NeuroUpdates
Neuroscience Updates, 2024; 2(1): 67-98

Review Article

Breaking Down Under Stress: Exploring the Impact of Stress on the Brain and Neurodegenerative Disorders

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0009-0004-2283-8776

Checked for Plagiarism: Yes
Peer reviewers approved by:
Dr. Melika Andrew
Editor who approved publication:
Dr. Nasrollah Moradikor
Language Editor:
Dr. Adeel Ahmed Abbasi

Article History:
Received: September 05, 2024
Accepted: November 20, 2024
Published: December 10, 2024

10.47176/update.2024.67

ABSTRACT

This review shows challenges neurological pathologies of various disorders inducing migraine, amyotrophic lateral sclerosis, Parkinson's, Alzheimer's, and Huntington's diseases caused by stress. Long-lasting stress triggers a series of biochemical reactions that cause the degeneration of neurons and causing long-lasting cognitive impairment. The most cause of neurological disorders are oxidative stress, neuroinflammation, and mitochondrial dysfunction. In the case of Alzheimer's disease, stress can exacerbate Alzheimer's pathology by enhancing tau protein to be phosphorylated and triggering the misfolding of amyloid-beta protein. Stress in Parkinson's disease is a leading factor in alpha-synuclein aggregation and the subsequent death of dopaminergic neurons. A variety of therapeutic strategies aimed at mitigating these stress-related pathways are under investigation as anti-inflammatory strategies, antioxidant therapies, and agents supporting mitochondrial function. The review outlines neuroprotective effects of lifestyle interventions: cognitive behavioral therapy, regular physical exercise, and diet-related approaches. current research underlines the need for comprehensive therapeutic approaches targeting stress-related mechanisms in attempts to delay the causes of neurodegenerative diseases and improve patient health.

KEYWORDS: Oxidative Stress, Chronic Stress, Brain Inflammation, Mitochondrial Dysfunction, Neurodegenerative disorders

[DOI: 10.47176/update.2024.67]

1. Introduction

The brain is highly vulnerable to the effects of stress, as it regulates the organism's response to environmental stressors via the HPA axis. Chronic stress triggers the constant release of glucocorticoids, which may include cortisol, and leads to lesions in neurons, especially those implicated in memory and cognition, including the hippocampus [1]. Long-term activation of these stress pathways leads to further dysfunction of neurotransmitter systems that contribute to mood and cognitive function, including serotonin and dopamine. Stress-induced synaptic plasticity has been associated with an inability to learn and remember-for the downregulation of BDNF, a key protein responsible for neurogenesis and synaptic growth [2]. Chronic stress was associated with neuroinflammation, known to play an important role in neurodegeneration. Stress may have a favorable influence on the activation of microglia (the immune cell of the brain) by releasing pro-inflammatory cytokines such as IL-1β and TNF-α. Neuroinflammatory response can cause additional neuronal damage by disrupting the neural circuitry homeostasis. Chronic stress also compromises the integrity of the BBB, which allows peripheral immune cells to penetrate the brain; this might act to further amplify neuroinflammatory events and foster the progression of neurodegenerative pathologies. Thus, a determination of how stress impacts neuroinflammation will be integral in the development of therapeutic strategies that mitigate these injurious effects of stress on the brain [3]. Chronic stress has been associated with ANS dysregulation, especially in the balance between sympathetic and parasympathetic branches. Over-activation of the sympathetic nervous system enhances the release of catecholamines, which promotes neurodegenerative changes by way of neuronal and glial cell damage. While the inability of the parasympathetic branch to counteract stress-induced sympathetic activation may impede the restitution of normal physiological function. This dysregulation of the ANS is presently under investigation as a therapeutic target, aimed at mitigating the neurotoxic effects of chronic stress on brain functioning [1]. Critical mechanism underlying the impairment of brain functions is through the stress-induced oxidative stress. The high levels of reactive oxygen species and diminished antioxidant defenses result in the oxidative damage of neurons and glial cells. Oxidative stress leads to mitochondrial dysfunction, an organelle critical in energy production in neurons, causing neuronal death and synaptic dysfunction of neurons. In recent years, much emphasis has been put on the role of antioxidants as neuroprotective agents in the neurodegenerative conditions caused by stress [4]. Stress is a factor that accelerates neurodegenerative processes through mechanisms involving neuroinflammation induction, oxidative stress, and mitochondrial dysfunction. One of the key proposed mechanisms of how stress accelerates neurodegeneration is neuroinflammation. Chronic stress leads to the activation of microglia and astrocytes, which release pro-inflammatory cytokines, thus causing neuronal damage and cell death This mechanism has been described in most neurodegenerative pathologies, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, indicating a common pathway through which stress may contribute to disease progression [2]. Apart from neuroinflammation, oxidative stress also constitutes a major factor contributing to neurodegeneration under conditions of stress. Overproduction of ROS, together with impaired antioxidant defenses, causes oxidative damage to proteins, lipids, and DNA, culminating in neuronal death. Various studies have substantiated that stress-induced oxidative stress is the factor that hastens neurodegeneration seen in diseases such as AD, PD, and ALS. These diseases are targeted for treatment with strategies that reduce oxidative stress, including antioxidant therapies as a means to decelerate disease progression [4]. Chronic stress has been closely associated with the progression of neurodegenerative diseases, especially Alzheimer's disease (AD). One indicated that the acceleration of Aβ accumulation, characteristic of AD, was caused by stress and that tau phosphorylation, going further to form neurofibrillary tangles, was enhanced. Chronic stress impairs Aβ clearance by microglia, promoting Aβ deposition and neurotoxicity [5]. Long-term exposure to stress has also been associated with shrinkage in the hippocampus, an area of the brain that is very important for memory formation and one of the most affected areas in AD patients. All this amplifies the previously presented findings that stress plays a major role in accelerating pathology and the cognitive decline associated with AD. In addition, Chronic stress has been found to increase the death of dopaminergic neurons in the substantia nigra of PD brains, one of the most affected regions in Parkinson's disease. Stress-induced neuroinflammation has

[DOI: 10.47176/update.2024.67]

become one of the proposed mechanisms in accelerating dopaminergic degeneration through activating microglia and astrocytes in large part. Moreover, stress was also implicated in the aggregation of alpha-synuclein protein involved in the pathogenesis of PD and oxidative damage of the dopaminergic neurons themselves [6]. Stress negatively influences another neurodegenerative disorder as Huntington's disease. Stress accelerates the progression of motor symptoms and cognitive decline in HD patients. Evidence has shown that chronic stress actually enhances mutant huntingtin protein aggregation-a hallmark of HD pathology. Besides, stress-induced neuroinflammation and oxidative stress have been implicated as accelerators of neuronal death in HD, especially within the striatum, which is the most affected region of the brain by the disorder. Thus, the need arises for therapeutic strategies aimed at targeting the stress-induced exacerbation of HD symptoms [7]. Stress also leads to amyotrophic lateral sclerosis, a progressive motor neuron disease. previous studies, chronic stress can enhance the neuroinflammatory and oxidative stress responses, accelerating motor neuron degeneration in ALS. It has been proven that stress has the potential to accelerate the development of muscle weakness and atrophy in ALS patients through disruption of neuromuscular junctions and also by promoting motor neuron death. More recently, dysregulation of the HPA axis in response to stress was associated with accelerated disease progression in ALS, pointing to the consideration of stress management as a potential therapeutic strategy in ALS [8]. The other key mechanism by which stress hastens neurodegeneration involves mitochondrial dysfunction. Mitochondria are the powerhouses of a neuron and play a very significant role in providing energy to the neurons. Their functioning is impaired due to chronic stress, leading to an energy deficit and neuronal death [9]. Mitochondrial dysfunction consequently promotes the development of neurodegenerative diseases, particularly in energetically demanding brain regions such as the hippocampus and striatum. The most recent research is targeted at the development of therapies directed toward protection against mitochondrial function in neurodegeneration due to stress. Acceleration of neurodegenerative processes also occurs through stress-induced dysregulation of neurotransmitter systems. Chronic stress causes an imbalance in the levels of important neurotransmitters, including dopamine, serotonin, and glutamate, which results in excitotoxicity and neuronal damage [10]. In this chapter we focus on such dysregulation that has been associated with many neurodegenerative diseases as Parkinson’s, Alzheimer’s, migraine and Stress-Induced Brain Changes and Huntington's, and interfere with neurotransmitter imbalance is a useful strategy against stress-induced neurodegeneration in addition to the therapeutic strategies for stress-related neurodegenerative diseases and how to manage behavioral and lifestyle interventions to reduce the stress.

2. Oxidative Stress and its Impact on Neurons

2.1. Role of Reactive Oxygen Species (ROS) in Neurodegeneration

Reactive oxygen species (ROS) have a dual role in cellular processes where low levels act as signaling molecules implicated in cell proliferation, differentiation, and survival, while high levels induce oxidative stress leading to cellular damage and death [11]. In neurons, which have a high metabolic rate and limited regenerative capacity, the harmful effects of excess production of ROS are even more pronounced. ROS induce cellular damage to proteins, lipids, and DNA, facilitating mitochondrial dysfunction, impaired synaptic transmission, and neuronal loss, which are significant contributors to the pathogenesis of neurodegenerative disorders such as AD and PD. For instance, in AD, ROS enhance Aβ toxicity, which accelerates neuronal death and decline in cognitive abilities [12]. ROS has also been associated with mitochondrial dysfunction, considering that mitochondria are one of the major sources and targets of ROS. Impaired mitochondrial oxidative phosphorylation is associated with the leakage of electrons from the transport chain, thus shifting to promote the generation of ROS. ROS formed inside the mitochondria may further cause deterioration of mitochondrial DNA, proteins, and lipids, aggravating mitochondrial dysfunction and contributing to neuronal death. In this regard, such a vicious cycle has been a critical mechanism in neurodegenerative pathologies, where neuronal cells with dysfunctional mitochondria are exposed to increased levels of oxidative stress in Huntington's disease [13]. ROS activate several pathways

[DOI: 10.47176/update.2024.67]

of cell death, including apoptosis, necrosis, and autophagy, all contributing to neurodegeneration. ROS-induced cellular protein and lipid damage activates pro-apoptotic proteins, such as Bax, and inhibits anti-apoptotic proteins, such as Bcl-2, leading to programmed cell death. This also leads to neuroinflammation, since the release of damaged cellular components will result in the activation of microglia and astrocytes, leading to the release of pro-inflammatory cytokines and further ROS production. Thus, a vicious circle of oxidative stress and inflammation is created, which self-accelerates neuronal loss [14]. Other emerging evidence indicates that neurotoxicity mediated by ROS does not occur only in the neurons but extends to other cellular components of the brain, which include astrocytes and oligodendrocytes. Astrocytes, vital in the maintenance of the BBB and metabolic support for neurons, are extremely susceptible to oxidative injury. ROS-induced impairment of astrocytes can promote defective glutamate clearance and subsequent excitotoxicity, causing further neuronal injury. Furthermore, oligodendrocytes damaged by the oxidative reaction disrupt the myelination of the axon, resulting in further damage to neuronal communications and possibly accelerating neurodegenerative processes [15].

2.2. The Effect of Chronic Stress on Neuronal Integrity

Chronic stress facilitates the state of oxidative stress in neurons; hence, there is an accumulation of various damages that impairs neuronal integrity and hastens neurodegeneration. Chronic stress promotes overproduction of ROS in neurons through the induction of high levels of glucocorticoids release, such as cortisol. Cortisol-induced oxidative stress is particularly destructive to the memory and learning parts of the brain, including the hippocampus, because it enhances neuronal death and synaptic dysfunction [16]. This has been associated with downregulation of brain-derived neurotrophic factor, a protein important for neuronal survival and synaptic plasticity, further exacerbating the adverse effect of chronic stress on brain function. Stress also diminishes the intrinsic defense against antioxidants within the brain and enhances neuronal damage. Typically, the brain utilizes various antioxidant enzymes such as superoxide dismutase and glutathione peroxidase to neutralize ROS and protect neurons against oxidative damage. These antioxidant systems become overwhelmed in chronic stress conditions or are downregulated, allowing unchecked increases in ROS levels. For instance, recent previous studies show that stress suppresses the transcription of the nuclear factor erythroid 2-related factor 2 (Nrf2), which is a major transcription factor of antioxidant response, thus declining the capacity of the brain to fight oxidative stress. This disequilibrium of ROS generation and cellular antioxidant defenses results in progressive neuronal damage and develops neurodegenerative disorders [17]. Chronic stress enhances mitochondrial function impairment in neurons, facilitating oxidative stress and promoting neurodegeneration. Indeed, it has been shown that stress-mediated glucocorticoid signaling disrupts mitochondrial oxidative phosphorylation, which in turn reduces ATP production while increasing the generation of ROS [18]. Besides, mtDNA becomes more susceptible to damage when under chronic stress conditions, further fostering impaired mitochondrial function and enhanced oxidative stress. This mitochondrial dysfunction is highly detrimental in neurons, as neurons have high energy demands and rely greatly on proper mitochondrial function for synaptic activity and plasticity. Besides oxidative stress, chronic stress also induces neuroinflammation that further exaggerates neuronal damage. Stress-induced activation of microglia and astrocytes releases pro-inflammatory cytokines, including IL-1β and TNF-α. These, in turn, facilitate ROS production and oxidative injury. Interplay between oxidative stress and neuroinflammation establishes a vicious feedback cycle that accelerates neuronal death and impairs neuronal integrity. The evidence in recent decades has shown that both oxidative stress and inflammation might be targeted to protect neurons from chronic stress-induced damage [19].

2.3. Stress Effect on Microglia and Astrocytes

Chronic stress is a factor that highly contributes to the activation of microglia and astrocytes, two of the major players in neuroinflammation. Microglia are resident immune cells of the brain that, after exposure to any form of stress, change from a resting to an activated state by producing pro-inflammatory molecules such as cytokines, chemokines, and ROS. This activation commonly originates with the chronic release of

[DOI: 10.47176/update.2024.67]

glucocorticoids, such as cortisol, occurring with chronic stress that impairs the ability of the immune system of the brain to maintain homeostasis. When the microglia are activated for too long, they can damage neurons and synaptic connectivity. Prolonged activation is thereby linked to neurodegenerative diseases, including Alzheimer's and Parkinson's [20]. Another type of glial cell is astrocytes; these also become reactive under chronic stress. Generally, these cells are involved in the nourishment of neurons through the maintenance of the BBB, neurotransmitter level control, and metabolic support. During stressful conditions, chronic stressors may provoke astrogliosis, which is made up of an increase in size and number of astrocytes to produce inflammatory mediators, enhancing neuroinflammation. The long-term activation outcome is a toxic environment for neurons, further accomplice to neuronal dysfunction and death. In this way, stress-induced astrogliosis is thought to interfere with the normal function of astrocytes in maintaining the levels of glutamate, therefore contributing to excitotoxicity-a mechanism of neuronal injury due to excess levels of glutamate [21]. Chronic stress-induced activation of microglia and astrocytes also causes the production of neurotoxic products, which include NO and prostaglandins, amplifying neuroinflammation. Such toxic substances trigger oxidative stress and impair both neuronal and glial cells, preparing the environment for a chronic neuroinflammatory response. This forms a vicious cycle in which chronic stress further exacerbates neuroinflammation, which in turn fosters progressive neuronal injury and promotes the pathogenesis of neurodegenerative diseases. Previous studies suggest that modulation of microglia and astrocyte activities may be one of the most effective pharmacological strategies against neurotoxic consequences caused by chronic stress. The effects of activated microglia and astrocytes by stress also extend beyond neuroinflammation to include synaptic plasticity impairments. Astrocytes regulate synaptic homeostasis via interactions with neurotransmitter systems. When both are activated, their protective functions at the synapse are disrupted, leading to impaired synaptic transmission and cognitive deficits seen in many stress-related neurodegenerative conditions [22].

2.4. The Connection Between Chronic Stress, Cytokines, and Brain Inflammation

Chronic stress strongly influences the brain's immune system, prominently by altering cytokine expression to drive neuroinflammation. Pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, are released in response to stressful events, and these are significant mediators of the inflammatory response in the brain [23]. These cytokines, secreted mainly by activated microglia and astrocytes, have been implicated in the promotion of cascades of inflammatory events impairing neuronal function. Increased levels of IL-1β have been associated with synaptic dysfunction and memory deficits, thereby linking chronic stress to cognitive impairments commonly observed in neurodegenerative diseases. Chronic stress is also associated with a development of an imbalance between pro- and anti-inflammatory cytokines, shifting the balance toward ongoing inflammation. Normally, anti-inflammatory cytokines, including IL-10, play a significant role in resolving inflammation and restoring tissue homeostasis. In chronic stress, however, there is suppression of anti-inflammatory cytokine production while that of pro-inflammatory cytokines remains elevated, leading to sustained brain inflammation. This continuous inflammatory environment mediates neuronal damage and disrupts synaptic communication, thereby promoting neurodegenerative pathologies in diseases such as Alzheimer's and Huntington's [24]. The integrity of the BBB was further disrupted by the overproduction of stress-related cytokines, allowing peripheral immune cells and inflammatory molecules to enter the brain and thereby further amplify neuroinflammation. The breach in integrity of the BBB serves to further heighten the neuroinflammatory response, with peripheral immune cells including macrophages, invading the brain and contributing to additional production of pro-inflammatory cytokines [25]. This inflammation impairs neuronal functions and enhances the aggregation of misfolded proteins, such as amyloid-β in Alzheimer's disease, thus accelerating the onset of neurodegeneration. Previous studies have also shown that cytokines produced due to chronic stress could affect the functioning of the HPA axis, which has an important regulatory role in the body's response to stress. Under chronic stress conditions, the HPA axis disorder promotes increased glucocorticoid secretion, which in turn increase cytokine production, thereby exacerbating neuroinflammation. Forming a feed-forward cycle among

[DOI: 10.47176/update.2024.67]

stress, cytokines, and neuroinflammation that perpetuates neuronal damage and may well be considered the central mechanism of development in stress-related neurodegenerative disorders [26].

2.5. Mitochondrial Dysfunction and Energy Deficits

Chronic stress impairs mitochondrial function that is important for neuronal health maintenance. Mitochondria are the necessary organelles in energy production, especially in the neurons of the brain, which require a great deal of energy. Such stressors disturb mitochondrial dynamics; it upsets the balance of mitochondrial fission and fusion, usually maintained for health [27]. Chronic stress disrupts this balance and results in mitochondrial fragmentation and dysfunction. Fragmentation is associated with lower production of ATP, which impairs neuronal functions and survival. Mitochondrial dysfunction caused by a stressor can result in overproduction of reactive oxygen species within neurons. Mitochondria normally produce ROS as a by-product of cellular respiration, but in conditions of chronic stress, this excess production of ROS results in oxidative damage to mitochondrial DNA, proteins, and lipids. Such oxidative damage further impairs mitochondrial efficiency to meet the energetic demands of neurons, especially in the hippocampus, an area of the brain associated with memory and learning. This chronic mitochondrial dysfunction, due to stress, in turn contributes to neuronal death and thus exacerbates neurodegeneration [28]. Stress-impaired mitochondria also disturb intracellular calcium homeostasis in neurons. Even though mitochondria participate in buffering intracellular calcium, chronic stress impairs this function and promotes neuronal dysregulation of calcium signaling [29]. This sets off a cascade of deleterious events such as activation of apoptotic pathways and excitotoxicity, which could result in neuronal death. Previous studies proved that stress-induced mitochondrial dysfunction can further contribute to the development of neurodegenerative diseases such as Alzheimer's and Parkinson's, in which impaired mitochondrial function accelerates neuronal degeneration. Mitochondrial dysfunction promotes the acceleration of neurodegenerative pathologies in neurodegenerative diseases like Alzheimer's and Parkinson's disease. Mitochondrial biogenesis-the formation of new mitochondria-is impaired under chronic stress conditions. This decreases the expression of transcriptional regulators that drive mitochondrial biogenesis, including PGC-1α, thereby limiting the ability of the neuron to replace damaged mitochondria with functional ones under conditions of stress. A decline in mitochondrial biogenesis, combined with increased oxidative damage, lowers mitochondrial population and function in neurons, contributing to neurodegenerative disease and cognitive decline associated with chronic stress [30].

2.6. Effects on Brain Energy Metabolism and Neuronal Death

Chronic stress inhibits mitochondrial function, which has a deep impact on the energy metabolism within the brain and is highly critical to the maintenance of neuronal health and cognitive functions. Neurons rely intensively on aerobic respiration inside mitochondria to perform ATP production; thus, such a decline in ATP availability directly results from mitochondrial dysfunction induced by stress. This energy deficit constrains vital neuronal processes, including synaptic transmission and plasticity, which are important in learning and memory. Therefore, the consequence of chronic stress is not only cognitive impairment but also acceleration of the neurodegenerative process because of the lack of energy supply for neuron maintenance [31]. Apart from the ATP deficit, the mitochondrial dysfunction caused by stressors perpetuates metabolic imbalance within the brain through changed glucose utilization-the major source of energy for neurons. Stress reduces glucose uptake and metabolism in neurons, hence influences the rates of both glycolysis and oxidative phosphorylation. With metabolic shift, neurons have to depend on less efficient energy sources, such as fatty acids, which could be more ROS-producing. All these accumulated ROS add to the energy deficit, forming a toxic environment in the brain that, over time, leads to damage and death of neurons [32]. The chronic energy deficits due to mitochondrial dysfunction also interfere with the ability of neurons to maintain ionic gradients across their membranes. This impairment affects ion pumps, including sodium-potassium ATPase critical for maintaining neuronal excitability and preventing excessive calcium influx. The resulting ionic imbalance can lead to excitotoxicity, a process in which excessive calcium entry into neurons is triggered by over activation of glutamate receptors. This in turn

[DOI: 10.47176/update.2024.67]

further enhances the dysfunction of mitochondria, as calcium overload in mitochondria triggers cell death pathways, including both apoptosis and necrosis, which leads to widespread neuronal loss [33]. The consequence of insufficient energy production along with oxidative stress, coupled with disturbed calcium homeostasis, is a result of the activation of the pathways that induce cell death in neurons. Indeed, under conditions of chronic stress, mitochondria, critical regulators of apoptotic signaling, become permeabilized to release several pro-apoptotic factors, including cytochrome c, into the cytoplasm. This precipitates an apoptotic cascade culminating in a form of programmed cell death. Over time, this contributes to the progressive loss of neurons seen in neurodegenerative disease-particularly in those regions of the brain most vulnerable to stress, including the hippocampus and cortex [34].

2.7. Protein Misfolding and Aggregation in Stress-Related Diseases

Protein misfolding and aggregation critically play a role in several neurodegenerative diseases, the pathology of which is enhanced by chronic stress. These include Aβ plaques, tau tangles, and alpha-synuclein aggregates that characterize AD, tauopathies, and PD, respectively. The stressful stimulation of oxidative stress and inflammation advances the misfolding and subsequently the aggregation of these proteins, thereby accelerating neurodegeneration. For instance, ROS generated by stress can directly affect Aβ precursor proteins, enhancing their tendency toward forming toxic plaques. An accumulation of these Aβ plaques interferes with neuronal function and thus contributes to cognitive decline in AD [35]. Chronic stress affects tau protein hyperphosphorylation and aggregation. Intracellular accumulation of hyperphosphorylated tau as tangles impairs microtubule stability and axonal transport. Chronic stress then activates various signaling pathways leading to tau hyperphosphorylation, including the glycogen synthase kinase-3β pathway. This pathway is further modulated by stress hormones such as cortisol, which can then enhance tau pathology and accelerate neurodegeneration in tauopathies. Tau aggregated through prolonged stress disrupts neuronal function and contributes to the progression of the two tauopathies, frontotemporal dementia and chronic traumatic encephalopathy [36]. Aggregation of alpha-synuclein forms Lewy bodies in Parkinson's disease, implicated in neuronal loss and motor dysfunction. Chronic stress enhances alpha-synuclein aggregation through the promotion of oxidative stress and inflammation, further enhancing the misfolding and accumulation of the protein. Interaction of alpha-synuclein with inflammatory cytokines, facilitated by stress, further promotes the development of Lewy bodies and neuronal death. This all contributes to the pathogenesis of Parkinson's disease and other synucleinopathies and underlines the role of stress in alpha-synuclein pathology [37]. Stress has also been shown to affect protein quality control machinery dealing with misfolded proteins. Stress conditions disrupt chaperone proteins and proteasomes important for the degradation of misfolded proteins. This impairment results in the accumulation of misfolded proteins, including Aβ, tau, and alpha-synuclein, thereby further accelerating neurodegeneration. Thus, chronic stress not only promotes protein misfolding and aggregation but also impairs the capacity of the brain to cope with these pathological proteins, thereby promoting neurodegenerative diseases [38]. The unfolded protein response (UPR) is involved in cellular responses that deal with proteins misfolded in the ER. Chronic stress disrupts the UPR, leading to increased misfolding and aggregation of proteins. Under normal conditions, activation of UPR promotes restoration of ER homeostasis through enhanced folding capacity and degradation of misfolded proteins, and decreased protein synthesis. However, chronic stress turns this into a sustained UPR that now becomes maladaptive and, in turn, leads to neurodegenerative diseases [39]. In neurodegenerative diseases, chronic stress activates UPR persistence, characterized by an increased expression of stress response genes such as ATF4, CHOP, and upregulation of XBP1. While initially UPR tries to manage protein misfolding caused by stress, its prolonged activation leads to cell death and neuronal damage. It constitutes a maladaptive UPR that contributes to the build-up of misfolded proteins, such as Aβ, tau, and alpha-synuclein, thereby exacerbating neurodegeneration. The chronic UPR is associated with increased apoptosis and cellular dysfunction, characteristics typical of neurodegenerative diseases caused by stress [40]. Chronic stress-induced UPR dysfunction influences mitochondrial health and energy metabolism. UPR and mitochondrial dysfunction are interlinked, indicating that chronic stress-induced UPR may lead to mitochondrial

[DOI: 10.47176/update.2024.67]

dysfunction through disrupting coordination between the ER and mitochondrial functions independently of each other. This disrupts mitochondrial ATP production, leading to increased oxidative stress, which, in turn, cause protein misfolding and neurodegeneration [41]. Indeed, the interplay between UPR and mitochondrial dysfunction puts into light the intricate relation among stress, protein homeostasis, and neuronal health Among the research approaches that have been proposed are modulating UPR pathways with pharmacological agents and enhancing protein quality control mechanisms. These strategies would allow the retrieval of proper UPR function, reduction of protein misfolding, and enhancement of neuronal survival in the context of chronic stress [42].

3. Stress Effect on Neurodegenerative Diseases

A number of risk factors, including aging, heredity, metal exposure, brain injury, lifestyle choices, malnutrition, diabetes, immunological dysfunction, cardiovascular problems, infections, and psychological disorders, have been linked to AD even though its precise mechanisms are still unknown [43,45]. Stress plays a major impact in aggravating AD as shown on (Figure.1). The "harmful stress cycle" model, stress can raise glucocorticoid (GC) levels, aggravating AD pathogenesis and hastening cognitive decline. Additionally, stress damages neural circuits, which results in neuropsychiatric symptoms like anxiety and depression [46-48]. The hypothalamus-pituitary-adrenal (HPA) axis is a crucial stress-response mechanism that releases hormones that raise GC levels, which exacerbates stress-related illnesses and accelerates the progression of AD [49]. Stress exposure has been shown in experimental models to increase the synthesis of amyloid-beta peptides and amyloid precursor proteins (APP), which are essential for the development of AD [50,51]. Stress also increases the production of amyloid plaques, a characteristic of AD, in mice models with family mutations [52,53]. In addition to inducing tau hyperphosphorylation, which is essential for the advancement of AD, chronic stress and GC also intensify amyloid-beta's detrimental effects on cognitive performance [54,55]. Lifelong stress and GC exposure can have a substantial impact on the development and course of AD, especially via their effects on tau hyperphosphorylation [55]. According to previous research on animals, stress-induced increases in glucocorticoids decrease motor function, whilst increased levels of corticosterone cause a notable loss of nigral neurons [57]. Additionally, it has been demonstrated that long-term stress lowers dopamine levels in important brain areas like the striatum, hippocampus, and frontal cortex [58]. Although gender differences are still unknown, stress causes a buildup of alpha-synuclein in male PD mice, which results in motor impairment [62]. Individuals with negative personality qualities typically have worse quality of life and more severe non-motor symptoms because they are more sensitive to stress. [59]. Dopaminergic neuron degeneration in Parkinson's disease (PD) is largely caused by oxidative stress and neuroinflammation, which includes mechanisms like microglial activation, proinflammatory cytokine production (IL-1β, IL-6, TNF-α, and IFN-γ), activation of the NF-κB pathway, overexpression of COX-2, and increased levels of oxidative stress markers [60-65]. Extended periods of stress can cause oxidative stress, which raises the peroxidation of proteins and lipids [66]. Quinones produced by the oxidation of catecholamines, including dopamine, harm cellular membranes and worsen neurodegeneration by causing lipid peroxidation [67]. Similar to other neurodegenerative illnesses, stress has been linked to HD. Studies employing an HD mouse model have revealed changes in HPA axis function, indicating a potential role for cortisol in the disease's progression [68]. Furthermore, Scarpa et al. found that beta-forkhead box O-3 transforming growth factor (TGFβFOXO3) is involved in the relationship between stress and HD [69].

[DOI: 10.47176/update.2024.67]

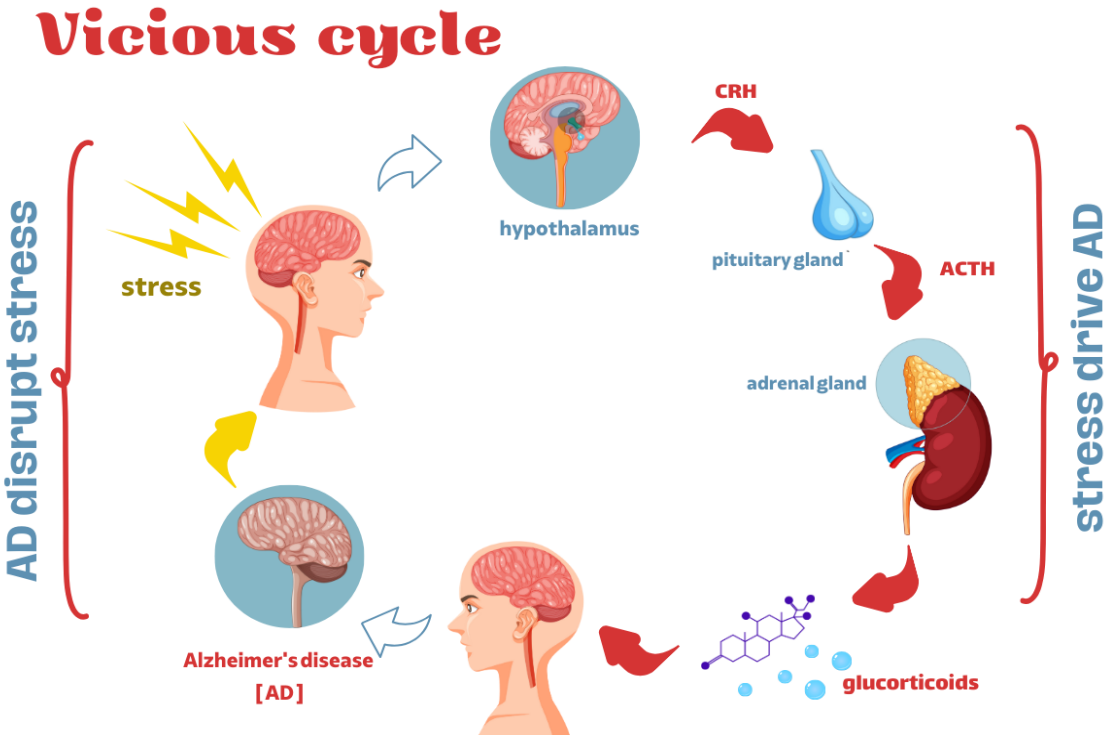

Fig 1: According to Justice's (2018) vicious cycle of stress, stress exacerbates Alzheimer's disease (AD) by hastening the illness's pathology's development and lowering cognitive performance (right side). AD then throws off the neuronal circuits in the brain that are susceptible to stress, which causes neuropsychiatric problems like anxiety, depression, and aggression (left side). The hypothalamic-pituitary-adrenal (HPA) axis, a network of direct effects and feedback loops including the pituitary, adrenal, and hypothalamus, is essential to this process (center). Under stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which in turn causes the pituitary to release ACTH. Glucocorticoids (GCs) are released by the adrenal cortex in response to ACTH. While having a variety of metabolic and behavioral impacts, elevated GCs are important in the development of neuropsychiatric disorders connected to stress and the exacerbation of AD.

Subsequent research in mice revealed that long-term stress can exacerbate a number of HD-related symptoms in a sex-specific way, including motor coordination, locomotor activity, and olfactory function [70]. Accumulating data indicates that stress may contribute to the rapid occurrence and progression of MND [71-74]. Chronic or severe stress has been shown to have deleterious effects on motor neurons through a variety of mechanisms, including dysregulation of the HPA axis, microglial activation, BBB disruption, mitochondrial dysfunction, excessive production of reactive oxygen species, accumulation of tau protein, cytoplasmic accumulation of TDP-43, which is neurotoxic, and gut dysbiosis. All of these systems work together to exacerbate MND and produce undesirable results. [75]. Glucocorticoids (GC) and mineralocorticoids (MC) are released when the HPA axis is over activated, as demonstrated by studies [76,77]. An overabundance of HPA axis activation triggers microglia, which in turn triggers the production of inflammatory cytokines and triggers autoimmune and BBB illnesses, among other mechanisms that impact neuronal function and internal environment balance. In stressed mouse models, HPA axis over activation causes neuroinflammation, which in turn promotes motor neuron injury [78], And protein accumulation [79], as BBB breakdown allows harmful proteins, like hemoglobin, to enter the central nervous system, worsening oxidative stress and causing neurotoxicity [80], increase in blood glucose levels, may be risk factors for MND in young patient [75]. There is a relationship between stress and migraine [81]. stress is a primary trigger for migraine episodes and high level of stress are documented in migraine patients Stress and migraines are associated to one another reciprocally, meaning that they influence one another cyclically throughout time [82]. About 70% of people report that stress is a cause for migraine attacks [83]. Patients with migraines have been found to be very stressed, especially those who experience daily chronic migraines [84]. When assessing people with migraine, stress susceptibility, life events, and

[DOI: 10.47176/update.2024.67]

concurrent psychosomatic disorders should be taken into consideration. Gender considerations should also be made [85]. Stress and migraine biology may be related in a number of ways. The first of them is the physiological stress response, which involves both the hypothalamic-pituitary adrenocortical axis, and sympathetic nervous system including adrenal medulla. Both of these systems are activated in reaction to stress, which causes the physiological and behavioral changes that are seen, which may in turn cause a migraine attack [86]. Chronic stress can cause hyperalgesia, and one possible mechanism is the activation of the μ-opioid receptor and N-methyl -D-aspartate receptors. Chronic stress may also affect the body in a way that affects headache physiology by changing the immune system in a way that facilitates pain transmission at the neuronal level. Inflammatory mediators, such as nitrous oxide, interleukin-6, beta-interleukin, and tumor necrosis factor alpha, may act as pain mediators and sensitize the pain matrix [86].

4. Antioxidant therapies in treatment stress induced Neurological disease

Oxidative stress, which is linked to neurodegenerative illnesses like Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), is marked by elevated levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These increases are frequently associated with deficiencies in the body's antioxidant defense systems, which hasten the course of disease [87]. The creation of drugs that particularly increase antioxidant activity presents a viable strategy for neuroprotection and shows promise in preventing harm from free radicals. Although food is the main source of antioxidants, medicinal plants are also a major commercial source. Investigating novel approaches to oxidative stress mitigation could augment free radical scavenging and advance neuroprotection [88].

4.1. Antioxidant Therapies in AD

Alzheimer's disease (AD) can now be effectively treated with antioxidant therapy. In preclinical models, new research indicates that the injection of CoQ10 or lipoic acid improves ATP and superoxide dismutase (SOD) levels while reducing Apolipoprotein E (ApoE) Aβ fragments, phosphorylated tau, and neuroinflammatory markers. Moreover, it has been demonstrated that these substances enhance hippocampus synaptic plasticity, a crucial aspect of cognitive function [89]. Furthermore, it has been discovered that carotenoids can lower inflammation, oxidative stress indicators, and Alzheimer's disease (AD) marker proteins. Improvements in cognitive performance were also shown by this medication, underscoring its possible therapeutic advantages in AD [90,91]. Rich in exogenous antioxidants, nutritious mushrooms have also demonstrated neuroprotective properties. Mushroom extracts have been shown to lessen behavioral impairments and neuronal degeneration in experiments utilizing sporadic Alzheimer's disease (AD) animals, suggesting their potential function in preventing neurodegeneration through antioxidant mechanisms [92,93]. It has been demonstrated that treating cells with different polyphenols, such as curcumin and resveratrol, can improve antioxidant capacity, modify glutamate-induced excitotoxicity, and encourage mitophagy and cell survival. These substances have the potential to be effective treatments for neurodegenerative illnesses like Alzheimer's because they provide neuroprotective advantages by lowering oxidative stress and promoting cellular health [94,95]. Many combinations therapy have shown synergistic promise in both transgenic and sporadic forms of Alzheimer's disease (AD). Treatments combining ubiquinol with ascorbic acid, lycopene with vitamin E, CoQ10 with Omega-3, and resveratrol with curcumin have shown efficiency in decreasing amyloid plaque development and tau hyperphosphorylation, important pathological hallmarks of AD. These pairings intensify neuroprotective effects, providing exciting new directions for potential treatment approaches. [96,97]. The effectiveness of antioxidants for Alzheimer's disease (AD) has been evaluated in a number of clinical trials. Oral curcumin treatment has been demonstrated to reduce cognitive deficits in AD patients. It did not, however, significantly improve general cognitive performance, according to Phase II clinical trial data, underscoring the need for more research to fully appreciate its potential advantages and disadvantages in the treatment of AD [98]. Furthermore, it has been discovered that resveratrol and epigallocatechin-3-gallate (EGCG) treatment lowers Aβ1–40 levels and delays cognitive decline in AD patients. These substances exhibit possible neuroprotective properties, indicating a potential role in slowing the rate of cognitive decline

[DOI: 10.47176/update.2024.67]

associated with AD [99]. Vitamin E has proven to be highly effective in combating peroxyl radicals, assisting in the reduction of their neurotoxic effects [100]. According to a study by Dong et al., vitamin E plasma levels were significantly decreased in AD patients [101] Moreover, vitamin E has been demonstrated to significantly reduce AD-related oxidative and nitrosamine damage [102]. causing a number of clinical investigations to investigate any potential therapeutic benefits in managing the illness. Together with extracts from Ginkgo biloba, vitamin E has also been connected to enhancements in cognitive performance [103]. Furthermore, in animal models, its preventive qualities can lessen tau-induced neurotoxicity [104]. Superoxide dismutase (SOD) and glutathione peroxidase (GPx) are two examples of antioxidant enzymes that are enhanced by melatonin, a hormone produced in the pineal gland and associated with circadian rhythms. Melatonin also scavenges oxygen and nitrogen-based free radicals, thereby reducing oxidative stress [105]. Melatonin has been demonstrated to decrease Aβ-induced neurotoxicity and its antioxidant qualities have been found to reduce Tau hyperphosphorylation, which in turn reduces the risk of neurofibrillary tangle formation [106,107]. Lipid peroxidation has been observed to decrease as a result of apple cider's enhancement of the activities of glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) [107]. Furthermore, it has been demonstrated that diets rich in carotenoids, flavonoids, polyphenols, vitamin C, and vitamin E help standard Alzheimer's disease therapy [108].

4.2. Antioxidant therapies in Parkinson disease

Supplementing PD patients with vitamin E, C, and CoQ10 has been demonstrated to improve corticosteroid synaptic plasticity, stop dopaminergic cell loss in the substantia nigra, and avoid microglial activation and astrogliosis in several PD models. These therapies have also been successful in enhancing behavioral modifications linked to Parkinson's disease [109,110]. By stimulating the Nrf2 pathway, resveratrol therapy has been demonstrated to improve survival and lessen behavioral changes in a pesticide-induced Parkinson's disease (PD) model. This pathway contributes to the neuroprotective effects of resveratrol therapy by boosting antioxidant responses and cellular protection [111]. Exposure to antioxidants such as crocin and fucoxanthin has been reported to drastically inhibit autophagy while upregulating mitochondrial enzyme activity. This increase in mitochondrial activity implies that these antioxidants are important for maintaining the integrity of cells and may have neuroprotective effects under different circumstances [112]. It has been demonstrated that quercetin and piperine combined therapy greatly improves behavioral changes. By enhancing the therapeutic benefits of both drugs in concert, this technique has the potential to be a promising strategy for addressing neurobehavioral impairments in a variety of disorders. [113]. in research on patients. Interestingly, glutathione (GSH) did not significantly affect motor scores in patients with Parkinson's disease (PD). On the other hand, idiopathic PD patients who took a higher dose of CoQ10 had significantly better ratings on the Unified Parkinson's Disease Rating Scale (UPDRS). It is noteworthy that prolonged usage of high doses of CoQ10 has been linked to increased oxidative damage, which serves as a contraindication [114]. Another clinical experiment that assessed the effectiveness of CoQ10 found that the tested dose was well-tolerated and did not cause any toxicity. Nevertheless, the trial failed to show any therapeutic promise, which prompted the decision to stop doing additional assessments [115].

4.3. Antioxidant therapies in Huntington Disease

Numerous of these antioxidant compounds have shown promise in treating Huntington's disease (HD). Strong antioxidant benefits have been shown for coQ10, lycopene, vitamins C and E, melatonin, and naturally occurring components contained in food products. These substances may also help delay the advancement of the disease [116]. Nuclear erythroid 2-related factor 2, or Nrf2, is a transcription factor that controls the expression of several genes involved in preserving the oxidative balance of cells by interacting with antioxidant response elements or ARE [117]. Certain medications, such as dietary flavonoids like rutin, myricetin, and hesperidin, which have had positive results in the treatment of Huntington's disease, by targeting the Nrf2 pathway to increase neuroprotective and cytoprotective effects [118,119,120].

[DOI: 10.47176/update.2024.67]

Additionally, the potential therapeutic benefits of novel synthetic drugs for Huntington's disease (HD) have been investigated. In animal models of Huntington's Disease (HD), XJB-5-131 is the first mitochondria-specific drug that has been demonstrated to greatly reduce oxidative damage to mitochondrial DNA and halt the pathophysiological processes [121]. The second substance, BN82451, is a neuroprotective drug that can penetrate the brain and shield mitochondria from oxidative damage [122]. It dramatically increases longevity, promotes motor performance, and improves striatal volume, shape, and neuronal regions. These findings are supported by experimental research. Moreover, BN82451 significantly lowers the quantity of cellular protein aggregates that are ubiquitinated [122].

4.4. Antioxidant therapy in Amyotrophic Lateral Sclerosis

Antioxidant compounds are also useful in the treatment of amyotrophic lateral sclerosis (ALS), according to a number of studies. An antioxidant called N-acetyl-L-cysteine (NAC) increases plasma levels of cysteine, a precursor to glutathione, and helps lessen the damage caused by free radicals. NAC reduces the generation of reactive oxygen species (ROS) in G93A SOD1-transfected SH-SY5Y human neuroblastoma cells, according to in vitro studies [123]. CoQ10 counteracts oxidative stress in neurons and other organs by scavenging free radicals, which has a positive effect on ALS patients [124]. It has been demonstrated that taking vitamin E supplements can provide some protection against the development of amyotrophic lateral sclerosis (ALS) [125,126]. Additionally, riluzole has antioxidant qualities, mostly through blocking protein kinase C [127]. Thus, by enhancing the body's antioxidant defenses and reducing oxidative damage, combining antioxidant therapies—such as vitamin E supplementation with riluzole may improve outcomes for people with ALS. This is made possible by larger amounts of glutathione, an essential antioxidant that is produced at a faster pace because of raised intracellular glutamate levels, which are a precursor required for the synthesis of glutathione. Moreover, thiobarbituric acid reactive species (TBARs), which are byproducts of lipid peroxidation and markers of oxidative stress, may decrease as a result of this combination therapy [128,129].

4.5. Antioxidant therapies in migraine disease.

The usage of antioxidants can lessen the effects of oxidative stress, which is a significant component in the development of migraines [130]. By scavenging free radicals, reducing molecular oxygen, preventing its origin and propagation, and serving as reductants, antioxidants help reduce oxidative stress [131]. Common antioxidants include carotenoids, polyphenols, and vitamins C and E [132-134]), in addition to other vital substances like riboflavin, coenzyme Q10, and alpha-lipoic acid. Certain metals' oxidation potential is increased and the redox balance is influenced by vitamin C [130, 135]. Studies suggest that vitamin C may regulate the activity of reactive oxygen species (ROS) and neuroinflammation in migraineurs [136]. Furthermore, after wrist injuries, vitamin C administration has been associated with a decrease in complicated regional pain syndrome; advantageous dosages range from 200 to1500 μg per day over 50 days [137]. Additionally, it has been demonstrated that intravenous vitamin C (5 g/day) therapy prevents post-shingles neuralgia [152]. Vitamin C and Pinus radiata bark extract effectively decreased migraine patients' frequency and severity of headaches in an open-label experiment [138, 139]. Reducing reactive oxygen species (ROS) and reactive nitrogen species (RNS) while balancing antioxidant levels (SOD and GSH), curcumin, known for its antioxidant capabilities, also supports brain health [140]. Curcumin's potential as a migraine therapy has been the subject of recent studies. Researchers Bulboacă et al. used a rat model of nitroglycerine-induced migraine to examine the effects of sumatriptan (ST) alone versus in combination with curcumin. Total antioxidant status (TAS), especially in its liposomal form, was increased by curcumin, while malondialdehyde (MDA), RNS, and total oxidative stress (TOS) were decreased [141]. Along with improving oxidative stress indicators and lowering pain, curcumin and naproxen together [142]. Curcumin may reduce tumor necrosis factor-alpha (TNF-α), which is linked to the development of migraines, according to research conducted on humans. Combining omega-3 fatty acids with curcumin decreased TNF-α expression in patients suffering from episodic migraines, according to Abdolahi et al. [143]. Curcumin has the potential to be a successful antioxidant treatment for migraines, as evidenced by a

[DOI: 10.47176/update.2024.67]

trial using coenzyme Q10 and Nano curcumin that showed a decrease in the frequency, length, and intensity of migraine attacks without any negative side effects [144]. Because there is a hypothesis linking migraines to mitochondrial malfunction, coenzyme Q10 is important for mitochondrial metabolism. Clinical research has shown that supplementing with coenzyme Q10 increases decreased glutathione levels and SOD activity in patients with fibromyalgia receiving pregabalin treatment. In addition, it lessens pain and mitochondrial oxidative stress and inflammation, and anxiety, suggesting its applicability in migraine treatment [145, 146].

5. Behavioral and lifestyle interventions

Behavioral and lifestyle interventions, such as physical exercise and mindfulness, reduce stress by lowering cortisol and increasing endorphins. Each of these techniques plays a vital role in managing stress. Physical exercise significantly impacts stress relief and overall health by triggering the release of endorphins and regulating stress hormones like cortisol and adrenaline. Aerobic exercises improve cardiovascular health, boost energy, and regulate sleep patterns, further contributing to stress reduction. Strength training not only builds physical strength but also lowers anxiety and improves self-esteem [147]. Yoga and Tai Chi, which combine physical postures with controlled breathing, activate the parasympathetic nervous system and enhance GABA production [148]. Techniques like deep breathing exercises activate the vague nerve, which triggers the relaxation response, lowering heart rate and blood pressure [149].

5.1. Molecular Mechanisms of Mindfulness Training in Neurodegeneration: Epigenetic and Oxidative Stress Pathways

Mindfulness Training (MT) includes practices such as Qigong, Tai Chi, yoga, and meditation. These ancient practices have been developed over thousands of years, primarily in China, with the goal of improving physical and mental fitness [150]. MT has been adapted to promote present-centered awareness and acceptance, offering significant therapeutic benefits. It has been widely utilized in managing conditions like chronic pain, anxiety, depression, and cognitive disorders as shown on (Figure 2) [151]. previous studies suggest that long-term MT practices may slow cognitive decline in older adults, although further research is required to confirm these effects [152]. Mindfulness helps reduce stress by modulating brain areas such as the prefrontal cortex and decreasing amygdala activity. Similarly, meditation, in its various forms (e.g., guided or transcendental), calms the mind and promotes a state of relaxation [153,154]. Neurodegeneration, characterized by neuronal loss and synaptic dysfunction [155]. The accumulation of β-amyloid (Aβ) and neurofibrillary tangles are key pathological features, leading to synaptic dysfunction and neuroinflammation. As a molecular indicator of chronic stress [156]. the upregulation of pro-inflammatory genes is believed to cause dysregulation of GC secretion, decreased sensitivity to GR in the brain and immune cells, and a lack of suppression of NF-κB-mediated [157,158], and RIPK2, which are associated with chronic stress and inflammation [156]. Studies show that MT can reduce levels of inflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6) [159]. These reductions in pro-inflammatory cytokines may help mitigate neurodegenerative processes. can be inhibited by the cortisol-GR complex, which prevents the transcription of inflammation-promoting genes. Meditation's effect on reducing Aβ deposition may offer protective or mitigating effects on the cognitive impairments. This effect is likely due to the methylation of ND-related genes, such as Nr4a2 and CLU, both of which play crucial roles in Aβ and tau metabolism, potentially slowing disease progression and alleviating symptoms. Nr4a2 agonists can speed up the degradation of amyloid-beta (Aβ) by significantly reducing γ-secretase activity, which upregulates the insulin-degrading enzyme responsible for breaking down Aβ. In a mouse model of AD, treatment with Nr4a2 agonists reduced typical AD [160,161]. However, it is important to note that long-term meditation may be required to accumulate these effects, as short-term meditation may not be sufficient to regulate gene expression. Aging is one of the primary risk factors for neurodegenerative diseases.

[DOI: 10.47176/update.2024.67]

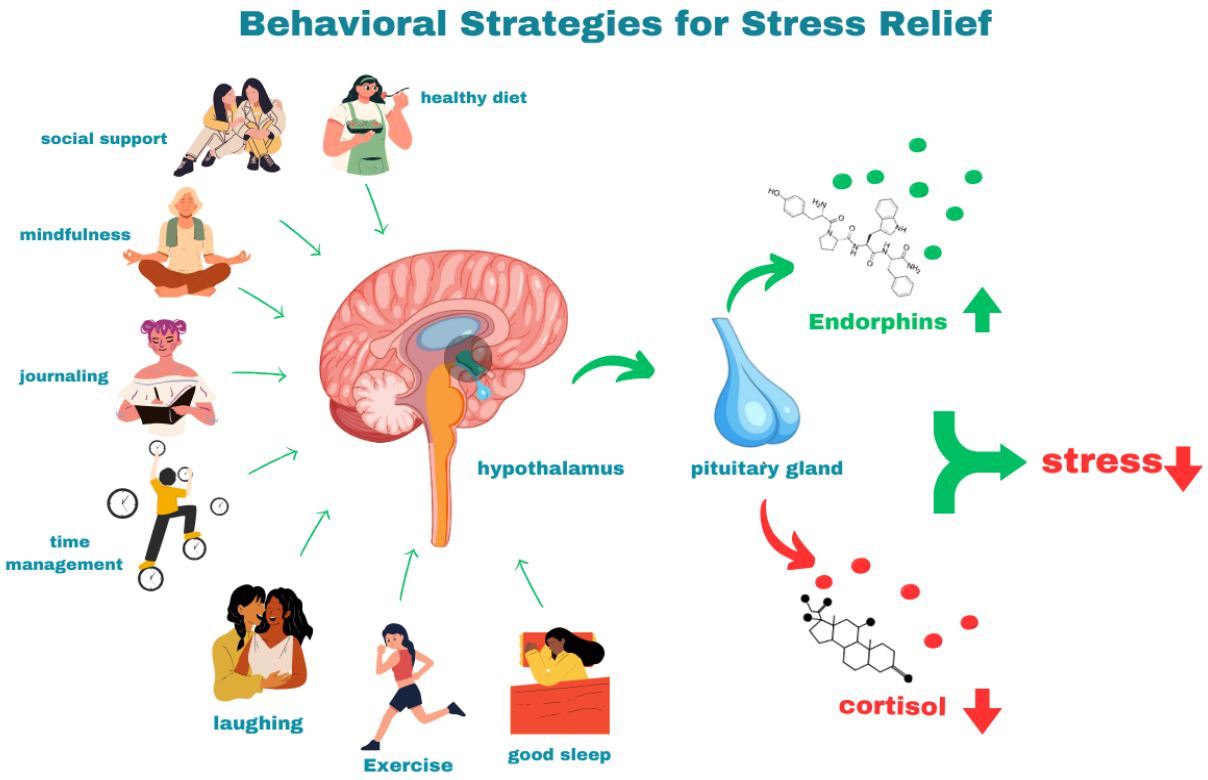

Fig 2: Behavioral Strategies for stress relief with healthy lifestyle

The physiological process of aging leads to a range of molecular and cellular anomalies, including oxidative stress, mitochondrial dysfunction, telomere shortening, and DNA damage [162,163]. MT has been shown to mitigate some of these effects by preserving telomere length and increasing telomerase activity in white blood cells and peripheral blood mononuclear cells(PBMCs) [164]. previous studies showed changes in the expression of the CLU gene, which is involved in multiple cellular processes such as lipid transport, cell death regulation, and protein folding. Reduction of CLU helps protect neurons from stress and injury. Meditation was found to reduce the expression of the CLU gene and the PSEN1 gene [165,166]. While the PSEN1 gene encodes a subunit of γ-secretase, which is crucial for the synthesis of Aβ peptides, its decreased expression following meditation may contribute to a reduction in Aβ peptide production. This suggests that meditation may reduce the synthesis of the γ-secretase complex, resulting in fewer Aβ peptides. By examining blood markers after meditation, it was found that the level of Aβ40 in meditators' blood was reduced [167,168]. MT has been shown to reduce oxidative stress by increasing antioxidant enzyme activity, lowering markers such as ROS and 8-hydroxy-2-deoxyguanosine [169,170]. These processes maintain brain homeostasis and reduce the risk of neurodegeneration. However, while oxidative stress markers are often reduced in individuals practicing mindfulness, these effects require more rigorous study, especially in healthy populations [171]. If the balance between the production and consumption of ROS is disrupted, the brain's equilibrium may be lost, leading to ND [172,173]. Epigenetic dysregulation can lead to cognitive impairment and neuronal death [174]. The researchers found 64 differently methylated areas in meditators compared to non-meditators, which corresponded to 43 genes. Notably, 48.4% of these regions were directly related to common human disorders, and 9 of these (14%) were linked to ND [175]. Among these ND-related genes, the nuclear receptor family 4 group A member 2 (Nr4a2) gene most differentially methylated. This gene encodes a nuclear transcriptional regulator that is a key player in the differentiation, survival, and maintenance of dopaminergic (DA) neurons. It is essential for neuronal development and is particularly important for the maintenance of the DA system [160]. Nr4a2 prevents inflammation-mediated DA neuron death and is critical for hippocampal synaptic plasticity and memory formation [176]. As such,

[DOI: 10.47176/update.2024.67]

it is hypothesized that promoting the methylation of this gene through meditation might be a potential strategy for treating ND. Another important gene is FKBP5. In Alzheimer's disease patients, the CpG sites of FKBP5's glucocorticoid response elements (GREs), located in intron 7 and the promoter region, decreased FKBP5 DNA methylation is associated with increased FKBP51 expression, worsening the disease. FKBP51 interferes with tau protein degradation, promoting the formation of toxic tau oligomers, which worsens the progression of AD [177]. Notably, long-term meditation which in turn reduces tau neurotoxicity and slows the progression of AD. Chronic stress may promote the loss of nigrostriatal cells in Parkinson's disease (PD), accelerating the disease's course [178]. Stressful conditions may also worsen the motor symptoms of PD, such as tremors. Furthermore, in human amyotrophic lateral sclerosis (ALS) fibroblasts prolonged stress stimulates the production of stress granules and pathogenic TDP-43 aggregates, speeding up the progression of ALS [179]. Stress causes a reduction in hippocampal volume and decreases the number of glucocorticoid receptors (GR) in the hippocampus, hypothalamus, and amygdala [180]. It stimulates the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, promoting the release of glucocorticoids (GC) and catecholamines. The reduction in GR and the increase in GC release lead to elevated GC levels, which cause brain atrophy, particularly in the hippocampus, put individuals in a state of extreme stress and anxiety [157]. In an AD rat experiment, it was demonstrated that Aβ25-35 amyloid toxicity affects the adaptive response of the HPA axis to stress [181], leading to chronically high cortisol levels in patients [182]. The HPA axis is a crucial neuroendocrine signaling system that regulates physiological homeostasis and stress reactions. In AD, an overactive HPA axis is a well-known characteristic, often indicated by excessive cortisol output [183]. The overproduction of cortisol by the HPA axis affects various bodily systems, including hemodynamic, endocrine, and immune system functions [184]. Meditation-induced reduction in stress may reduce the hyperactivity of the HPA axis. By reducing pro-inflammatory cytokines, MT may help delay brain shrinkage and memory impairment. Regular MT training could have beneficial effects on ND by improving neuroendocrine stress responses, enhancing HPA axis function and causing nuclear receptor-mediated transcriptional changes that reduce neuroinflammation [185].

5.2. Molecular impact of Physical exercise on neurodegeneration diseases

Exercise activates the neuroendocrine system, and when performed at sufficient intensity and duration, it can reduce the release of stress hormones such as cortisol, β-endorphin, adrenocorticotropic hormone (ACTH), and vasopressin [186]. This activation involves the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, which trigger a series of coordinated physiological reactions [187]. The intensity of these responses varies based on factors such as exercise type (aerobic, strength), duration, and individual characteristics (e.g., gender, prior training) [188]. Exercise modulates key neurotransmitter systems, including the dopaminergic, serotonergic, and noradrenergic systems, helping to adjust peripheral disturbances in homeostasis. Experimental studies have demonstrated that exercise significantly increases the release of neurotransmitters such as dopamine (DA), noradrenaline (NA), and serotonin (5-HT), particularly in regions like the striatum, midbrain, and hippocampus [187,189]. These monoamines are crucial for regulating mood, cognition, and stress responses during and after physical activity. Exercise increases dopamine production through the up-regulation of serum calcium, which is transported into the brain and affects calcium/calmodulin-dependent dopamine synthesis also contributing to improved motor and cognitive functions [189]. This process activates tyrosine hydroxylase, the rate-limiting enzyme in dopamine production [188]. The protective mechanism of physical exercise (PE) against stress is partly due to the expression of galanin in the locus coeruleus. Galanin hyperpolarizes noradrenergic neurons, inhibiting neuronal firing in the locus coeruleus, which reduces the release of norepinephrine (NE). NE is a neurotransmitter that targets the amygdala and frontal cortex, both of which are involved in anxiety and memory processes [189,190]. The serotonin (5-HT) system is also modulated by exercise, with effects determined by the intensity and duration of the activity. For instance, moderate treadmill exercise decreases hippocampal 5-HT levels without affecting its metabolism, while seven days of high-intensity treadmill exercise significantly increases 5-HT levels in the hippocampus, enhancing

[DOI: 10.47176/update.2024.67]

cognitive function [190]. Exercise significantly increases Brain-derived neurotrophic factor BDNF levels, particularly in the hippocampus, supporting brain growth and cognitive function. Studies in transgenic mice show that physical exercise (PE) increases BDNF/TrkB signaling molecules and reduces amyloid-β levels, suggesting that exercise may delay the onset of Alzheimer's disease [191]. BDNF is a neurotrophic which plays a vital role in neural plasticity, neuronal stress resistance, and neuron differentiation [192]. Four weeks of treadmill exercise led to a significant increase in BDNF mRNA and protein levels, a rise in synaptic load, and changes in astrocyte morphology in the dentate gyrus, suggesting an increase in TrkB receptor levels [193] BDNF can also regulate dopamine content and its release, which is essential for neuronal plasticity, survival, and memory processes. BDNF modulates these processes through its interaction with the TrkB receptor [194]. Insulin signaling in the brain is critical for the survival and function of neurons, playing a role in the regulation of BDNF transmission [195]. Defective insulin signaling can lead to conditions such as diabetes, cardiovascular diseases, and neurodegenerative disorders, suggesting that proper insulin signaling is essential for brain health. Insulin also has anti-inflammatory and anti-apoptotic effects, which protect neurons from damage [196]. In recent years, dietary supplements have garnered increasing attention for their potential role in supporting brain health and improving cognitive function, particularly in the context of neurodegenerative disorders. These supplements, comprising essential vitamins, minerals, and bioactive compounds, contribute to neuroplasticity, synaptic transmission, and cellular repair mechanisms. However, while they offer considerable benefits, dietary supplements alone cannot replace the therapeutic efficacy of pharmacological interventions in managing neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Instead, they may serve as adjunct therapies, complementing conventional treatments by enhancing brain function and mitigating disease progression [197].

6. Future Directions in stress-related Neurodegenerative stress

6.1. New Molecular Targets for Therapeutic Development

As stress increasingly impacts the lives of many people, researchers have been exploring novel approaches to protect against its harmful effects on the brain. One major area of focus has been preventing neurodegenerative disorders and promoting brain health. Cutting-edge therapies are being developed to target molecular pathways that are crucial for maintaining cognitive function. These include pathways like ISR, cGAS-STING, and SIRT1, which play significant roles in the response of body to cellular stress. When combined with other therapies, these pathways offer a synergistic potential for drug development, paving the way for more effective treatments aimed at preserving brain health and combating neurodegeneration. The Integrated Stress Response (ISR) is a molecular pathway activated in response to various stressors to help restore cellular homeostasis. When cells are exposed to stress the ISR is activated, eIF2α (eukaryotic initiation factor 2 alpha) becomes phosphorylated, leading to a reduction in global protein synthesis. This phosphorylation is regulated by four key kinases: PERK (Protein kinase R-like endoplasmic reticulum kinase), which responds to ER stress; PKR (Protein kinase RNA-activated), activated by viral infections; GCN2, triggered by amino acid deprivation; and HRI (Heme-regulated inhibitor), which responds to oxidative stress [198]. However, selective translation of certain mRNAs, such as ATF4 and CREB2 (Cyclic AMP response element-binding protein 2), occurs. These transcription factors play critical roles in managing cellular stress by promoting genes involved in stress adaptation, and restoration of cellular balance. Cells regulate ISR activity through protein phosphatase 1 (PP1), which dephosphorylates eIF2α in conjunction with either GADD34 (growth arrest and DNA damage-inducible protein) or CReP (constitutive repressor of eIF2α phosphorylation). GADD34 is upregulated as part of a negative feedback loop to limit the duration of ISR activation. If the ISR remains active for too long, it can lead to CHOP-dependent apoptosis, a process where severe or unmanageable stress results in programmed cell death [199]. ISR has a dual role: it protects cells by restoring protein quality control and maintaining synaptic function, but it's over activation can promote cellular damage. Specifically, the prolonged overexpression of ATF4 (Activating Transcription Factor 4) can exacerbate stress responses, leading to apoptosis and contributing

[DOI: 10.47176/update.2024.67]

to neurodegenerative disorders [200]. Currently, several therapeutic strategies targeting the ISR are being explored, for example, inhibitors of ATF4 or agents that modulate eIF2α phosphorylation are under investigation in clinical trials, although these approaches are still in the experimental phase [201]. Sirtuins (SIRTs) are a class of histone deacetylases that regulate various metabolic pathways by deacylating specific proteins, leading to the activation of those proteins depending on their type and context. SIRTs play a vital role in neurodegenerative disorders, due to their anti-oxidative and anti-inflammatory properties. For instance, SIRTs can decrease inflammation by inhibiting NF-κB, a key regulator of immune responses. NF-κB, which contains the crucial subunit p65 with seven acetylation sites, is known to promote the buildup of amyloid-beta (Aβ) peptides when acetylated. This accumulation contributes to microglial toxicity, a hallmark of neurodegeneration [202]. Neurodegenerative disorders are often characterized by the accumulation of abnormal proteins within neurons, leading to the formation of inclusion bodies and dysfunctional mitochondria. This process impairs autophagy, which exacerbates the progression of neurodegeneration [203]. Impaired mitophagy, the selective autophagy of mitochondria, is a common feature of PD [204]. The AMP-activated protein kinase (AMPK) indirectly increases SIRT activity through NAD+, promoting autophagy. SIRT1, specifically, can deacetylate and activate LKB1 kinase, which enhances the phosphorylation of AMPK, leading to increased AMPK activity and further promoting autophagy. Moreover, under genotoxic stress, SIRT1 plays a crucial role in regulating apoptosis through its interaction with p53. In models of neurodegeneration, phosphorylation of the cell cycle regulator Cdk5/p25 leads to the suppression of p53 and the accumulation of Aβ peptides in the brain [205]. Activation of SIRT1 leads to the deacetylation of p53, which suppresses its pro-apoptotic function and may mitigate neurodegeneration [206]. Additionally, SIRT1 preserves the levels of brain-derived neurotrophic factor (BDNF), a key factor in neuronal survival and synaptic plasticity [207]. In Huntington's disease (HD), reduced BDNF transcription leads to neural degeneration. SIRT1 can enhance BDNF transcription by activating the cAMP response element-binding protein (CREB) and interacting with the transducer of regulated CREB activity 1 (TORC1), promoting BDNF production [208,209]. Cyclic GMP-AMP synthase (cGAS) is a DNA sensor and a key regulator of the innate immune response. It detects cytosolic DNA from pathogens or self-DNA released by damaged host cells due to apoptosis, cancer, or autoimmune disorders. Upon binding to foreign or damaged DNA, cGAS undergoes a conformational change, using ATP and GTP as substrates to synthesize cyclic GMP-AMP (cGAMP) [210]. cGAMP then binds to the Stimulator of Interferon Genes (STING), located on the membrane of the endoplasmic reticulum (ER). This binding triggers the translocation of STING from the ER to the Golgi apparatus, where it activates signaling pathways, including the phosphorylation of TANK-binding kinase 1 (TBK1). TBK1 phosphorylates STING at Ser366 in humans (or Ser365 in mice), which is essential for the recruitment of downstream signaling molecules [211]. This phosphorylation event allows STING to recruit and activate TBK1, which in turn phosphorylates Interferon Regulatory Factor 3 (IRF3). Phosphorylated IRF3 dimerizes and translocate to the nucleus, where it induces the expression of type I interferons (IFNs) and other pro-inflammatory cytokines. The cGAS-STING pathway is tightly regulated to prevent excessive inflammation or autoimmune reactions. Mechanisms such as the degradation of cGAS, dephosphorylating of STING, and inhibition of downstream signaling components are employed to avoid over activation [212]. In recent years, several cGAS inhibitors have been developed, many of which are synthetic [213,214]. Some natural products have also been shown to inhibit cGAS activity [215]. Additionally, anti-sense oligonucleotides have been designed to reduce cGAS expression [216,217]. Two primary types of cGAS inhibitors have been identified: one targets the active site of cGAS [218-220], and the second blocks the interaction between cGAS and dsDNA, either by binding directly to the enzyme or to dsDNA [221,222]. Other strategies include inhibiting cGAS dimerization or modulating its post-translational modifications [223,224]. Further studies are needed to unravel the therapeutic potential of cGAS inhibitors for treating neurological disorders, particularly their impact on central nervous system homeostasis [225,226].

[DOI: 10.47176/update.2024.67]

Conclusion

The interplay between stress and neurodegenerative diseases has recently become more obvious. Chronic stress actually accelerates the development of neurodegenerative disorders, such as Alzheimer's, Parkinson's disease, Huntington, Amyotrophic lateral sclerosis and migraine. rather than simply worsening conditions. The molecular mechanisms linking stress to neurodegeneration, including oxidative stress, neuroinflammation, and mitochondrial dysfunction, are multifaceted trigger neuronal damage. The potential of therapies directed at antioxidant, anti-inflammatory strategies, and mitochondrial protection to ameliorate the effects of stress on neuronal health. Strategies that enhance protein homeostasis and induce autophagy are also critical to prevent toxic accumulation of protein aggregates related to stress-exacerbated neurodegeneration. Behavioral and lifestyle interventions further enhance the possibility of improving outcomes in individuals at risk or with active neurodegenerative diseases. Cognitive approaches, such as mindfulness and CBT reduce stress and improve cognition. These could also be complemented with regular physical exercise and nutritional approaches supporting neuroprotection, forming a multifaceted approach in mitigating the effect of stress on the brain and Neurological system. More studies should be done to explain the mechanisms by which stress contributes to neurodegenerative diseases. It is therefore envisioned that future studies would consider precision medicine in the elaboration of personalized therapeutic interventions based on individual stress responses and genetic predispositions. This is an attempt at integrating a multidisciplinary approach using pharmacological interventions together with lifestyle changes in an effort to ensure that treatment packages are tailor-made to meet particular needs.

Authors contribution statement

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Conflict of Interest

The authors declare they have no competing interests

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