Investigating the effect of mitochondrial dysfunction and oxidative stress in cardiological and neurological diseases

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Abstract

Oxidative stress is a condition characterized by the surplus of reactive oxygen species, which in turn requires the organism to endure additional cellular stress in order to remove the surplus of reactive oxygen species, which is detrimental in high amounts. (20) When oxidative stress occurs in the mitochondria, it can lead to mitochondrial dysfunction. (20,21) Furthermore, the unfolded protein response in the mitochondria can lead to excessive cell death, thus perpetuating the state of mitochondrial dysfunction, to the point where the cell can no longer carry out its normal functions. (4,31) Oxidative stress and mitochondrial dysfunction have been deeply implicated in the pathogenesis of neurological and cardiological diseases, such as Alzheimer's disease and hypertension. (12,16) Current treatment methods for mitochondrial dysfunction and oxidative stress are inefficient, vague, or not feasible. (2,38) There is potential in future treatments, such as medicinal plants, taurine, and peripheral blood mononuclear cells and platelets, that have demonstrated improvement in preventing, reducing, and identifying mitochondrial dysfunction caused by oxidative stress. (2,4,10)

Introduction

In 2020, cardiovascular and neurological diseases were in the five leading causes of death in the U.S., with cardiovascular disease ranking number one continuously for several years. (34, 25, 9) It has been demonstrated that cardiological and neurological diseases pathology is exacerbated when mitochondrial dysfunction is also present. (13,16) Mitochondrial dysfunction is a state in which the mitochondria are no longer able to perform its regular functions, such as harnessing energy (ATP) through oxidative phosphorylation, and can be caused by a variety of factors. (4) The most significant factor that contributes to mitochondrial dysfunction is oxidative stress, a condition characterized by the excessive presence of reactive oxygen species within a cell. (20) Extensive oxidative stress that results in mitochondrial dysfunction can be extremely detrimental to a cell, and henceforth the organism. (21)

Effects of mitochondrial dysfunction are varied, from telomere erosion and mitochondrial DNA deletion to cell death. (35) However, for the scope of this literature review, oxidative stress and mitochondrial dysfunction impacts is specifically reviewed on neurological and cardiovascular diseases. (13,16) In neurological diseases, such as Parkinson's disease, oxidative stress can cause dopaminergic neuron deterioration, which aids in disease progression. (37) In cardiovascular diseases, such as hypertension, oxidative stress increases the inflammatory response and blood pressure through the recruitment of additional inflammatory cells, which in turn creates hyperinflammation of the heart's muscles.(34) Current treatments for cardiovascular and neurological diseases in which mitochondrial dysfunction is implicated can be ineffective or unfeasible. (2,38,14) However, there is much hope with the future treatments through use of medicinal plants, taurine, and improved biomarkers, specifically peripheral blood mononuclear cells for mitochondrial dysfunction to improve the methods for not only treatment of neurological and cardiological diseases exacerbated by mitochondrial dysfunction, but for early detection of mitochondrial defects as well. (2,3,10)

Oxidative Stress

Oxidative stress is characterized by the excess accumulation of reactive oxygen species (ROS) to the degree that the cell can no longer remove the excess ROS to maintain redox homeostasis. (20, 30) Redox homeostasis, also known as oxidation-reduction, is the process of an oxygen molecule gaining an extra, unpaired electron, or free radical, (reduction) from another chemical species that loses an unpaired electron (oxidation), which is most commonly a hydrogen proton. (8) The term oxidation is used when the electron is lost, while reduction is when the electron is gained. (8) When redox homeostasis is disturbed, redox homeostatic mechanisms are typically activated. However, it has been found that in many neurological and cardiological diseases that these protective

homeostatic mechanisms that are supposed to be activated are defective, essentially providing the cell with no feasible mechanism to eliminate reactive oxygen species. [33]

While ROS is generally considered as a cellular stress, it is necessary for ROS to be present for many endogenous cellular processes to occur smoothly. [20] ROS surplus can be caused by environmental factors such as X-ray radiation, UV exposure, cigarette smoke, and other external factors, it can also be an endogenous result of abnormal oxygen metabolism through the electron transport chain in the mitochondria. [17,20] The electron transport chain is a process that leads to the production of ATP through oxidative phosphorylation. This process oxidizes oxygen (the conversion to ROS) to pump protons through the inner mitochondrial matrix to energize ATP synthase for the production of ATP, while also reducing the oxidized oxygen to neutralize the ROS.[5,6] While the electron transport chain naturally undergoes ROS reduction, this basal ROS reduction is not sufficient to maintain redox homeostasis, which requires consistent anti-oxidation methods to maintain redox homeostasis and to allow the mitochondria to function. [17]

The effects of oxidative stress can range from mild to severe, initiating cell death. [20] Furthermore, excessive oxidative stress can impair the function of the mitochondria through a multi-faceted approach by mutating mitochondrial DNA, modifying nascent mitochondrial proteins, and impairing the function of ATP synthase in the production of energy. [20] While oxidative stress has global effects in the cell, such as causing telomere erosion which can lead to cellular dysfunction and cell death, most significantly extensive oxidative stress can lead to mitochondrial dysfunction. [21, 35]

Mitochondrial Dysfunction

Mitochondria is known as the powerhouse of the cell due to its involvement in many cellular processes such as apoptosis, cellular debris removal, protein aggregation, ATP formation, Ca2+ regulation, and reactive oxygen species production. [4,12] Therefore, when the mitochondria functioning irregularly, it can have specific and global consequences, such as inhibiting the prevention of aggregated tau and amyloid-β proteins (which leads to the progression of neurological diseases such as Alzheimer's Disease) to initiating apoptosis. [4,12] Mitochondrial dysfunction can be a consequence of many mitochondrial defects such as the dysregulation of the mitochondrial transmembrane potential, mutations in key proteins that act in the electron transport chain, deficiency in mitochondrial metabolites, decreased ATP production, inhibited oxidative phosphorylation, and excess ROS. [4,11]

While the aforementioned mitochondrial defects contribute to mitochondrial dysfunction, it has been demonstrated that excessive ROS presence most detrimentally impacts mitochondrial function and global cellular function. Furthermore, excessive ROS presence feeds into many other mitochondrial defect mechanisms, making it the most deleterious form of mitochondrial dysfunction. [22] An example of excessive ROS creating a positive feedback loop to perpetuate mitochondrial dysfunction is the fact that excessive ROS initiates the unfolded protein response. [22] The unfolded protein response is an endogenous protective mechanism that protects nascent proteins from ROS modification (reduction of thiols on proteins), to allow the cell to continue to function, and ideally eliminate the excess ROS within the cell through the upregulation of ROS protecting proteins (chaperones) and ROS eliminating proteins (reductases). [22] However, if the excess ROS accumulation is too significant, the perpetuated activation of the unfolded protein response can in turn contribute to mitochondrial dysfunction. [31] Prolonged activation of the unfolded protein response will inhibit or decrease efficiency of normal cellular processes, while aiding deleterious processes such as protein aggregation, which aids in the pathogenesis of many neurological and cardiological diseases.

Mitochondrial Dysfunction and Neurological Diseases

In 2020, neurological diseases were one of the top five leading causes of death in the US., exemplifying the necessity in the research of neurological diseases. [9] Neurological diseases are defined as illnesses that produce abnormal nervous system functions that are caused by damaged electrical impulses. [8] It has been demonstrated in many neurological diseases that oxidative stress and disease progression are tightly linked. [13] Oxidative stress can occur in the nervous system from a variety of factors such as excess unsaturated lipids in tissue,

metals of mixed valence, free radical neurotransmitters, and excessive reactive oxygen species production. [13] However, the most important contributing factor is the dysregulation of mitochondrial metabolites (sugars), which is vital to the brain as brain tissue is the most active cellular respiration cell type, with 90% of the functions of the brain requiring ample oxygen supply, thus linking the importance of mitochondrial function to normal neuronal function. [13]

Neurological diseases such as Alzheimer's Disease, Parkinson's Disease, and Schizophrenia have been demonstrated to worsen with mitochondrial dysfunction, and in some cases be caused by underlying mitochondrial dysfunction conditions. [13] For example, in Parkinson's Disease, mitochondrial dysfunction can damage and kill dopaminergic neurons. [37] Dopaminergic neurons are responsible for the neurotransmission of dopamine throughout the central nervous system, which is required for basal neuronal communication (transmission). [37] In conjunction to the defect in dopaminergic neurons in Parkinson's disease, those with both Parkinson's Disease and underlying mitochondrial dysfunction have shown to result in the abnormal transmission between axons, with irregular mitochondrial distribution also being present. [11] While mitochondria are the general producers of reactive oxygen species, they can also serve to remove reactive oxygen species through the utilization of specific catalases, called reductases. [39]

This same link between mitochondrial dysfunction and neuronal disease progression can also be seen in Alzheimer's Disease, in which it has been demonstrated that patients with Alzheimer's Disease are likely to also suffer from mitochondrial deficiency, which leads to the decrease of mitochondrial reductase activity, causing the accumulation of reactive oxygen species, which in turn exacerbates the current mitochondrial deficiency through the destruction of nascent mitochondrial proteins. [12] Furthermore, mitochondrial dysfunction, which is tightly linked to excessive reactive oxygen species, contributes to the aggregation and fibrillation of tau and amyloid-β proteins, a hallmark of disease progression in Alzheimer's Disease. [12]

Schizophrenia, on the other hand has a link between oxidative stress and disease progression on the genomic level. Patients with schizophrenia are genetically more susceptible to oxidative stress, with genome wide association studies (GWAS) inferring that genes linked to mitochondrial dysfunction correlate to schizophrenia pathogenesis. [13] Furthermore, it has been demonstrated in schizophrenia patients that differential gene expression of mitochondrial regulatory proteins promotes a pro-oxidant state, a state where reactive oxygen species conversion occurs more readily while dually undermining the function of the antioxidant system within the cell. [33] This pro-oxidant state dysregulates redox signaling, causing abnormal expression of redox mediating proteins, which in turn perpetuates mitochondrial dysfunction of the cell. [13]

Mitochondrial Dysfunction and Cardiological Diseases

Being the leading cause of death in 2019, it has been demonstrated that cardiovascular diseases in conjunction to excessive reactive oxygen species are extremely detrimental to the organism wholly. Extensive research has found that excessive reactive oxygen species are the root cause of many cardiological diseases due to cell clusters that are experiencing the presence of excess reactive oxygen species hyperactivating the inflammatory response to that exact location, which in turn significantly damages heart tissue specifically. [2,33,34] This damage can lead to the progression of hypertension, as the damaged heart tissues must work harder to pump blood efficiently throughout the body. [16]
Any oxidative stress has the potential to injure nascent proteins. Protein production in heart cells is much higher than other cell types, which makes the heart especially susceptible to further damage when excess reactive oxygen species are present. Therefore, when oxidative stress and mitochondrial dysfunction are combined with hypertension, the damage can be irreversible. [16] Furthermore, the effects of the damaged proteins, such as protein dysfunction or degradation, can itself cause cell, tissue, and organ damage or failure. [16]

Treatments of Underlying Mitochondrial Dysfunction in Neurological and Cardiological Diseases

With two leading causes of death in 2020 being influenced by mitochondrial dysfunction and oxidative stress, early detection of mitochondrial dysfunction and utilizing effective treatments for mitochondrial dysfunction is extremely vital. [9] Current treatments for excessive oxidative stress conditions and mitochondrial dysfunction are

vague, mostly suggesting lifestyle changes that help to increase general health, such as eating more antioxidants, exercising more, and straying from excessive environmental pollution exposure. [38] By increasing antioxidant intake, the cell is able to utilize these antioxidants to assist with neutralization of reactive oxygen species when the cell is dealing with excessive oxidative stress. [24] However, there are some treatments in clinical trials to directly treat mitochondrial dysfunction through neurohormonal modifications, such as natriuretic peptide guided therapy. [2] However, this method produces very minimal effects and is not considered effective. [14] Due to natriuretic peptide guided therapy being in its infancy, this method should be explored more before dismissing it as a valid treatment for mitochondrial dysfunction. Furthermore, the option to treat patients with mitochondrial-targeted molecules remains a possible treatment method, but it does require significant additional research to fully elucidate said processes and its effects. [3] Thankfully, many options still stand for future treatment methods, such as medicinal plants, and cytoprotective molecules. [2,3,10]

Medicinal plants demonstrate the potential to decrease oxidative stress through its flavonoids, phenolics, and saponin. [10] All three, found in medicinal plants, offer various benefits. Flavonoids offer anti-inflammatory properties, phenolics present antioxidant properties, and saponin demonstrates properties that decrease blood lipids, cancer risks, and blood glucose response. [7,29,32] Cytoprotective molecules, specifically taurine, exemplifies several preventative properties regarding oxidative stress. [3] Taurine can aide in the maintenance of a typical electron transport chain, increasing the responsiveness to antioxidants, supporting a stable membrane, and decreasing inflammation, henceforth preventing the progression of prime factors that would promote a pro-oxidant state. [3]

Unfortunately, treatment for mitochondrial dysfunction is not the largest problem at present. Identifying mitochondrial dysfunction is very difficult, in most cases it requires tissue samples for a biopsy, which is not always feasible and nonetheless is very invasive. [2] However, current research is very promising for the improvement of biomarkers to detect mitochondrial dysfunction early. [2,3,10] Analyzing peripheral blood mononuclear cells and platelets have demonstrated great potential to become a biomarker of oxidative stress. [2] Furthermore, mitochondria can be easily isolated from peripheral blood mononuclear cells and platelets, allowing for the more accurate detection of mitochondrial dysfunction. [2]

Conclusion

Oxidative stress, a condition that is characterized by excess reactive oxygen species in a cell, can cause mitochondrial dysfunction. [21] Mitochondrial dysfunction has many adverse effects, from telomere erosion and deletion of mitochondrial DNA to tissue damage and cell death, which ultimately promote conditions favorable for neurological and cardiological disease progression. [16,35] Current treatments are vague, ineffective, and not always feasible. [14] However, utilizing medicinal plants, taurine, and improved biomarkers, there are putative treatment methods to explore further in the future. [2]

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