International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijarbs Coden: IJARQG (USA) Volume 9, Issue 7 -2022

Review Article

DOI: http://dx.doi.org/10.22192/ijarbs.2022.09.07.028

Targeting cellular organelles for Neuroprotection in Neurodegenerative Diseases-A Narrative Review

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Abstract

For the scientific community, preventing neuronal cell death in neurodegenerative diseases will always be a challenging problem. In order to address these problems, which are dependent on safeguarding cellular organelles, numerous pharmacological methods have been tested. Even though some medications have demonstrated some good neurological protection, more study has to be done to further safeguard these cellular organelles. The neuroprotective medication therapy that targets cellular organelles has been highlighted in the current narrative review as a strategy to protect neuronal cells in neurodegenerative illnesses.

Keywords: Neurodegeneration, Mitochondrial Dysfunction, Endoplasmic Reticulum Stress, Golgi Disassembly

Introduction

Neurodegenerative diseases are becoming more prevalent as the population ages, Alzheimer's[1], ischemic -reperfusion injury, cardiac arrest[2], traumatic brain injury[3], and stroke[4] yet the mechanisms that lead to synapse destabilization and neuronal death remain elusive. The advent of proteomics has led to methods for high-throughput screening to search for biomarkers that can be used for the early diagnosis and treatment of various diseases and to identify alterations in the cellular proteome that can provide insight into disease etiology and potential avenues for treatment. Furthermore, cellular organelles malfunction like mitochondrial dysfunction, endoplasmic reticulum stress, DNA damage, mRNA overexpression or reduced expression, Golgi body stress, and cellular membrane disorganization has been very well reported[2,5,6]. Thus, targeting those cellular organelles could be a potential therapeutic approach in multiple neurodegenerative diseases.

In this current review, we seek to propose the application of drugs that have been used as an extensive pharmaceutical to target the cellular organelles in neurodegenerative diseases to explore their therapeutic approach.

Method

We used PubMed/Medline, Lilacs and Redalyc, and EBSCO for our search from 2000-2022 in the current narrative review.

Alzheimer's disease (AD): The hallmark of AD, a multifaceted and complicated neurodegenerative condition, is gradual, severe dementia accompanied by neuropsychiatric symptoms. About 70% of all cases of dementia are caused by AD, making it the most frequent cause of progressive dementia among seniors. Over the age of 65, it affects 5-10% of the population, and over the age of 80, it affects 40% of the population. Most occurrences of AD are sporadic, although early-onset familial AD accounts for 5% of cases. Amyloid plaques and neurofibrillary tangles are the two primary neuropathological abnormalities in AD (NFT)[1].

Cardiac Arrest: A frequent and treatable cause of mortality and disability is cardiac arrest. Outof-hospital cardiac arrest (OHCA), as determined by emergency medical services (EMS), affects around 424 000 persons annually in the United States[2]. Because a sizable portion of OHCA is unreported, the true burden is probably much higher. In a prospective investigation of deaths in a US county, cardiac arrest was responsible for 5.6% of annual mortality.[2] Many OHCA victims don't get quick cardiopulmonary resuscitation (CPR). Many people who get CPR do not survive because spontaneous circulation cannot be restored or because of anoxic brain injury even after circulation has been restored[2]. According to a metabolomics study done on tissues and plasma, cardiac arrest alters a number of pathways that lead to neuronal degeneration[7,8]. During the initial stages of resuscitation following cardiac arrest, substantial pro- and antioxidant disbalance in plasma has also been documented along with metabolic change[9].

Traumatic Brain Injury: Traumatic brain injury (TBI) can manifest in a variety of ways, from minor changes in consciousness to persistent comatose state and death. The full extent of the brain is affected by a diffuse type of injury and edema in the most severe form of TBI. Depending on the severity of the injury, there are many different treatment options, from daily cognitive therapy sessions to extreme surgery like bilateral decompressive craniectomies[10,11].

Stroke: Secondary neurodegeneration (SND) caused by a stroke describes the unrelenting and gradual loss of tissues in locations connected to the infarcted area. After stroke, SND has repeatedly been seen to develop in both humans and animals. It's interesting to note that stroke-induced SND remarkably resembles other neurodegenerative illnesses like Alzheimer's disease, most notably in terms of the large buildup of the neurotoxic protein amyloid-. The combination of this finding with others (progressive neuronal loss and neuroinflammation) raises the idea that a stroke may precipitate a neurodegenerative disorder. Undoubtedly, this is somewhat reinforced by the unusually high incidence of dementia following stroke[4,12].

Focal Cerebral Ischemia: The most frequent cause of focal brain ischemia is blockage of the brain's arterial blood supply, frequently as a result of thrombosis or embolism. An ischemic stroke develops when the ischemia lasts long enough to cause irreversible neuronal death. Ischemia will occur in the area supplied by the afflicted artery if there is a sudden thrombosis of a previously ruptured internal carotid artery plaque or a previously stenotic cerebral artery. The majority of brain TIA and stroke cases—between 60 and 70 percent—are caused by embolization of a clot that has developed in the heart or a major artery[13,14].

Overview of the Various Cellular

Organelles Damage

Mitochondrial damage: The mitochondria aid in maintaining the cell's energy balance and carry

out their essential functions via the complex 1-V via electron transport chain and energy production. Mitochondrial dysfunction is linked to impaired energy metabolism in AD[15]. Other neurodegenerative illnesses, including as ischemia and reperfusion injury, have also been extensively documented to cause mitochondrial damage[16], cardiac arrest[17], traumatic brain injury[18], and stroke[19]. Furthermore, an alteration in the mitochondrial phospholipids has also been reported after cardiac arrest[20].

Endoplasmic Reticulum: The folding of membrane and secreted proteins, the production of lipids and sterols, and the storage of free calcium all take place in the endoplasmic reticulum (ER). An imbalance between the need for protein folding and the ER's capacity for protein folding can result from physiological stresses like an increase in secretory load or pathological stresses like the presence of mutated proteins that cannot fold correctly in the ER. This condition is known as ER stress. Eukaryotic cells have developed a collection of signal transduction pathways known as the unfolded protein response (UPR) in order to detect and react to ER stress (reviewed in Reference 1). A group of transmembrane ER resident proteins, such as inositol-requiring protein 1 (IRE1), PKR-like endoplasmic reticulum kinase (PERK), and the majority of ER-proximal regulators of the UPR, make up the majority of these regulators. These proteins have cytosolic effector domains connected to ER stress-sensing regions that protrude into the ER lumen. When the ER's ability to fold proteins reaches saturation, ER stress happens. In the end, signals from these stress-sensing proteins either cause cell death or save the cell. Intense interest in the relationship between neurodegenerative illnesses and UPR signals that result from pathologic situations evoking ER stress has been sparked by the function of ER stress[21]. Other neurodegenerative disorders such as ischemia-reperfusion injury, cardiac arrest, traumatic brain injury, and stroke documented to cause ER stress induced cell death[22].

Golgi Complex: The secretory pathway's main organelle, the Golgi complex, is where cargo is sorted and processed. The unique organization suggests additional possible activities, even if the Golgi structure is crucial for the effective processing of secretory cargo. After various cellular pressures, the Golgi disassembles, and some research theorizes that Golgi disassembly activates a stress signaling pathway. If conceivable, this process would function to alleviate the stress, with irreparable stress leading to apoptosis[23]. According to the early breakdown of the organelle, several neurodegenerative disorders are correlated with neurons' apparent heightened sensitivity to Golgi stress[24].

Nucleus: By regulating molecular traffic across the nuclear membrane, the cell nucleus assists in controlling gene expression. The division of a system into its cytoplasmic and nuclear compartments has stochastic characteristics similar to a motif with negative feedback. The nuclear barrier delays the concentration of nuclear proteins, which makes it possible for them to behave like switches[25]. Numerous disorders, including ischemia-reperfusion injury, have been linked to DNA damage, increased or decreased mRNA expression[26], cardiac arrest[27], traumatic brain injury[28], and stroke[29].

Plasma Membrane: Multiple neurodegenerative diseases, including stroke, ischemic-reperfusion injury, cardiac arrest, traumatic brain injury, and Parkinson's and Alzheimer's diseases, have been associated to dysregulated plasma membrane[30,31].

Therapeutic Drug Approaches

Metformin: Known to interact with the mitochondria to give mitochondrial protection in ischemia-reperfusion injury, metformin, the first line medication for diabetes, has demonstrated encouraging outcomes in the treatment of neurodegenerative disorders such as CA[32-34]. Treatment with metformin has also been suggested for diabetic patients to lessen Alzheimer's-related dementia[35].

Inhaled Gas: The author of this article provides a summary of the usage of NO and Xe in treating ischemia-reperfusion injury brought on by cardiac arrest. These gases have cytoprotective properties against ischemia-reperfusion injury brought on by cardiac arrest, according to recent scientific and clinical research. However, there are probably variations in the ways that these gases affect reperfusion damage after CA[36].

H_2 Gas: H_2 gas was initially mixed with extracorporeal cardiac resuscitation because of its antioxidant properties, which increased intraresuscitation brain oxygenation and survival time in a rat model of highly fatal CA[37]. H_2 gas therapeutic effect has also been demonstrated in Alzheimer's diseases [38].

Targeted Temperature Management: After brain damage, targeted temperature management (TTM) has been shown to protect tissue function and improve neurological outcomes[39]. Somatosensory evoked potentials (SSEP) were quantified by Young et al. to examine their potential to track brain recovery in the early period after CA under graded hypothermia. They also suggested that deeper hypothermia can aid in better brain recovery and showed that quantified SSEPs have the ability to objectively track recovery after CA with graded TH[40].

Mitochondrial Transplantation: Authors of the review article have provided a concise overview of the history and possible uses of mitochondrial transplantation in ischemia reperfusion injury, which has the potential to be a revolutionary treatment strategy for conditions like cardiac arrest, stroke, and traumatic brain injury[17,41,42].

Lysophosphatidylcholine:

Phosphatidylcholines are the source of lysophosphatidylcholine (LPC, lysoPC), also known as lysolecithins. LPCs are small phospholipids that are found in blood plasma and cell membranes (3% each)[43]. After cardiac arrest, it was discovered that low levels of LPC were linked to higher rates of mortality and neuronal dysfunction, but its supplementation boosted survival and neuroprotection[44-46]. LPC has also been demonstrated to be neuroprotective in Alzheimer's[47].

Micro RNA (miRNA): It has been shown that neuronal-specific miRNAs regulate neuronal development, excitability, and function. These brain-enriched miRNAs function as disease causing genes, biomarkers, or pathogenesis related players in a variety of neurodegenerative disorders[47]. Parkinson's, Alzheimer's, cardiac arrest, and stroke are just a few of the neurodegenerative disorders for which a miRNA based therapy approach has been suggested[48].

Vagus Nerve Stimulation (VNS): The food and drug administration (FDA) has approved vagus nerve stimulation (VNS) as a treatment for epilepsy and depression. The application of threshold-adjusted vagus nerve stimulation right away upon cardiac arrest and resuscitation has recently been proposed by Choudhary et al. as a way to improve survival and prevent neurodegeneration[49]. Given that it aids in lowering inflammation and enhancing mitochondrial protection, VNS demonstrates a variety of treatment modalities[50].

Endoplasmic Reticulum Stress Inhibitor:

Salubrinal (inhibits eIF2 dephosphorylation and reduces apoptosis), Kinase Inhibiting RNase Attenuators (KIRA) (IRE1 inhibition and the blockage of XBP1 splicing), Guanabenz, Glaxo Smith Kline (GSK) 2606414 (PERK inhibitor), and sephin 1 are just a few of the medications that have been used to prevent endoplasmic reticulum stress (inhibitior of GADD34)[51].

Conclusion

The narrative review paper suggests that function of multiple cell organelles are severely dysregulated in multiple neurodegenerative diseases caused by Alzheimer's, ischemic - reperfusion injury, cardiac arrest, traumatic brain injury, and stroke. Thus, targeting these cell organelles in neurodegenerative diseases could be a good potential therapeutic approach to protect neural damage.

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DOI:10.22192/ijarbs.2022.09.07.028

How to cite this article:
Amit Ranjan, Rashmi. (2022). Targeting cellular organelles for Neuroprotection in Neurodegenerative Diseases-A Narrative Review. Int. J. Adv. Res. Biol. Sci. 9(7): 281-288.
DOI: http://dx.doi.org/10.22192/ijarbs.2022.09.07.028