo JM, et al. Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. Neuron. 2000; 28:713–26.
22. Shen Q, Goderie SK, Jin L, Karanth N, Sun Y, Abramova N, Vincent P, et al. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. Science. 2004; 304:1338–40.
23. Curtis MA, Penney EB, Pearson AG, van Roon-Mom WM, Butterworth NJ, Dragunow M, Connor B,et al. Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain. PNAS. 2003; 100:9023–7.

24. Haughey NJ, Liu D, Nath A, Borchard AC, Mattson MP. Disruption of neurogenesis in the subventricular zone of adult mice, and in human cortical neuronal precursor cells in culture, by amyloid beta-peptide: implications for the pathogenesis of Alzheimer's disease. Neuromolecular Med. 2002; 1:125–35.

25. Seki T, Arai Y. Age-related production of new granule cells in the adult dentate gyrus. Neuroreport. 1995;6:2479–82.

26. Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E. Hippocampal neurogenesis in adult Old World primates. Proc Natl Acad Sci USA. 1999; 96:5263–7.

27. Jin K, Sun Y, Xie L, Batteur S, Mao XO, Smelick C, Logvinova A, et al. Neurogenesis and aging: FGF-2 and HB-EGF restore neurogenesis in hippocampus and subventricular zone of aged mice. Aging Cell. 2003; 2:175–83.

28. Lichtenwalner RJ, Forbes ME, Bennett SA, Lynch CD, Sonntag WE, Riddle DR. Intracerebroventricular infusion of insulin-like growth factor-I ameliorates the age-related decline in hippocampal neurogenesis. Neuroscience. 2001; 107:603–13.

29. Cameron HA, McKay RD. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. J Comp Neurol. 2001; 435:406–17.

30. Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, Khan S, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry. 2003; 160:924–32.

31. Lloyd AJ, Ferrier IN, Barber R, Gholkar A, Young AH, O'Brien JT. Hippocampal volume change in depression: late- and early-onset illness compared. Br J Psychiatry. 2004; 184:488–95.

32. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N,et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science. 2003; 301:805–9.

32. Meshi D, Drew MR, Saxe M, Ansorge MS, David D, Santarelli L, Malapani C, et al. Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment. Nat Neurosci. 2006; 9:729–31.

33. Haughey NJ, Liu D, Nath A, Borchard AC, Mattson MP. et al. Disruption of neurogenesis in the subventricular zone of adult mice, and in human cortical neuronal precursor cells in culture, by amyloid beta-peptide: implications for the pathogenesis of Alzheimer's disease. Neuromolecular Med. 2002; 1:125–35.

34. Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. J Neurosci. 2001; 21:6718–31.

35. Mattson MP. Pathways towards and away from Alzheimer's disease. Nature. 2004; 430:631–9.

36. Klintsova AY, Dickson E, Yoshida R, Greenough WT. Altered expression of BDNF and its high-affinity receptor TrkB in response to complex motor learning and moderate exercise. Brain Res. 2004; 1028:92–104.

37. Will B, Galani R, Kelche C, Rosenzweig MR. Recovery from brain injury in animals: relative efficacy of environmental enrichment, physical exercise or formal training (1990–2002). Prog Neurobiol. 2004; 72:167–82.

38. Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci. 2001; 21:5678–84.

39. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci USA. 1999; 96:13427–31.

40. Trejo JL, Carro E, Garcia-Galloway E, Torres-Aleman I. Role of insulin-like growth factor I signaling in neurodegenerative diseases. J Mol Med. 2004; 82:156–62.

41. Aberg MA, Aberg ND, Hedbacker H, Oscarsson J, Eriksson PS. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. J Neurosci. 2000; 20:2896–903.

42. Lichtenwalner RJ, Forbes ME, Bennett SA, Lynch CD, Sonntag WE, Riddle DR. Intracerebroventricular infusion of insulin-like growth factor-I ameliorates the age-related decline in hippocampal neurogenesis. Neuroscience. 2001; 107:603–13.

43. Li J, Yuan J. Caspases in apoptosis and beyond. Oncogene. 2008 Oct 20;27(48):6194-206.

44. Robertson GS, Crocker SJ, Nicholson DW, Schulz JB. Neuroprotection by the inhibition of apoptosis. Brain Pathol. 2000;10(2):283-92.