Brain Aging: Rejuvenation & Regeneration

Beyin Yaşlanması: Yenilenme ve Gençleşme

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**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


**Anahtar Kelimeler:** Beyin yaşlanması, nörojenz, apoptoz, mitokondri

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) loss. 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 deterioration. However, sometimes revealed no significant correlation between hippocampal volume and age, suggesting that this structure may be relatively preserved in normal aging. 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 aging 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 regions 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.

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 rodents, non-human primates and humans. In rodents, it was shown that undifferentiated neural stem/progenitor cells (NSCs) are concentrated in the subventricular zone (SVZ) of the lateral ventricle wall and the subgranular zone (SGZ) of the dentate gyrus of the hippocampus. 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 interneurons. 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 established 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 microenvironments containing glial and endothelial cells21. The activation of neurogenic processes as a response to chronic damage is much less well documented, although some 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 primates. In aged rats, the proliferation rate of NSCs in the SGZ of the dentate gyrus is reduced by 80%. 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-1)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-

**BRAIN ATROPHY**

**NEUROGENESIS**
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 du-
during aging in rodents since like in young rodents experi-
ience, the stimulation of neurogenesis and improved
functional outcomes may be causally linked in aged bra-
ins 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 hippocam-
pal atrophy, while chronic antidepressant treatments re-
result in an increase in hippocampal neurogenesis.
Antidepressant action may require neurogenesis in mi-
ce31, although hippocampal neurogenesis was not re-
quired for the anxiolytic effects of environmental
enrichment32. It has been proposed that the age-related
decline in neurogenesis may underlie age-associated le-
arning and memory declines and may contribute to path-
ological 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 inter-
ventions even in older rodents34 suggests that the en-
dogenous 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 ro-
stral caudate, SVZ and frontal cortex rostral to the olfac-
tory 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 hu-
mans18. Endogenous augmentation of trophic factor ex-
pression (such as brain-derived neurotrophic factor
(BDNF), nerve growth factor (NGF), and FGF-2) in bra-
ins of laboratory animals has been achieved by behavio-
ral interventions35 such as enriched experience,
voluntary exercise36 and training/learning37. Both en-
riched housing and training have been shown to in-
crease synaptogenesis38 and neurogenesis39 as well. IGF-I
has neuroprotective and neurogenic effects40 and it has
been shown that peripheral infusion of IGF-I can in-
crease 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 decli-
nes, and mood disorders. Behavioral interventions such
as the diffusion of information required for lifestyle cho-
ices, the socialization of institutions providing access to
continuing education, creative occupation, physical ac-
tivity and the enjoyment of the arts may help societies
increase their overall “cognitive reserve” and reduce the
human, economic and social burden associated with in-
creased numbers of cognitively impaired elderly in de-
veloped 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 disap-
peared by apoptosis. During the development phase and in
the adulthood, physiological apoptosis “physiological cell
death” is occurred continually by the rule. Apoptosis oc-
curs 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 aszymogens (active
precursor) and called as cystein proteases since they pos-
sess 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 activ-
ating 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 affec-
tor caspases. And the affector caspases cause apoptotic
cell morphology by degrading relevant proteins (e.g. cell
skeleton proteins actin or fodrin, nuclear membrane pro-
tein lamin A, poly (ADP-ribose) polymerase (PARP) play-
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 re-
lease of cytochrome c, IAP (“inhibitors of apoptosis”), a
caspase inhibitor family, selectively inhibit caspases and
thus they stop the apoptotic mechanism. According to a recent thought on apoptosis is not only occurring in a caspase-dependent manner but there is also a caspase-independent 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 (nuclic 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.

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