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The Aging Brain: Impact of Iron Metal in Neurotoxicity

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ABSTRACT

Critical changes in cellular and molecular processes that occur with ageing disturb the central nervous system's homeostatic equilibrium. Metal accumulation makes the brain more vulnerable to neurotoxic shocks through mechanisms such mitochondrial failure, calcium-ion dyshomeostasis in neurons, a buildup of damaged molecules, reduced DNA repair, decreased neurogenesis, and impaired energy metabolism. These characteristics have been shown to be the cause of neuronal damage that result in a variety of neurological diseases. According to several studies, the development of neurodegenerative disorders including Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis is strongly correlated with metal buildup, aberrant protein expression, and protein synthesis. This review illustrates iron metal's accumulation and impacts on the development of neurological disorders in relation to the ageing brain.

Keywords: Blood-Brain Barrier; Reactive Oxygen Species; Neurodegerative Disorders; Oxidative Stress, Neurotoxicity

Abbreviations: MRI: Magnetic Resonance Imaging; CNS: Central Nervous System; BBB: Blood-Brain Barrier; ROS: Reactive Oxygen Species; PIR: Peripheral Insulin Resistance; GLUT: Glucose Transporter; FE: Iron; FTN: Ferritin; BFR: Bacterioferritin; ISC: Iron Sulphur Cluster

Introduction

Aging is a natural biological process that appears periodically. According to estimations, there will be about 70 million more persons in the age group more than 65 of age than there were ten years ago [1]. Meanwhile, physiological and functional changes in the brain are common with healthy or normal aging and have been linked to a general reduction in cognitive ability [2]. Considering gradual healthy aging, several magnetic resonance imaging (MRI) studies have revealed that the frontal cortex, which is involved in cognitive processes including speed processing and working memory, regularly decreases volume with age. A decrease in the amount of grey and/or white matter is another sign of healthy aging [3]. The grey matter and frontal cortical alterations brought on by aging have an influence on executive functioning in the elderly. The prefrontal-executive theory suggests that changes to the frontal cortex's structure and operation will result in a precise decline in executive functions, which eventually leads to a generalized cognitive impairment [4]. Additionally, aging has an undesirable effect on the rate at which information is processed. The processing speed theory, which claims that a single or universal mechanism that may be caused by damage to the integrity of the white matter across the brain may be responsible for the cognitive decline associated with aging, supports this [5].

The accumulation of damaged proteins, the breakdown of nucleic acids, changes in gene expression, increased cellular oxidative stress, and dysregulated energy balance and signaling systems are all factors that contribute to aging. The altered brain physiology, which includes cognitive dysfunctions in addition to reduced motor and sensory capabilities, shows that the central nervous system's (CNS) cells are

susceptible to these alterations [6-8]. The blood-brain barrier (BBB) isolates the brain from the rest of the body on a structural and functional basis. It selectively allows certain nutrients, lipid vesicles, and other tiny molecules to enter while blocking the passage of poisonous substances that are harmful to the brain. It also excretes neurotoxic proteins in addition to other harmful substances [9]. Numerous environmental toxins, industrial chemicals, naturally occurring toxins, and pharmaceutical medications are assumed to have negative health effects because of the nervous system's toxicity [10]. Numerous neurodegenerative illnesses have neurotoxicity as a primary contributing aspect [11]. According to studies, the normal process of healthy aging is accompanied by cellular and molecular changes in the neurons. These changes render the neurons more susceptible to environmental neurotoxins, metal ion dyshomeostasis, degeneration, and genetic insults associated with certain diseases. This review aims to present findings on the impact of iron toxicity on the aging brain.

Aging and its Hallmarks in the Brain

The nervous system experiences many morphological and functional changes as we age, which is also true for other organ systems. According to cellular and molecular data, aging causes oxidative stress, mitochondrial dysfunctions, protein aggregates, ion dyshomeostasis, decreased clearance of toxins, metabolic impairment, DNA damage, and death in neurons and glia in the brain. These alterations lead to neuronal death and are made severe in a few susceptible neurons that have been specifically chosen [12]. Numerous metals have been implicated in neurotoxicity throughout aging. These metals include lead, mercury, tin, aluminum, calcium, cobalt, copper, iron, magnesium, manganese, molybdenum, selenium, sodium, zinc, nickel, and cadmium. These metals are necessary for a variety of internal biological processes [13]. The dysregulation of these metals in the aging brain results in many abnormalities and raises the possibility of age-related neurodegenerative disorders.

Mitochondria Dysfunction in the Aging Brain

Age-related changes start to manifest as people become older. Aging is linked to changes in the morphology, compositions, and functions of the mitochondria [14]. Alterations in the concentration and effectiveness of the intracellular respiratory chain complexes, an increase in mitochondrial DNA mutations, an expansion of the mitochondria due to an increase in calcium ion loads, and the production of reactive oxygen species (ROS) are just a few of the changes that the mitochondria experiences during old age [15,16]. The synergistic catabolic actions of antioxidant enzymes often control these free radicals [17]. Damage to tissue and DNA will result from these free radicals' incapacity to catabolism. Because ROS triggers oxidative stress, which enhances the sensitivity and fragility of the mitochondrial lipid bilayer, there is less ATP available for energy metabolism [18]. Additionally, this oxidative stress triggers various types of improperly functioning calcium pathways in the mitochondria's intracellular space, which impairs the processing of calcium ions and triggers catabolic and apoptotic pathways [19,20]. The rate of neuronal death brought on by mitochondrial dysfunction increases with normal aging in both humans and animals. There is still a role for SNV in this situation because some brain areas are more susceptible to neuronal mitochondrial dysfunctions [15]. Numerous age-related neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis, become severe by a higher incidence of neuronal death caused by mitochondrial dysfunction and diminished neurogenesis [19,21].

Reduction in Neurogenesis

Primarily in the neuronal population of the hippocampus, dentate gyrus, and olfactory bulb in the adult brain, normal aging is frequently linked with decreased neurogenesis [22]. The reduction in neurogenesis in these regions has an impact on olfactory function, learning, and memory decline [23]. This decreased neurogenesis is predicted to be caused by a number of altered metabolic pathways that come with aging. Increased oxidative stress, malfunctioning mitochondrial oxidative metabolism, impaired DNA repair, and neuroinflammation are a few of them.

Impaired Energy Metabolism

In the brain and numerous cells in the peripheral tissues, aging dramatically impairs many metabolic processes, including the metabolism of glucose and lipids [24]. It has been proposed that the cell's diminished capacity to respond to insulin is what causes the decline in glucose metabolism that is related to aging. Because these cells are unable to boost glucose transport to offset the high quantity of glucose circulating in the circulation, this impaired response of the cells to insulin is possible. Peripheral insulin resistance (PIR) enhances the risk of several serious illnesses, including type 2 diabetes, heart disease, Alzheimer's disease, and stroke [25,26]. Another consequence of the increase in oxidative stress and the accumulation of HNE molecules, which are known to be associated with aging, is reduced neuronal glucose metabolism for energy production. The glucose transporter (GLUT3), a membrane protein that promotes the transit of glucose across the cell membrane neuron, was negatively affected by these events, which is what caused this impairment [27]. Dyslipidemia is caused due to an increase in the metabolism of different lipid species with aging. Dyslipidemia is regarded as a risk factor for vascular dementia, Alzheimer's disease, and stroke [28].

Impact of Iron Metal Neurotoxicity in Aging Brain

The dysregulation of heavy metals in the aging brain can cause several cellular and metabolic changes, as well as raise the risk of age-related neurodegenerative disorders [29]. The impact of iron metal is discussed in this section of the review. This is because of the curious fact that, although the body requires this iron element for several crucial biological processes [30]. In the following, we discuss iron metal neurotoxicity.

Iron

The brain contains an enormous amount of iron (Fe), a significant metal. It is crucial for many of the brain's physiological functions, such as the production of ATP, the development of the neuronal myelin sheath, and the proper function of neurotransmitters [31]. In addition to serving as an enzyme cofactor, it has a role in regulating synaptic activity and neuronal development [32]. Therefore, a wide range of metabolic reactions depends on Fe homeostasis. The ferritin family of proteins (Fe-storage proteins) regulates the homeostasis of iron. The canonical ferritin (FTN), the heme-containing bacterioferritin (BFR), and the DNA-binding proteins of starving cells (DPS) are the three subfamilies that together make up the ferritin family. The oxidation of Fe2+ to Fe3+ and the production of Fe core minerals are carried out, respectively, by the two subunits of the FTN, the H-chain, and L-chain [33]. The BBB should stop iron-regulating proteins like ferritin, transferrin, ceruloplasmin, and others from freely moving from the bloodstream to the CNS. The cerebrovascular endothelial cells of the BBB bind to the differic-transferrin that is circulated, and the resultant complex passes over into the intercellular compartment [34]. Studies have indicated that certain parts of the brain, such as the substantia nigra and the globus pallidus of the basal ganglia, have higher Fe concentrations in older individuals age [35]. This results from the BBB and cerebrospinal fluid barrier being affected by aging [36]. ROS are produced more often as a result of the Haber-Weiss and Fenton reactions at this higher Fe level [37].

Since aging has connections to a reduction of the antioxidant system, ROS causes oxidative stress, which encourages mitochondrial malfunction, damages DNA, and enhances protein misfolding and accumulation. Age-related neurodegenerative disorders are the outcome of these. The cellular toxic stress brought on by the elderly brain's elevated iron concentration may be a factor in the decline in cognitive function that is associated with aging [38]. In eukaryotic cells, the production of heme and the iron sulphur cluster (ISC) takes place in the mitochondria. Heme and ISCs are essential components required for the assembly of electron transport complexes [39]. According to the report, heme biosynthesis declines with age. The cytochrome C oxidase, also known as complex IV, which is capable of creating a transmembrane proton gradient across the inner membrane of the mitochondria, is selectively reduced in expression and function in heme shortage. As a result, the mitochondria's capacity to produce energy is compromised. Similar outcomes were seen in a rat hippocampus and a human brain cell line after heme production was reduced, which causes mitochondrial malfunction [40]. Higher Fe concentrations in the substantia nigra tend to increase oxidative stress, which increases the risk of age-related neurodegenerative diseases like Parkinson's disease [41,42]. The development of a neurodegenerative illness that resembles Parkinson's disease in older persons has been linked, interestingly, to increased Fe intake in neonates, according to research using mouse models [30].

According to the investigation of Ashraf and colleagues in an aging brain, the ratio of iron to microglia is increased, especially in the basal ganglia, whereas the ratio of iron to astroglia is low in the striatum but elevated in the substantia nigra and globus pallidus [43]. The astrocytes become more sensitive as they aged to iron deposition and oxidative damage. The alteration of iron homeostasis also affects astrocytes and microglia. It accelerates aging and raises the risk of acquiring neurodegenerative illnesses by causing the microglia to overproduce inflammatory cytokines [43,44].

Conclusion

The biological process of aging is a natural phenomenon. The cognitive and motor deterioration seen in older individuals is recognized to be caused by accompanying morphological, functional, and molecular changes in the aging brain. Alzheimer's disease, Parkinson's disease, and Huntington's disease are examples of age-related neurodegenerative diseases that are brought on by certain characteristics of the normal aging process. Although industrialization continues to grow, more people are being exposed to environmental toxins, notably metals. The current review thus concentrated on identifying the potential effects of iron on the aging brain. Oxidative stress, molecular accumulation, neuroinflammation, and neurodegeneration are frequent features of iron's neurotoxic effects on the aging brain. In future, more studies will be required for understanding how iron accelerates brain aging. This will make it easier to identify possible therapeutic targets for addressing the neurologic issues that aging iron causes.

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