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Mitochondrial Dysfunction – A Major Contributor to Parkinson's Disease Progression

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ABSTRACT

Parkinson's disease (PD) is identifiable by widespread neurodegeneration within the brain as well as a discerning yet protuberant and precocious loss of nigrostriatal dopaminergic neurons. Mitochondrial dysfunction takes mainstream pathogenesis of PD, out of the multitudinous theories proposed for this illness. Mitochondria are viscerally important organelles engaged in a series of functions. The foremost notable is their prominent role in energy metabolism, where they generate over 90% of our cellular energy within the sort of ATP through the organic process. The inhibition of the Electron transport chain results in the generation of reactive oxygen species and depletion of cellular energy levels, which may consequently cause cellular damage and death mediated by oxidative stress and excitotoxicity. This paper intent, for instance, the deal of information relating to mitochondrial dysfunction with neuronal necrobiosis within the substantia nigra pars compacts (SNpc) of PD patients. We also review peculiar mitochondrial durability pathways that anticipate promising innovations in neuroprotective therapies and which in the future will reconnoiter as a possible therapeutic intervention in the pathogenesis of PD.

1. INTRODUCTION

Parkinson's disease (PD) may be a slowly progressive neurodegenerative disease clinically characterized by progressive motor impairment in affected people. Synaptic and axonal degeneration is followed by the loss of dopaminergic neurons within the substantia nigra results in reduced levels of dopamine within the nigrostriatal circuitry.

PD may be a complex, composite disease during which various factors contribute to the pathogenic process.[1] Parkinson's disease (PD) is that the second commonest neurodegenerative disorder, characterized by an outsized number of motor and nonmotor features that will affect function to a variable degree.

The loss of midbrain dopaminergic (DA) neurons within the substantia nigra par compacta (SNpc) extrapolating to the striatum and abnormal cytoplasmic inclusions enriched in α-synuclein, the Lewy bodies, deposited in surviving neurons of the brain is the main pathological hallmark in PD.[2] The exact mechanism by which SNpc necrobiosis in PD occurs is poorly understood, but several lines of evidence implicate mitochondrial dysfunction as a possible primary cause because of the major role of mitochondria in energy production, along with oxidative stress, excitotoxicity, and ubiquitin system impairment, all of which can be interlaced [3–5]. Complex I deficiency and impaired electron transfer in Mitochondrial dysfunction within the substantia nigra in PD are reported. [3, 4] With the magnitude of the direct relationship between genetic PD loci and mitochondria, mitochondrial dysfunction has been implicated as a fundamental disease component. [6] This review focuses on understanding recent advances within the role that mitochondrial dysfunction plays in the pathogenesis of PD.

2. NEUROTOXICITY:

The term neurotoxicity usually is a form of toxicity caused by exposure to either man-made or natural or toxins which alter the normal activity of the brain or peripheral nervous system. This type of toxicity includes a biological, chemical, or physical agent producing an adverse effect on the structure or function of the CNS. These toxins can alter the activity of the nervous system in ways in which can disrupt or kill nerves.[7]

There are several mechanisms related to neurotoxicity in neurodegenerative diseases like Excitotoxicity, Oxidative Stress (OS), Mitochondrial Dysfunction, Neuro Inflammation, Loss

of Trophic Factor, Apoptosis, and Protein Aggregation. This paper is going to be focused on the mechanism of neurotoxicity mediated by the deregulation of the mitochondrial mechanisms.

3. MITOCHONDRIAL DYSFUNCTION:

3.1. Normal function and pathology of mitochondria:

Mitochondria are the intracellular powerhouse that performs important cellular reactions, including the assembly of energy through the mitochondrial respiratory chain (RC), the regulation of necrobiosis, calcium metabolism, and therefore the production of ROS. Mitochondria are a significant source of free radicals within the cell, leading to OS, but mitochondria also are integral to the OS response. Moreover, the inner mitochondrial membranes enclose the RC which constitutes four enzymatic complexes (complexes I-IV), which catalyze the transmission of reducing equivalents from high-energy compounds produced by the reactions of the Krebs cycle to oxygen, with the ultimate production of an electrochemical gradient through the inner mitochondrial membranes to drive the synthesis of ATP by ATP synthase. [8]

3.2. Mitochondrial Dysfunction: Mitochondrial diseases are a gaggle of disorders caused by dysfunctional mitochondria, the energy generated for cells. Mitochondria are found in every cell of the physical body except red blood cells and convert the energy of food molecules into the ATP that powers most cell functions. Mitochondrial dysfunction may cause oxidative stress and generate reactive oxygen species (ROS).[9] The generation of free radicals and deficiencies in energy supply, calcium buffering, or regulation of apoptosis contributes to a progressive decline of the central systema nervosum in aging and neurodegeneration. Mitochondrial dysfunction, which may account for these problems, is usually involved in neurodegenerative diseases like Parkinson’s disease (PD), Alzheimer's disease (AD), and Huntington disease (HD). [10] Mitochondrial diseases combat unique characteristics both due to the way the diseases are often inherited and since mitochondria are so critical to cell function. Mitochondria are found in virtually all eukaryotic cells and performance to get cellular energy within the sort of ATP (ATP) by organic process and are thought to be derived evolutionarily from the fusion of prokaryotic and eukaryotic organisms.[11] Mitochondria are composed of a double lipid bilayer with a phospholipid outer membrane

and inner membrane which surrounds the intra compartmental matrix. The space between the 2 membranes is vital in and contains the main units of, organic process.[12]

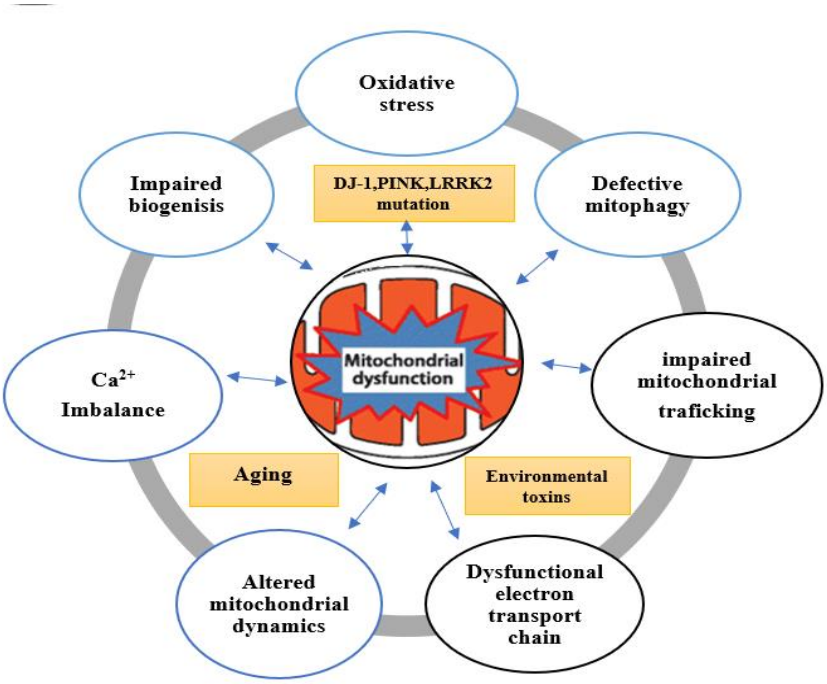

Figure No. 1: Representative pathways of mitochondrial dysfunction in PD pathogenesis. Multiple factors, including genetics, aging, and environmental toxins, or combinations, are implicated in the etiology of PD. Abnormal metabolic function, abnormal morphology, and impaired fission-fusion balance have all been observed in mitochondria in a minimum of some sort of PD. Increased OS can cause impaired function of the UPS (Mitochondrial ubiquitin-proteasome system), thereby further affecting cell survival of these may unswervingly affect the mitochondrial function of protein degradation systems, including UPS and ALP (autophagy lysosomal pathway), and thereby, cause the degradation of dopamine neurons that ultimately results in neurodegeneration that underlies PD pathogenesis and progression.

3.3. CAUSES OF MITOCHONDRIAL DYSFUNCTION:

Mitochondrial disorders could also be caused by mutations (acquired or inherited), in mitochondrial DNA, or nuclear genes that code for mitochondrial components. They'll even be the results of acquired mitochondrial dysfunction thanks to the adverse effects of medicine, infections, or other environmental causes. [13] This "Threshold expression" is a phenomenon where the mitochondrial disease or dysfunction may become clinically apparent

once the amount of affected mitochondria reaches a particular level. [14] Most mitochondrial function and biogenesis are controlled by nuclear DNA. 13 proteins of the respiratory chain are encoded in human mitochondrial DNA, while most of the estimation of about 1,500 proteins and components that are targeted to mitochondria are nuclear-encoded.[15] There are several clinical disease phenotypes like anaemia, dementia, hypertension, lymphoma, retinopathy, seizures, and neurodevelopmental disorders which are analogous to defects in nuclear-encoded mitochondrial genes.[16]

3.4. MECHANISM OF MITOCHONDRIAL DYSFUNCTION:

3.4.1. Electron transport chain dysfunction in PD:[17]

The electron transport chain consists of five complexes including an ATP-synthase located within the inner mitochondrial membrane. The function of the chain is to get cellular energy within the sort of ATP. This is often accomplished by the transport of electrons between complexes causing proton (H+ ions) movement from the matrix to the intermembrane space generating a proton concentration gradient employed by ATP-synthase to supply ATP (Figure 2). As neurons have a substantial energy need and also are highly equipped with mitochondria they're extremely sensitive to mitochondrial dysfunction. Many of those neurological disorders are related to mitochondrial dysfunction and demonstrate enhanced production of free-radical species. The outline of Complex I (CI) deficiency within the post-mortem SNpc of PD patients gave a piece of front-line evidence for a link between mitochondrial dysfunction and its role in the pathogenesis of PD and has been suggested to be one of the elemental causes of PD. This CI insufficiency was also recorded within the frontal area in PD, and also within peripheral tissues such as platelets and striated muscle indicating that there's a huge reduction in mitochondrial CI activity in PD. This defect could also be thanks to oxidative damage to CI and misassembly since this is often a feature of isolated PD brain mitochondria. Incidental Lewy body disease (ILBD) which is taken into consideration by some as a preclinical indicator of PD, has been reported to possess a transitional level of CI activity within the SNpc between PD patients and healthy patients which additionally supports the idea of mitochondrial dysfunction. A variety of mechanisms like increased oxidative stress and excitotoxicity can inhibit CI and further cause degeneration of affected neurons. A drop within the function of Complex III has also been proclaimed within the lymphocytes and platelets of PD patients. Impairment of mitochondrial CIII assembly, a rise in free radical production, and PD have also been interlinked. This

increase in the radical release could also be thanks to the increased leakage of electrons from CIII. Alternatively, a severe reduction within the levels of functional CI in mitochondria is caused by inhibition of CIII assembly which could lead to a rise in the production of free-radical through CI deficiency in addition to this, the CI and II electron acceptor ubiquinone has also been shown to be reduced within the mitochondria of PD patients and loss of DA neurons was recorded in aged mice exposed to Parkinsonian neurotoxin 1-methyl4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was attenuated by ubiquinone, providing more evidence for the major contribution of mitochondrial dysfunction in the pathogenesis of PD.

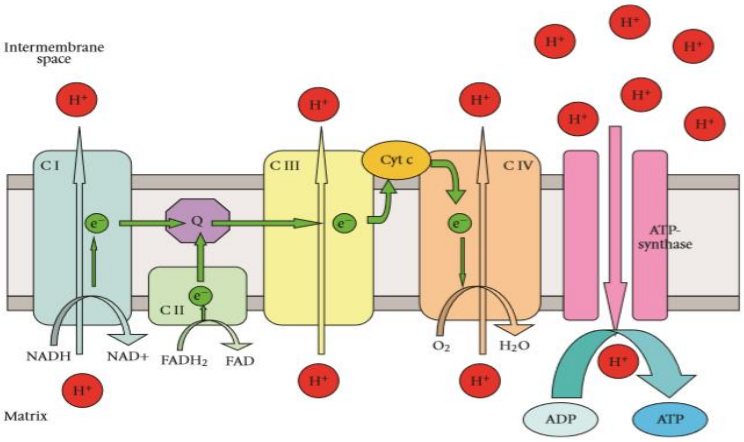

Figure No. 2: Mitochondrial electron transport chain: Diagrammatic representation of the ETC in mitochondria which is involved in oxidative phosphorylation. CI and II (Complexes I and II) transport electrons (e-s) generated by the conversion of NADH to NAD+ (CI) or FADH2 to FAD (CII) through Q (ubiquinone), CIII, Cyt c (cytochrome c), and finally the CIV uses an e- to convert O2 to H2O. During electron transfer, CI, II, and IV pump protons (H+s) from the mitochondrial matrix into the intermembrane space generating an H+ concentration gradient that drives the formation of ATP from ADP by ATP-synthase (Complex V).

3.4.2. Production of ROS by Mitochondria in PD:

The electron transport chain releases a significant number of electrons into the mitochondrial matrix because of Complex I or III inhibition which then further reacts with oxygen to make Oxygen free radicals, hydroxyl radicals, and nitric oxide synthase which are termed as reactive oxygen species (ROS). This escalation within the normal electron leakage occurs by the hindrance of electron movement along the chain to an ensuing acceptor molecule. A

specimen of this finding that siege of the electron-accepting capability of the ubiquinone binding site of Complex I results in an increased generation of electron radicals in striated muscle of rat mitochondria.[18] The ROS formed is expected to act as signaling molecules by promoting excitotoxicity or causing lipid peroxidation, all resulting in the modification of proteins and eventual necrobiosis.

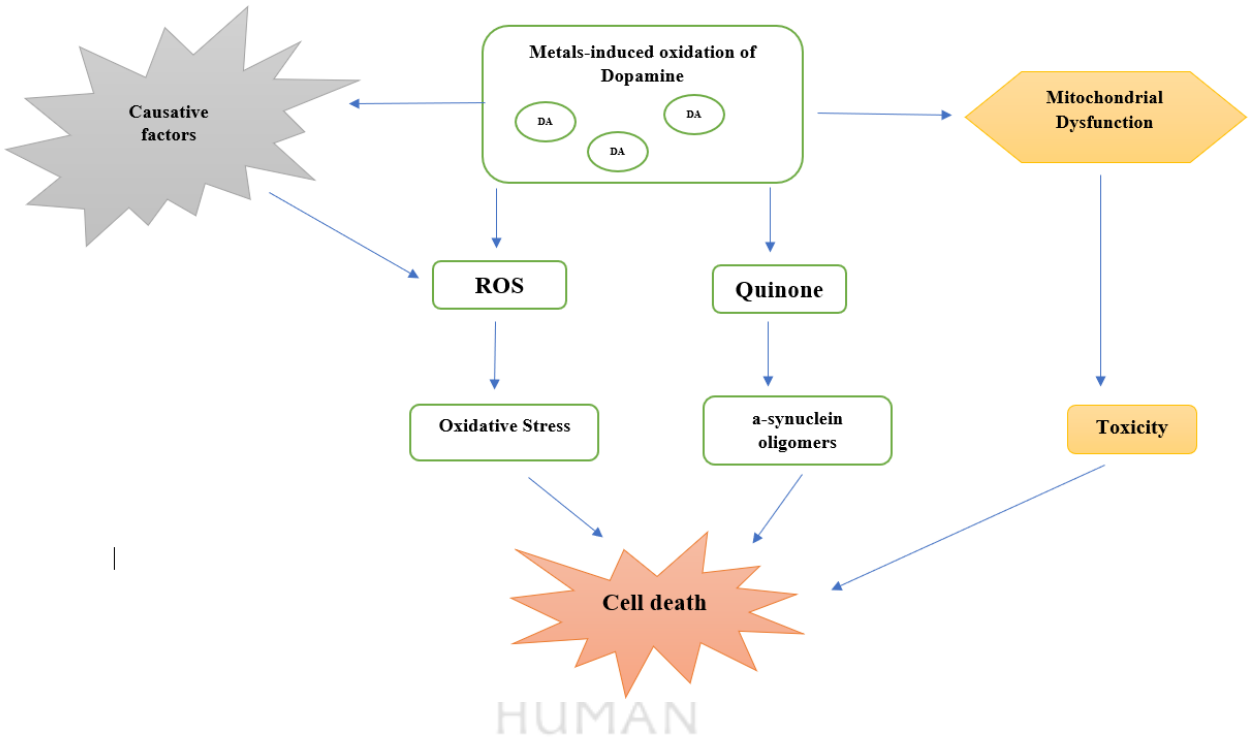

Figure No. 3: PD is caused by several factors such as gene mutation, neuroinflammation, and iron accumulation this all factors could induce ROS generation by Mitochondria, and this ROS would further cause dopaminergic neuronal death by causing oxidation of protein, lipids, and other macromolecules in the cells.

3.4.3. Protein Damage facilitated by ROS:

Amongst the foremost common mechanisms of protein damage caused by ROS is oxidation to make carbonyl groups on proteins and nitration by peroxynitrite. Reactive ROS can readily oxidize amino acids on various cellular proteins to make carbonyl groups, which may disrupt the physiological function of the affected protein and cause cytotoxic protein aggregates, activation of necrobiosis pathways, and impairment of neuroprotective pathways.[19] Per oxy nitrite[20] and other ROS[21]can also oxidize sulphydryl groups on glutathione, resulting in depletion of antioxidant defenses, and other thiol-containing cofactors disrupting various cellular processes and structures. The final loop between PD and ROS generated by

mitochondria through protein damage comes with the origination of nitrated and oxidatively damaged misfolded proteins that have powerful genetic links with the disease like α-synuclein, DJ-1, Parkin, and PINK1 suggesting that these disease-associated proteins are major targets of free-radical damage in sporadic sorts of PD.[22-27] Lipid peroxidation is another of the most sorts of cellular damage caused by ROS occurring when ROS react with hydrogen. There are strong links between increased lipid peroxidation and PD with increased levels shown to be present and cause necrobiosis within the nigral cells of PD patients [28,29], suggesting a task for it within the mechanisms of neuronal death. Since there are elevated markers of oxidative damage within the brains of PD patients, including lipid peroxidation protein damage and oxidative DNA damage, oxidative stress is a long-time event in PD. This evidence combined with the PD-like effects of known Complex I inhibitors like MPTP [30] and rotenone [31] and a rise within the activity of neutralizing SOD (SOD), particularly the mitochondrially localized MnSOD, being found in neurodegenerative disease patients [32] points to a robust link between ROS, possibly caused by mitochondrial dysfunction and PD.

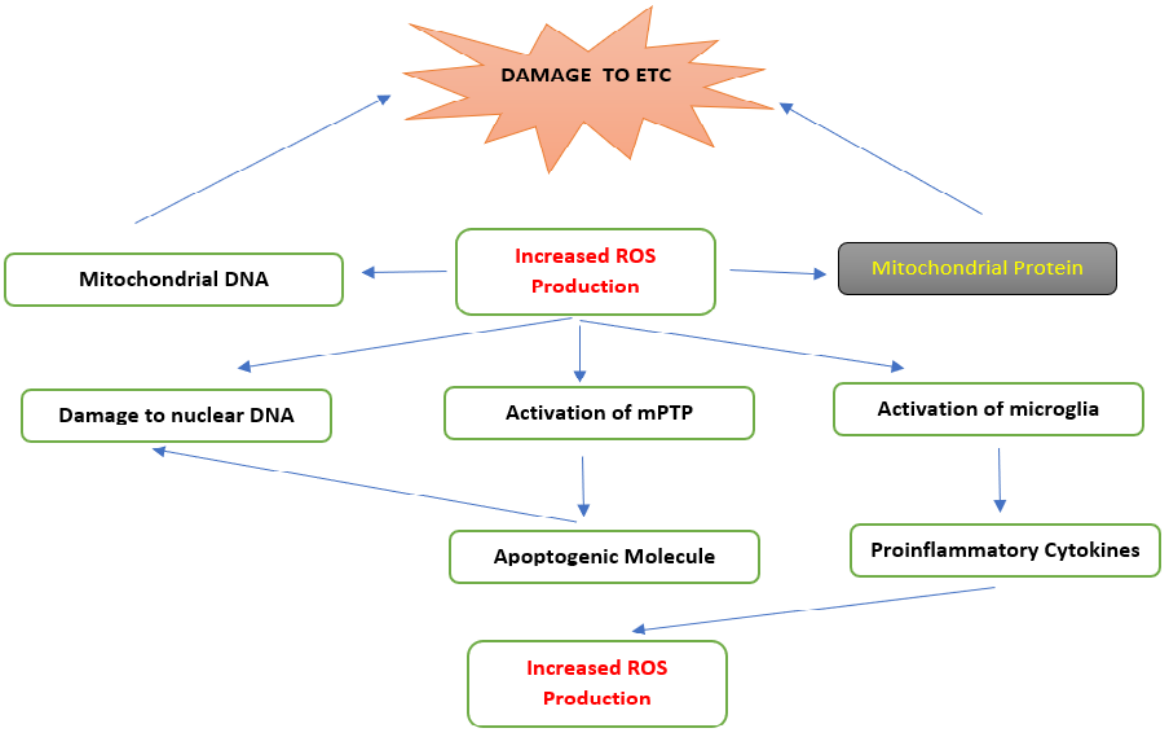

Figure No. 4: ROS triggers a series of events that ultimately leads to neurodegeneration. Oxidative stress plays a central role in the neurodegenerative process by triggering a series of events which include mitochondrial dysfunction, neuroinflammation, and impairment of nuclear and mitochondrial DNA, which in turn cause more ROS production, thus damaging

the mitochondrial protein. These events lead to an uncontrolled pathogenesis condition that drives the progressive degeneration of dopaminergic neurons in Parkinson's disease.

3.5. Role of Ca^{2+} in Mitochondrial Dysfunction and PD:

3.5.1. Excitotoxicity:

The cellular destruction caused by electron transfer chain hindrance may contribute to neuronal excitotoxicity exacerbating neurotoxicity in PD. Several mechanisms for excitotoxicity in neurodegenerative conditions are proposed [33, 34] Excitotoxicity occurs when depolarization of the neuronal cell wall from −90 mV to between −60 and −30 mV results in a decrease within the magnesium blockade of N-methyl-D-aspartate (NMDA) receptors. This, in turn, results in NMDA receptor activation by latent levels of glutamate and causes an intracellular Ca^{2+} accumulation. This increase in Ca^{2+} is then thought to cause neurotoxicity by two main mechanisms. Firstly, Ca^{2+} causes a rise in intracellular NO via activation nitric oxide synthase (NOS) the surplus of NO within the cell can react with ·O2− to make peroxynitrite,[35] which may cause necrobiosis by mechanisms almost like those caused by ROS and mentioned above. Besides the peroxynitrite, NO itself can cause cell damage via nitrosylation of varied proteins. A second mechanism driven by intracellular Ca^{2+} increase causes toxicity in DA neurons by working on mitochondria themselves. The Ca^{2+} influx is extensively accumulated within the mitochondria and results in effects on mitochondrial membrane potential and ATP synthesis also as the generation of ROS [36] contributing to the oxidative damage. This also all feeds back causing further malfunction of the cell's Ca^{2+} homeostasis and extracellular damage. Further to being integrally involved in mitochondrially generated excitotoxic necrobiosis in PD, Ca^{2+} has been implicated in other mechanisms of necrobiosis within the disease which will involve compromise of the role of mitochondria together of the main intracellular Ca^{2+} stores. This implies that excitotoxicity derived by mitochondria might be a prime and serious contributor to the pathogenesis of PD.

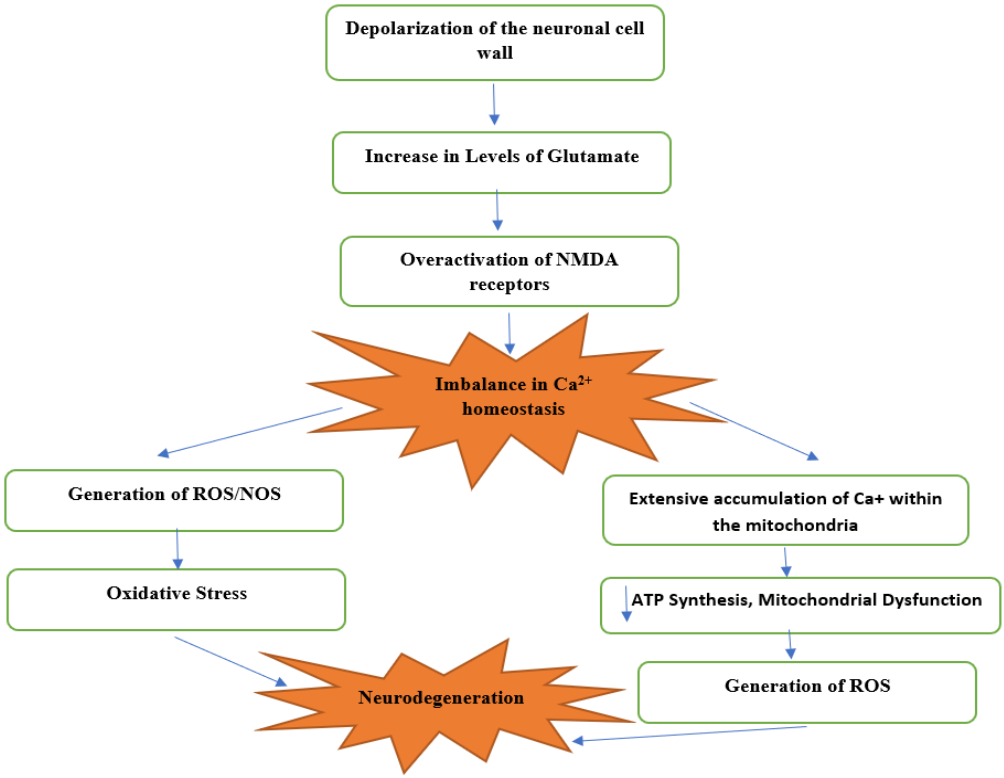

Figure No. 5: Imbalance of Ca^{2+} homeostasis causing Mitochondrial Dysfunction and PD.

3.6. Dopamine Metabolism and Mitochondrial Dysfunction in PD:

Oxidative stress generated by dopamine metabolism has long been implicated in PD.[37] However, more recently, it's been reported that ROS or reactive quinones generated by oxidation of dopamine, either spontaneously or by MAO (MAO), may prohibit effect on the mitochondrial respiration chain proteins.[38-40] It's been shown that that dopamine inhibits Complexes I and IV, most likely by acting on the dopamine-generated quinones and not through ROS.[41] The outer mitochondrial membrane constitutes MAOA which may oxidize dopamine to make the metabolite 3,4 di hydroxyl phenyl ethanoic acid (DOPAC), which locally inhibits Complexes I and IV [40,42] itself, or through oxidation of quinones, although a contradictory report suggests dopamine but not DOPAC inhibits the electron transport chain.[43] These links between mitochondrial dysfunction and dopamine are supported by reports that the PD neurotoxins and sophisticated I inhibitors MPTP and rotenone increase dopamine oxidation and turnover [44,45] although whether this is often indirectly thanks to the ROS generating effects of the toxins aren't clear. This hypothesis could offer a shred of evidence on why DA is more susceptible than other neurons to a toxin or mutation-mediated

mitochondrial dysfunction PD, as they're already under a better level of oxidative stress thanks to dopamine metabolism generated electron transfer chain.

4. STRATEGIC TREATMENT IN MITOCHONDRIAL DYSFUNCTION:

As Mitochondrial dysfunction is a prime contributor to the pathogenesis of PD, there has been an excellent deal of interest in developing drug targets that can attenuate mitochondrial abnormalities by exhibiting neuroprotective effects. A good range of candidate drugs that focus on mitochondrial dysfunction is studied in several experimental models of PD and other neurodegenerative disorders of those several drugs, two of the drugs, Coenzyme Q10 (CoQ10) and creatine have shown enormous potential and have made it to clinical trials for PD.

4.1. CoQ10 in the treatment of PD: CoQ10 is an electron transport chain cofactor that is lipid-soluble a visceral compound that accepts electrons from complexes I, II, and III.[46] By regenerating α-tocopherol it has proved to be a potent scavenger of free radical within the inner mitochondrial membranes and microsomal lipid membranes.[46] CoQ10 is a significant cofactor for mitochondrial uncoupling proteins as they regulate by producing ATP and thus reducing the generation of free radicals.[46] In PD patients CoQ10 levels in platelets are reduced and it correlates with defalcation in mitochondrial complex I activity.[47] CoQ10 is also known to block death due to oxidative stress,[48] apoptotic cell death by blocking BAX association with mitochondria,[49] and inhibiting mitochondrial permeability transition pore[50] known to cause cell death by increased retention of mitochondrial calcium. The efficacy of various formulations of CoQ10 in blocking nigrostriatal dopaminergic neurodegeneration using different neurotoxic models and various ages of mice using the MPTP model of PD has been demonstrated.[51,52] Although the phase III trials are advancing to further establish the efficacy of CoQ10 in a large population of PD patients, the studies so far indicate it as a potential therapeutic candidate drug for PD further.

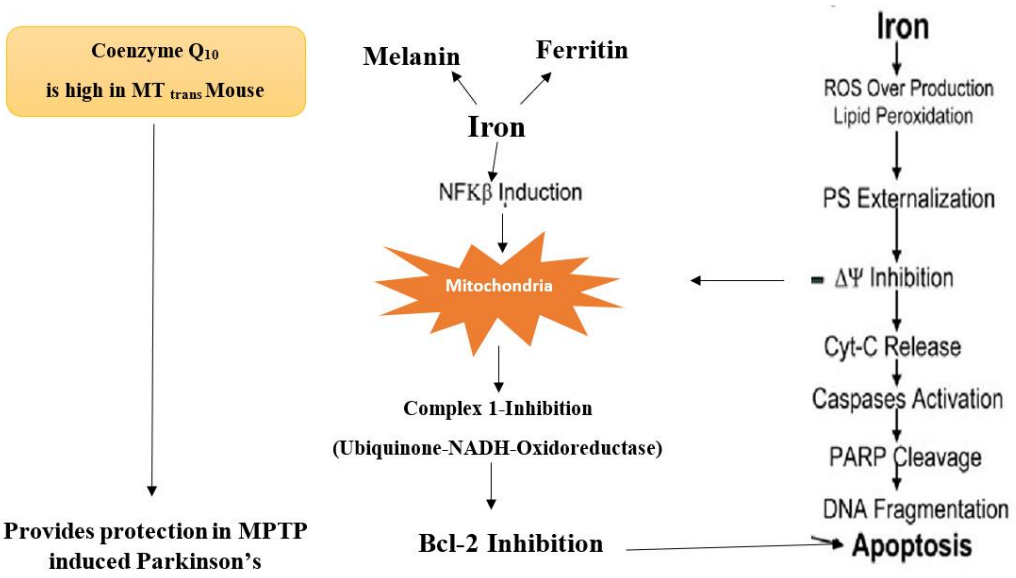

Figure No. 6: Coenzyme Q10- Mediated Neuroprotection

4.2. Creatine in the treatment of PD

Creatine being a guanidine compound is a pivotal energy reservoir for ATP and is a component of the creatine-phosphate system. Most of the creatine is found in the skeletal muscle and is taken up into various organs including the brain by specific creatine transporters, and serves as a substrate for mitochondrial and cytosolic creatine kinase.[53] Creatine has been shown in multiple independent studies to block neuronal death and increase lifespan in experimental animal models of neurodegenerative disorders.[46] Creatine has demonstrated a marginal but statistically significant improvement when used in clinical trials for de novo PD patients based on the UPDRS scale in the creatine group compared to placebo treatment.[54] This study has led to a randomized multicentre clinical trial for creatine that is currently underway.[55] Although a detailed mechanism of role for the efficacy and potency of creatine in the pathogenesis of PD is missing, it may help to maintain dysfunctional energy metabolism which may be possible due to mitochondrial dysfunction.

4.3. Combination of COQ10 and creatine for PD:

Studies carried out on patients with mitochondrial disorders [56] and animal models of PD using the combinatorial approach have shown synergistic effects.[57] A study using a combination of creatine and CoQ10 shows notable synergistic neuroprotective effects in the MPTP-mouse model of PD than when administered singly (Yang *et al*., unpublished results).

This data further suggest the improved efficacy of combinatorial drug therapy and justifies future clinical trials involving a combination of CoQ10 and creatine for PD.

The neuroprotective strategies which involve the drugs directly targeting mitochondria hold promising efficacy in the pathogenesis of PD as well as other neurodegenerative disorders where mitochondrial dysfunction plays a major role in disease pathogenesis.

5. CONCLUSION

Parkinson's disease (PD) is a progressive neurodegenerative disorder. PD is caused by several mechanisms which include Mitochondrial dysfunction, Oxidative Stress, Excitotoxicity, Loss of trophic factors, Neuroinflammation, Protein aggregation & misfolding. Many studies conducted using various genetic and toxin models of PD have contributed that mitochondria dysfunction plays a pivotal role in the pathophysiology of this illness. In this article, we conclude that Mitochondrial Dysfunction is an important target to prevent Neurotoxicity. Therapeutic strategies to prevent mitochondrial dysfunction include CoQ10 & Creatine. Various other mechanisms such as Ca+ mediated Excitotoxicity, Oxidative Stress, etc. are involved in mitochondrial dysfunction. Combination therapy of CoQ10 & Creatine may provide improved efficacy in the future. Exploration of mitochondrial homeostatic processes used as a model of the PD pathogenesis is functional for introducing innovative therapeutic interventions to discover a cure for PD.

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