Review Paper:

Oxidative Stress in Neurodegenerative Illness: A Comprehensive Overview

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Abstract

Age is the primary risk factor for various human diseases including neurological conditions such as Alzheimer's, Parkinson's and amyotrophic lateral disease, which affect a growing population of senior adults. These disease illnesses are marked by the progressive degeneration of neuronal cells, impaired motor or cognitive skills and the buildup of improperly aggregated molecules. Mitochondrial (MC) dysfunction is a primary characteristic of advancing age, especially in energy-demanding organs such as the heart, muscle tissue, brain and liver. Neurons depend predominantly on MC, which generates the energy necessary for several cellular functions such as the plasticity of synapses and neurotransmitter production.

The brain is especially susceptible to oxidative stress (OS) and injury due to its elevated use of oxygen, inadequate defences against antioxidants and high levels of polyunsaturated lipids, which are highly prone to oxidation. Safeguarding systems, particularly those that produce antioxidants, is crucial for preserving neuronal functionality and longevity. The research examines the influence of MC OS on aging, particularly neurological diseases. Comprehending the biological processes associated with MC and OS in aging and neurodegeneration could facilitate the identification of novel techniques for enhancing health and prolonging longevity.

Keywords: Oxidative Stress, Neurodegenerative Illness, Pathology, Biochemistry.

Introduction

Age is the principal risk factor for several human diseases and neurological disorders, affecting an expanding population of senior adults. These pathological conditions encompassing Alzheimer's Disease (AD)[18], Parkinson's Disease (PD)[19], Huntington's Disease (HD)[12], Amyotrophic Lateral Stroke (ALS)[6] and Spinocerebellar Apathy (SCA)[11], are distinguished by the progressive degeneration of neuronal cells, impaired motor or mental abilities and a buildup of aberrantly aggregated amino acids. An expanding corpus of information underscores bioenergetic dysfunctions and modifications in redox equilibrium in the brain associated with advancing age. The brain consists of highly specialized cells that inhabit various anatomical locations and necessitates approximately 20% of the body's baseline oxygen for functioning[16]. It is unsurprising that modifications in cerebral metabolism of energy result in degeneration.

Cellular power is primarily generated through oxidative phosphorylation occurring in Mitochondria (MC) which are essential organelles for various cellular functions including energy metabolism, calcium regulation, the production of lipids and apoptotic[15]. Glucose metabolism is the primary energy source in the brain due to its high output rate which is essential for meeting neuronal energy requirements[2]. Neurons depend predominantly on MC, which generates the energy necessary for several cellular functions including synaptic plasticity and neurotransmitter production. Moreover, due to the pivotal function of MC for energy expenditure and the maintenance of redox equilibrium, the investigation of age-related MC diseases is increasingly gaining attention. This review examines the function of MC in aging management, particularly emphasizing MC Oxidative Stress (OS) in Neurodegenerative (NG) disorders[4].

NG disorders are primary contributors to disability and mortality globally, garnering significant attention due to their substantial effects on the aging population[10]. These disorders primarily involve the progressive decline of neuronal activity, resulting in cerebral atrophy. The study presents the following prevalent NG illnesses: AD, PD, HD and ALS. Despite the varied brain regions and various etiologies associated with different neurological conditions, they influence analogous cellular and molecular mechanisms. Despite the growing initiatives to create suitable therapeutics for NG illnesses, there remains a significant demand for effective therapeutic molecules, yet numerous hurdles persist[5].

The precise methods by which processes in cells and molecules influence the evolution of these illnesses, remain unclear to this day. The absence of reliable biomarkers impedes the potential for early identification of most of these disorders. Personalized therapy is necessary due to side consequences, such as inflammatory processes, arising from illness development; the primary concern is biological obstacles.

To ensure therapeutic drug access to the Central Nervous System (CNS), developing suitable vectors capable of traversing the Blood-Brain Barrier (BBB) is essential[20].

There is an ongoing necessity for the advancement of novel methodologies that facilitate the entry of neuroprotective molecules into the brain, thereby enabling more effective therapies for central nervous system illnesses. This research examines the importance of OS in NG diseases. The emphasis will be on the connections among neuroprotection, antioxidants, OS, neural inflammation and MCl disorders, along with recent developments in the field.

MC and OS

Adenosine Triphosphate (ATP) is vital for cellular function, signaling and general activity and is acknowledged as the cell's energy exchange[7]. MC facilitates ATP synthesis via the electron transportation chain and phosphate oxidation. They synthesize chemicals to mitigate OS, regulate programmed cell death and reduce other cellular respiratory processes. The accumulation of MC with diverse redox proteins and MC malfunction is believed to contribute to generating Reactive Oxygen Species (ROS) in the physiological milieu (Figure 1).

Literature indicates that OS biomarkers associated with aging and neurological illnesses include macromolecules such as lipids, proteins and deoxyribonucleic acid (DNA)[17]. ROS harms lipids by participating in lipid peroxidation, resulting in malondialdehyde (MDA), protein carbonyls and the oxidation of 8-oxo-deoxyguanosine in DNA[14]. Cardiolipin (CL) is a phospholipid located in the membrane of the MC and is significantly associated with protein components of the electron transportation channel[8]. It is only necessitated by adenine triphosphate translocase, which operates as an inner membrane transporter. The accumulation of cardiolipin in polymorphic fats, including linoleic acid and its proximity to ROS generation sites in the electron transportation chain of MC render it a principal substrate for ROS.

CL is susceptible to oxidation, resulting in MC electron transportation chain impairment and is believed to participate in releasing pro-apoptotic proteins. ROS directly impairs proteins and lipids, obstructing MC bioenergetics. It exerts a detrimental impact on DNA in MC, which is directly linked to promoter inactivation and a decrease in MC expression of genes. It is posited that increased production of ROS in MC, characterized by prolonged half-lives such as hydrogen peroxide, lipid hydroperoxides, or reactive aldehydes like MDA and acrolein (originating from other sites but ultimately accumulating in MC) induce dysfunction in the MC and impede processes in the body, resulting in different illnesses[3]. The role of MC and dysfunctional MC due to ROS in many diseases is illustrated in figure 2.

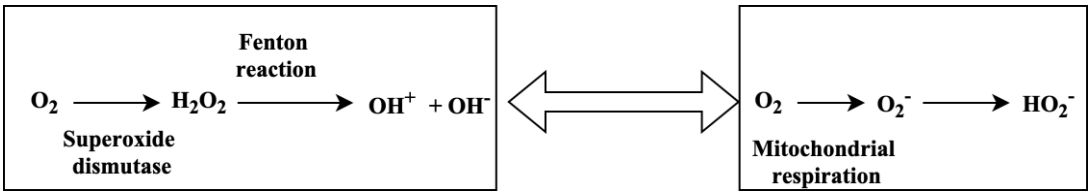

Figure 1: ROS process

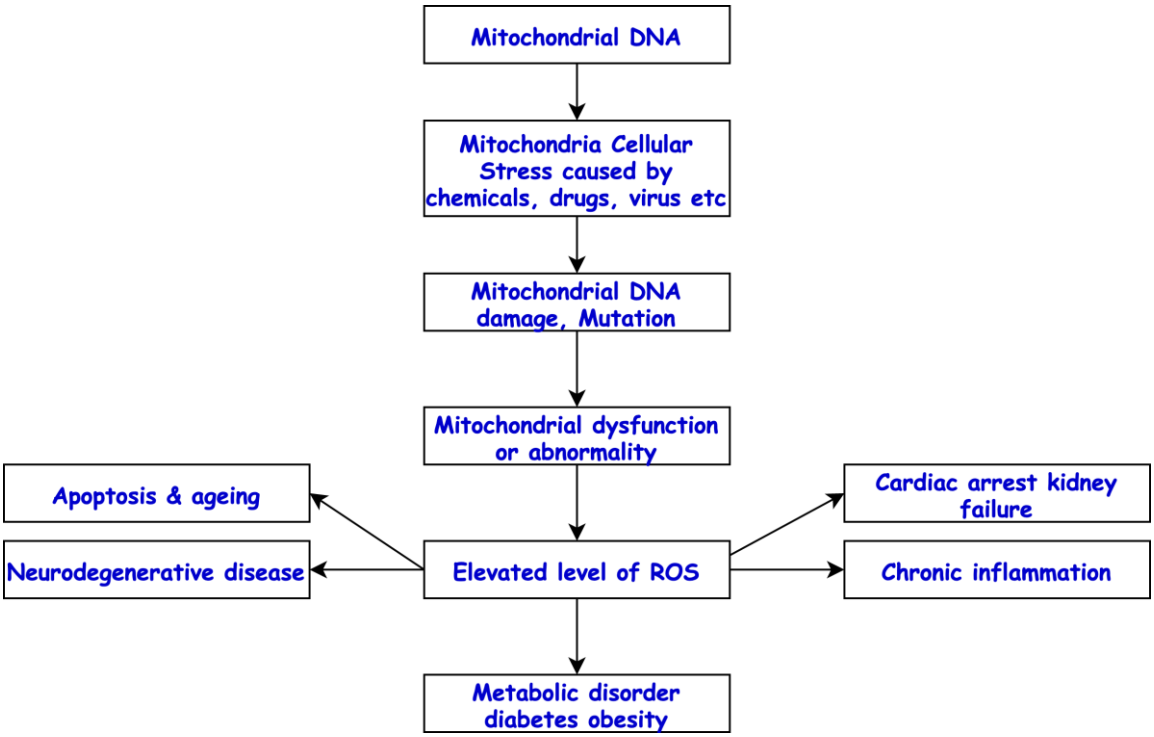

Figure 2: Metabolic disorder diabetes obesity analysis

The brain is significantly abundant in oxidizable substrates such as polyunsaturated fatty acids and catecholamines. The elevated oxygen demand, comparatively fewer antioxidant enzymes and prevalence of catalytic transition metals in specific brain areas render it more susceptible to OS. Extensive studies have demonstrated that the buildup of diverse OS markers in fatty acids, proteins and DNA contributes to cerebral aging. An elevated concentration of 8-OH-dG is detected as significantly greater in MC DNA than in nuclear DNA[1]. Oxidatively degraded MC DNA results in numerous point mutations, as evidenced by sequential and cloning techniques.

A prevalent deletion observed in elderly individuals, accumulated in MC DNA, results from ROS-induced OS. The primary cause of the highest accumulation of this alteration is the brain's active participation in the OS of serotonin[9]. The quantity of various DNA glycosylases responsible for mt-DNA repair diminishes with age, resulting in somatic changes in mt-DNA within the elderly brain. OS to MC lipids and amino acids impedes bioenergetic operations; additionally, modifications to mt-DNA and DNA in the genome can disrupt these functions by downregulating the amino acids' replication in phosphorylation by oxidation[13].

MC Impairment in Senescence

Aging is a destructive physiological process caused by the buildup of cellular damage, resulting in gradual organ malfunction and mortality. Despite the limited comprehension of the aging process, elucidating the fundamentals of human aging is a paramount objective in biomedicine. The most recognized and enduring idea regarding aging is the "liberated radicals concept of aging" which posits that aging and age-related degenerative disorders stem from free radical assaults on cells and organs. The idea was expanded to emphasize MC as the primary source of ROS in aged cells. The scientists elucidated how MC disarray significantly contributes to age-related alterations in postmitotic tissues including neurons and muscles. This perspective was founded on particle microscopic and biochemical analyses of insects and animals.

A theory was proposed regarding intrinsic MC aging and its potential association with age-related alterations in other cellular organelles. This theory is currently referred to as the MC hypothesis regarding aging. Since its initial publication, scientific proof regarding the role of MC in aging has proliferated. MCs are crucial for energy production via phosphate oxidation and maintaining cellular metabolic balance, signaling, distinction and aging. MC dysfunction is a primary characteristic of aging, especially in energy-demanding organs such as the heart, muscles, brain and liver. While substantial data corroborate the significance of the nuclear production of ROS in aging, fresh evidence has indicated the participation of its permeability shift in the aging mechanisms. The nuclear potential at the membrane was initially lower in older animals and intracellular peroxide concentrations were elevated in cells from older animals compared to younger ones.

The age-related decline in the membrane potential of MC has been linked to diminished ATP generation in the tissues of aged animals and cells of humans from older individuals. The MC permeation transition results from a generic pore associated with the MC permeability transition which occurs when organelles are overwhelmed with magnesium.

Aging modifies cytosolic calcium uptake and increases the susceptibility of the mPTP to calcium under OS conditions. Numerous investigations conducted over the past several decades utilizing separated MC have demonstrated that the function of respiration complexes of enzymes in the electron transport chain progressively diminishes with age in livers, skin fibroblasts, the brain and muscle tissue of people (Figure 3). The shape of MC altered with age. Electron microscopy investigations revealed that MC disarray increases with aging across many cells and organs. The MC are living organelles capable of structural remodeling via fusion and division; aberrations in these processes have been associated with aging in mammal cells.

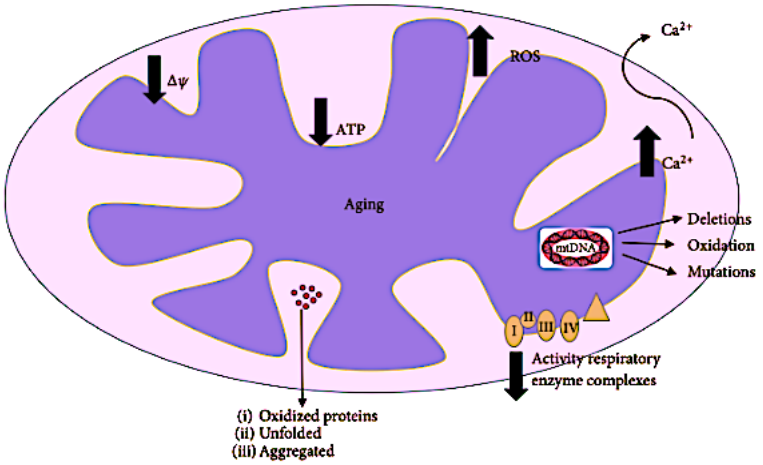

Figure 3: MC investigations

OS to mt-DNA related to age was demonstrated to be associated with MC degradation in the liver, kidney and brain of rabbits and mice. Mt-DNA losses corresponded with the concentration of damaged guanosines in mt-DNA. Moreover, mt-DNA progressively accumulated mutations with aging throughout many human tissues, encompassing single mutations, large-scale modifications and simultaneous duplications. Membrane rRNAs were oxidized and destroyed in response to OS settings.

Oxidized peptides build rapidly with aging, leading to the unfolding phenomena that result in protein aggregates. Numerous respiratory digestive enzymes including complex I and ATPase are recognized as targets of oxidizing. The oxidation of lipids is especially significant in the membrane surrounding the MC because of its high cardiolipin concentration. OS was observed to reduce cardiolipin concentrations more significantly than other fatty acids and this reduction was directly correlated with the diminished function of the cytochrome oxidase enzyme.

A transition from glycolysis to pulmonary glycolysis in yeast has been observed to enhance ROS production, stimulate the antioxidant reaction and elevate synthesis, resulting in a longer lifespan and a hormetic response. MC failure has been associated with an additional aging-related phenomenon, a shorter telomere. PGC-1a/b are the primary controllers of MC biogenesis and function, linking reduced telomere length to MC dysfunction. Upon DNA damage, p53 levels rise, resulting in the inhibition of PGC-la/b and subsequent MC malfunction. PGC-la was observed to diminish its function, resulting in reduced activity and malfunctioning MC, especially in muscle tissue. Amplification of PGC-1a can enhance aging muscles and significantly contributes to longevity.

Neuroinflammation

A feature of NG processes is the dysfunction of the immune system. Neuroinflammation and OS are critical factors that must be considered in both the onset and development of NG illnesses, as they are intricately connected in their pathogenesis. Cells that are inflammatory release reactive substances that generate OS. Specific ROS and Reactive Nitrogen Species (RNS) might enhance intracellular signaling pathways, resulting in elevated expression of pro-inflammatory proteins. Neuroinflammation and OS can mutually exacerbate each other, particularly under pathological conditions. When the body's reducing and reduction processes (redox) are equilibrated, the inflammation response functions as a defense system; however, a redox imbalance occurs in NG incidents. The inflammatory response is inadequate, resulting in neuroinflammation inside the central nervous system.

Neuroinflammation is an inflammatory reaction of the central nervous system to events that disrupt homeostasis. This reaction encompasses various cell types throughout the CNS, including astrocytes and microglials. In addition to NG illnesses, this reaction can be detected in multiple neurological incidents, including ischemia, viral and traumatic occurrences. Studying the interactions between the body's immune and central nervous systems is essential due to their significant role in the onset and development of these disorders.

The MC electron transport chain in OS is the primary source of intracellular reactive oxygen species. In contrast, the predominant inflammatory OS in neuroinflammation is the hyperactivated phagocytic oxidase 2. It is essential to emphasize that OS and neurological inflammation are separate disease phenomena. These two processes influence and/or precipitate one another throughout the progression of the disease, the restriction of one leads to the suppression of the other.

Microglia activation is the principal component of neurological inflammation. Microglia swiftly react to disruptions in cerebral homeostasis caused by stress, trauma, illness, or disease. The stimulation of microglia leads to the release of several pro-inflammatory and cytotoxic substances that contribute to neurological inflammation and neurodegeneration. Microglia demonstrate advantageous functions in preserving homeostasis and restructuring neural networks. Microglia protect the brain through the phagocytic removal of Aß. When microglia forfeit their advantageous activities, inflammatory processes, synaptic degradation and brain injury ensue. The absence of aggregated Aß elimination amplifies harmful signaling networks, exacerbating inflammation, OS and neurotoxicity. Figure 4 synthesizes the roles of microglial in the pathological condition.

The Function of Pro-Oxidants in OS

In addition to other external and endogenous reports, numerous pro-oxidants significantly contribute to OS. Reports indicate that vegetables and fruits are abundant in polyphenols, serving a significant function as effective antioxidants. This knowledge enhances the incorporation of these components into everyday meals. The persistent health issues and NG disorders suggest that in addition to antimicrobial agents, other elements linked to OS, subsequently recognized as pro-oxidants, are involved. Pro-oxidants absorb any endobiotic or exotic food entities, inducing OS by generating ROS or RNS or impairing the protective antioxidant system's functionality in cells or organs. Pro-oxidants can be classed as either exogenous or endogenous, with additional subdivisions: exogenous includes pathogens, medications, toxicants and dietary components while endogenous include anxiety, ion flux, weather, pollutants in the environment and drug intermediates.

Certain antioxidant polyphenols are documented to act as pro-oxidants in the form of specific transitional metals. The flavonoid structure mainly influences the antioxidant capabilities and the copper-initiated pro-oxidant activity.

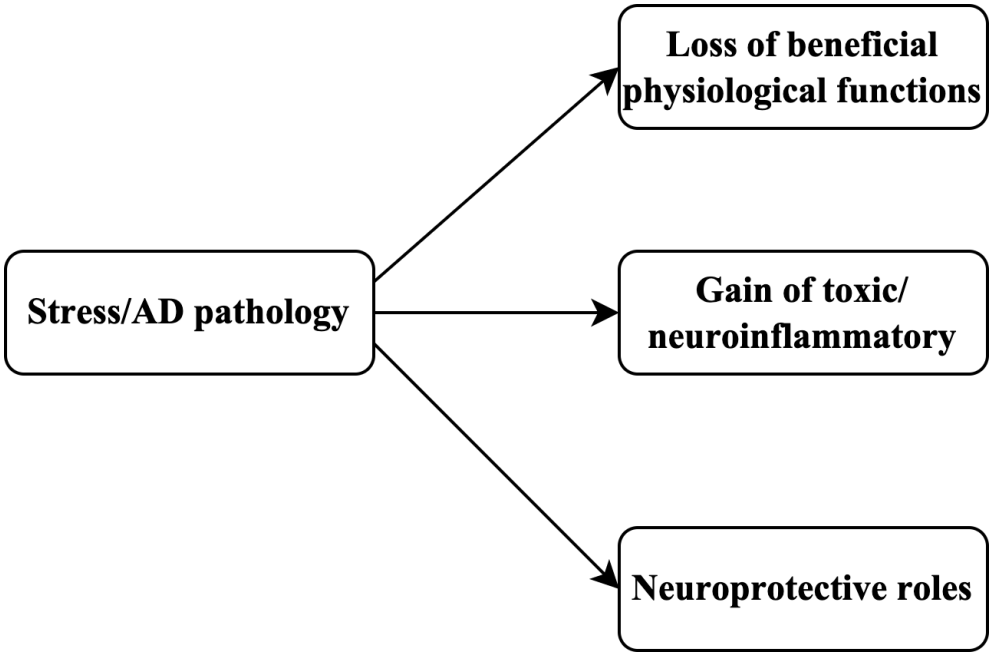

Figure 4: Stress / AD pathology classification

In flavonoids, -OH substitution confers antioxidant capabilities whereas flavone and flavanone are lacking -OH substitution and are serving as the structural backbone of flavonoids. All exhibit neither antioxidant nor copper-based pro-oxidant effects. The pro-oxidant and antioxidant benefits of the quercetin myricetin were examined through variations in the deoxyribose breakdown test.

Flavonoids and polyphenols are acknowledged for their dietary scavenger properties against pro-oxidants. They protect against oxidative-induced illnesses by neutralizing detrimental free radical actions, especially quenching reactive elements that generate ROS/RNS. Similarly, depending on the dosage, ascorbic acid can act as an antioxidant and a pro-oxidant. Vitamin C has a harmful effect due to its auto-oxidation, affecting gene expression. Given that pro-oxidants, alongside antioxidants, significantly contribute to OS and related illnesses. Understanding pro-oxidants is essential for addressing OS and neurotoxicity.

The Influence of Heavy Metals on OS: The impact of heavy metals on OS and their detrimental consequences on the circulatory, cardiovascular, reproductive and central neurological systems along with vital organs such as the renal system, lungs, liver and mind is indisputable. Multiple behaviors lead to the bioaccumulation of metal ions in both the environment and individuals. Metals that are toxic in conjunction with other xenobiotics, such as pesticides, adversely impact hematological and immune function.

Extensive studies indicate that being around elevated amounts of heavy metallic substances, such as lead (Pb) and mercury (Hg), along with deficiencies in critical metals like selenium, or Se and zinc (Zn), results in OS. This results in an aberration in the cellular redox status, adversely affecting biomolecules (DNA, RNA, amino acids and fats) and essential organs such as the kidneys, liver and central nervous system. Reports suggest that mercury (Hg) is unnecessary for biological processes; its presence and buildup harm living things. Mercury-induced OS harms membranes and biomolecule burning while facilitating the formation of H_2O_2, oxidizing lipids in the respiratory membranes and oxidizing proteins. Mercury is identified as neurotoxic and continuous exposure results in detrimental effects on the brain, leading to shyness, tremors, cognitive impairments and alterations in auditory and visual perception.

Lead, a widely utilized metal, is recognized as harmful to humans primarily due to its creation of OS. The extent of damage caused by lead is contingent upon the exposure method, health condition, dosage, duration of exposure and the individual's age. Lead exhibits a strong affinity for the -SH group (found in amino acids) and metal cofactors, leading to diminished activity of anti-oxidant enzymes that participate in many biological reactions. It is linked to increased OS and metabolic malfunction which causes the failure of essential organs.

Moreover, arsenic, a metalloid, is recognized as harmful to living creatures, as prolonged contact results in carcinogenesis, toxicity and gene toxicity in mammals. Arsenic readily binds to the -SH group of glutathione, subsequently producing H_2O_2. Arsenic inhibits glucose absorption in cells, leading to gluconeogenesis and lipid oxidation. It has a detrimental impact on the Krebs cycle, resulting in MC malfunction. Metallic substances are implicated in producing ROS and RNS, resulting in OS that ultimately compromises MC and biological molecules, influencing cell growth, differentiation and mortality.

The Function of OS Communication in the senescence compared to Apoptosis: Aging and cell death are inherent processes that result in the deterioration of numerous biological functions. Countless neurological disorders such as AD, PD, HD and ALS, are associated with the aging process. Cellular death, or programmed dying of cells, is a natural occurrence that transpires as a spontaneously controlled process inside a biological system. In addition to normal aging, ROS significantly contributes to cell death, resulting in a substantial rise in the number of senescent cells within tissues. Biomolecules serve as indicators of OS, facilitating the detection of OS-induced cell death and apoptosis. Increased levels of ROS coupled with a reduction in antioxidants can lead to numerous age-related pathologies and illnesses including cancer, cardiovascular disorders and neurological conditions.

Exposure to increased quantities of ROS disrupts cellular equilibrium, resulting in detrimental consequences on biomolecules. Cellular senescence can occur in various cell types including epithelial, lymphoid, cartilage, nerve and vascular cells. OS and MC ROS induce telomere shortening and malfunction, leading to cell senescence. ROS harms neuronal cells, leading to adverse effects on the brain. ROS-mediated cellular signaling serves as a reliable biomarker of cell apoptosis. The cumulative effect of ROS and senescence of cells contribute to aging. It is instrumental in numerous neurological disorders (AD, PD, HD, ALS etc.).

Literature provides substantial data illustrating the function of ROS in the onset and advancement of various pathologies, ranging from cardiovascular diseases to NG disorders. Diverse chemicals, particularly antioxidants (such as vitamins, polyphenols and quercetin), mitigate OS and diminish the incidence of severe diseases. This category of antioxidants is noteworthy due to its efficacy in illness prevention and therapy, which is devoid of side effects. Investigating additional synthetic and natural antioxidant molecules that facilitate novel approaches for treating illnesses induced by OS is imperative.

OS: Regulator of NG Disorders: Oxygen is an essential element of the breathing process and is vital for the existence of a living thing. OS encompasses numerous free radicals and compounds originating from molecular oxygen. Despite MC being a center for oxygen and ROS, the cell has a homeostatic mechanism to regulate ROS levels under normal conditions. NG disorders are defined by apoptosis or necrosis and the malfunctioning of neurons, resulting in detrimental effects on the nervous system. The brain is particularly susceptible to OS as the most metabolically active organ. The brain has a greater demand for air, consuming 20% more than other body components. The brain is abundant in redox-active metals, such as copper and iron, which are crucial in forming ROS.

The membranes of brain cells, abundant in polyunsaturated fatty acids (PUFA), have a heightened susceptibility to the peroxidation of lipids. The amino acid glutathione significantly contributes to detoxifying ROS in neuronal cells when present in optimal concentrations. A diminished concentration of glutathione in the brain is associated with an increased amount of ROS, resulting in NG disorders such as AD, PD, HD and ALS.

Conclusion

NG illnesses are more common among aging populations, constituting a significant health issue for this demographic. Considerable efforts have already been undertaken to find neuro-pathological, biological and genetic indicators for earlier disorders identification. Over the past thirty years, substantial research has been conducted to elucidate the role of MC and OS in natural aging and NG disorders. The overall result unequivocally confirms that these mechanisms deteriorate with aging and are established characteristics which are extensively implicated in NG disease progression, if not the initiation. Whether MC malfunction and OS can indicate an early diagnosis of aging-related dysfunctions or viable treatment targets, remains uncertain. A deeper understanding of the mechanisms linking MC and OS in aging and neurotoxicity yields novel techniques to enhance the quality of life for older people, positively affecting modern society.

In conclusion, despite numerous studies investigating the efficiency of radicals in mitigating NG signs, compelling evidence demonstrating their neuroprotective impact remains limited. Current clinical research yields more favorable results, particularly in using antioxidants as adjunctive therapeutic agents with additional therapies. A comprehensive study is essential for elucidating the specific functions of ROS in diverse NG disorders and formulating antioxidant-based treatment strategies. Moreover, an enhanced understanding of MC processes and OS in lifespan and Alzheimer's facilitates novel techniques to improve the level of life for elderly individuals and benefit contemporary society broadly.

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