

Brain Aging and Molecular Aspects of Age-Related Neurodegenerative Diseases

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Abstract

Brain is a complex organ, which undergoes many morphological and biochemical changes during aging process. Brain aging not only alters cellular, vascular and structural characteristics, but also results in a cognitive dysfunction, and partial loss of memory. Age-related neurodegenerative diseases are caused by the onset of oxidative stress, neuroinflammation, axonal transport deficits, protein oligomerization and aggregation, calcium deregulation, mitochondrial dysfunction, genetic abnormalities and immune system problems.

Keywords: Neurodegenerative; Dysfunction; Demographic studies; Nutrients; Mild chronic inflammation

Introduction

Aging is an irreversible, time-dependent, progressive, and functional impairment process that leads to mortality. The most prominent feature of aging process is the progressive decrease in physiological capacity, reduction in ability to respond adaptively to environmental stimuli, and increase in susceptibility to age-related diseases. Demographic studies have indicated that by the year 2050, the global population of individuals aged 60 and above is expected to reach 2.1 billion, effectively doubling the figure reported in 2020. Additionally, the number of adults over 80 years old will triple and reach 426 million according to United Nations Department of Economic and Social Affairs, 2022 [1].

Effect of age on the brain

Brain is a highly complex organ, which undergoes many molecular and morphological changes during aging process, such as cerebral atrophy, gray and white matter changes, volume loss, ventricular enlargement, and sulci widening [2,3]. The volume of the brain and its weight decreases with age at a rate of around 5% per decade after 40 years of age. Furthermore, the rate of decline acutely increases after the age of 70 years [4]. In individuals of 80 years or older, brain mass is reduced by 10% compared with that of young adults [5]. Brain contains several types of neural cells including neurons, oligodendrocytes, astrocytes, microglial cells, and endothelial cells. These cells are responsible for a variety of functions including receiving, processing sensory information, 'housekeeping' processes (e.g., macromolecule turnover and axonal transport), biosynthesis of many types of neurotransmitters, and maintenance and restoration of membrane potentials.

Normal aging is accompanied by decline in cognition, including deficits in memory and processing speed. It is speculated that aging negatively influences cognition. The function of neural cells not only depends on cerebral blood flow, which not only delivers oxygen and nutrients to neural cell, but also on the removal of carbon dioxide and other by-products of metabolism from the brain's interstitial space [6]. In aging brain, the deposition of cholesterol and other lipids on the inner surface of blood vessels during aging process may result in

decreased blood supply to the brain compromising cerebrovascular and cognitive functions [7]. In addition, brain aging may result in changes in neurotransmitters (acetylcholine, monoamine, and hormones). At the molecular level, aging is also accompanied by shortening of telomeres, accumulation of DNA damage, changes in gene expression, induction of oxidative stress, and onset of mild chronic inflammation [6,7].

Age-related neurodegenerative diseases

Age-related neurodegenerative diseases are a heterogeneous group of conditions with distinct clinical phenotypes and genetic aetiologies. Most age-related neurodegenerative diseases (95%) are sporadic with unknown mechanisms of pathogenesis. Only less than 5% age-related neurodegenerative diseases are of genetic origin [8]. Symptoms of age-related neurodegenerative diseases appear only when neurodegeneration has reached to an advanced stage. The pathogenesis of neurodegenerative diseases involves oxidative stress, neuroinflammation, mitochondrial dysfunction, intracellular Ca^{2+} overload, proteasomal impairment, axonal transport deficit, synaptic dysfunction, protein oligomerization and aggregation (protein misfolding), and immune system problems [8,9].

Age-related neurodegenerative diseases include Alzheimer's Diseases (AD), Parkinson's Disease (PD), Huntington's Disease (HD), and Amyotrophic Lateral Disease (ALS) [10]. At the molecular level, these diseases are accompanied by the accumulation of β -amyloid ($\text{A}\beta$) and Tau protein (τ -protein) in brains of AD patients, α -Synuclein (α -Syn) deposition in substantia nigra of PD patients, accumulation of mutated Huntingtin (Htt) in neurons of the basal ganglia in HD patients, and changes in activity of mutated Cu/Zn-Superoxide Dismutase 1 (SOD1) in motor neurons of ALS patients [8]. Considerable evidence suggests that the Blood Brain Barrier (BBB) integrity and damage to neuromuscular unit are also compromised in patients with age-related neurodegenerative diseases [8,9].

Risk factors for neurodegenerative diseases

Important risk factors for neurodegenerative diseases include old age, positive family history (genes), long term consumption of western diet (high calorie diet), sedentary lifestyle (lack of exercise), and environmental factors. The onset of neurodegenerative diseases is often subtle and usually occurs in mid to late life and their progression depends not only on genetic, but also on environmental factors [10]. These diseases lead to progressive cognitive and motor disabilities with devastating consequences to their patients.

Biomarkers for neurodegenerative diseases

As stated above, AD, PD, HD, and ALS are accompanied by the accumulation of $\text{A}\beta$ in AD, α -Syn in PD, mutated Htt in HD, and mutated Cu/Zn-Superoxide Dismutase 1 (SOD1) in ALS respectively. Levels of $\text{A}\beta$, α -Syn, mutated Htt, and mutated SOD1 in Cerebrospinal Fluid (CSF) and blood have been used as biomarkers for AD, PD, HD, and ALS. ELISA for $\text{A}\beta$, α -Syn, Htt, and SOD1 have been developed

and used in many clinical laboratories [11]. The main problems in developing ideal biomarkers for neurodegenerative diseases have been the slow understanding of pathogenesis of neurodegenerative diseases, unavailability of histopathological and biochemical diagnosis during patient lifetime, and lack of information on progression and treatment of neurodegenerative diseases.

Alzheimer's Disease

AD, the most prevalent neurodegenerative disease in humans, is characterized by chronic neurodegeneration in the nucleus basalis, hippocampus, and cerebral cortex and deposition of two lesions in the brain-extracellular Amyloid-Beta ($\text{A}\beta$) plaques (senile plaques, SP) and intracellular Neurofibrillary Tangles (NFTs) with brain atrophy. The extracellular deposits of $\text{A}\beta$ plaques contain aggregated $\text{A}\beta$ peptides, while intraneuronal NFTs have aggregates of hyperphosphorylated forms of the tau protein [12].

Parkinson's Disease

At the molecular level, PD is accompanied by the accumulation of misfolded proteins (α -syn), ubiquitin-proteasome system dysfunction, formation and accumulation of Lewy bodies (α -syn), deposition of $\text{A}\beta$ and hyperphosphorylation of tau along with elevation in oxidative stress and neuroinflammation [13]. These parameters are prognostic markers for cognitive deficits in PD. Recent studies have indicated that α -syn interacts with tau as well as $\text{A}\beta$ [13]. These interactions contribute to the formation of hybrid oligomers (heteroaggregates) in brains of PD patients.

Huntington's Disease

HD is an autosomal dominant inherited neurodegenerative disease characterized by the CAG expansion mutation of the Htt gene. This gene is located on chromosome 4p16 in humans, resulting in the clinical manifestation of HD [14]. In normal healthy individuals, the number of CAG repeats is typically less than 35, whereas individuals with HD have 36 or more CAG repeats. The range of CAG repeats in the majority of HD patients is usually between 40 and 50 and causes adult-onset symptoms [14,15]. Huntingtin protein is expressed ubiquitously throughout the body. Normal huntingtin protein plays an important role in intracellular trafficking, including membrane recycling, clathrin-mediated endocytosis, neuronal transport and postsynaptic signaling [15]. Mutant huntingtin protein has been reported to alter intracellular Ca^{2+} homeostasis, disrupts intracellular trafficking, promotes mitochondrial and synaptic dysfunctions, and impairs gene transcription [14,15].

Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a complex, progressive, multifactorial disease, characterized by the progressive loss of upper and lower motor neurons leading to weakness in limb and bulbar muscles with atrophy, spasticity, weight loss and ultimately respiratory failure. The majority of ALS cases ($\approx 82\%$) are sporadic [16]. Less than 5% cases are familial, which are caused by mutations in the 43-kDa trans-activating response region DNA-binding

protein (TDP-43). Familial ALS cases also involve mutation in Cu, Zn Superoxide Dismutase (SOD1), a principal cytoplasmic superoxide dismutase in humans. It plays a major role in redox potential regulation. It catalyzes the transformation of the superoxide anion ($O_2^{\cdot-}$) into hydrogen peroxide [17]. Collective evidence suggests that induction of neuroinflammation [16,17], excessive production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), onset of mitochondrial dysfunction, axonal deterioration, and deposition of toxic ubiquitinated neuronal inclusions are closely associated with the pathogenesis of ALS [16-18].

Effects of Anti-Aging Diet and Sirtuin on Age-Related

Neurodegenerative diseases

Diet, exercise, and sleep play important roles in maintaining good health and longevity. A healthy diet not only provides energy and building material for the body, but also has ability to promote longevity and protect against age-related chronic diseases. Regular exercise not only supports cardiorespiratory, cardiovascular, cerebrovascular, and muscular fitness but also boosts energy, improves insulin sensitivity, increases blood flow, elevates the expression of neurotrophic factors, reduces inflammation, oxidative stress. As stated above, aging is a natural and irreversible process where humans have no choice. However, modern days humans are more focused on living a quality healthy life despite persistent aging. Anti-aging diet is generally used to oppose the effect of aging on human body.

Humans have also used anti-aging diet to delay the onset of age-related neurodegenerative diseases. Among various diets patterns (Mediterranean diet, Western diet, vegetarian, and Okinawan diet, and keto diet), the Mediterranean diet is healthiest. Mediterranean diet is characterized by the consumption of fresh green vegetables (potassium, and magnesium), colored fruits (carotenoids and flavonoids), whole grain pasta (fiber), legumes (fiber), fish (docosahexaenoic and eicosapentaenoic acid), extra-virgin olive oil (tyrosol, hydroxytyrosol, oleuropein, and oleocanthal), fresh garlic (allicin, S-allyl cysteine, diallyl sulfide, diallyl disulfide, and diallyl trisulfide), low levels of dairy products (low amounts of cheese and yogurt), nuts and seeds, and moderate amounts of red wine (resveratrol and flavonoids) [19]. It is suggested that long-term consumption of Mediterranean diet [19], not only inhibits neuroinflammation and oxidative stress throughout the body, but also maintains telomeres length, and retards the onset of neurodegenerative diseases [19-21].

Another most promising targets for anti-ageing research are proteins belonging to the sirtuin family [22]. Mammals contain seven members of sirtuin family (SIRT1-SIRT7) including SIRT1, SIRT6 and SIRT7, which are present in the nucleus, whereas SIRT3, SIRT4, and SIRT5 localized to the mitochondria. SIRT2 is localized in the cytosol. Sirtuins contain both mono-ADP ribosyl-transferase and NAD^+ -dependent histone deacetylase activities [22]. Histone deacetylase activity of sirtuins is associated with the removal of acetyl groups from the target proteins resulting in either inhibition

or activation. SIRT1, SIRT6 and SIRT7 have many functions including: regulation of transcription, control of cellular metabolism, DNA repair, cell survival, tissue regeneration, inflammation, circadian rhythms and neuronal signaling [23]. SIRT3-5 are important for switching to mitochondrial oxidative metabolism during Caloric Restriction (CR) and modulate stress tolerance [24]. Importantly, sirtuins not only promote health and lifespan extension in animals, but also their dysregulation has been linked to age-related chronic diseases such as neurological disorders (AD, PD, HD, ALS, metabolic syndrome, and type 2 diabetes), cancer, and heart disease [25-27].

Recent studies on CR in the aging of rodent models of AD suggests that CR activates sirtuins, decreases ROS, increases O_2 consumption, inhibits chronic neuroinflammation, and boosts cellular functions. The molecular mechanisms between the over-expression of sirtuins and extended healthy aging or delaying age-related diseases in humans have not been fully understood. However, it is suggested that sirtuins cooperate with many transcription factors, including PGC-1 α , NF κ B, p53 and FoxO [28,29]. In addition, more research on the effect of CR mimetic on expression of sirtuins may eventually lead to therapeutic strategies not only for healthy aging, but also provide information on molecular mechanisms associated with the delay in disease progression in patients with AD, PD, HD, ALS, type 2 diabetes, cancer, and heart disease [28,29].

Conclusion

Brain aging is accompanied by gross morphological changes, including cerebral atrophy, sulci widening, and cerebrovascular changes. The inability to repair neuronal damage leads to impaired physiological functions, loss of intercellular communication among neural cells, onset of chronic inflammation and oxidative stress, and induction of cognitive decline. These processes increase the risk of age-related neurodegenerative diseases. Understanding the molecular mechanisms associated with the involvement of sirtuins in brain ageing and age-related neurological disorders may support the development of new strategies to delay ageing and onset of age-related neurodegenerative diseases.

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