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Review article

Beneficial role of mitochondria & sirtuin-3 enzyme in Parkinson's disease

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ABSTRACT

Parkinson's disease is the second most common neurological disorder associated with the gradual loss of dopaminergic neurons in the substantial nigra due to mitochondrial impairment.The available therapies cannot attenuate neurodegeneration. Recent studies support the mitochondrial dysfunction cascade in disease, increasing reactive oxygen species levels and triggering inflammatory mediators that lead to neuronal death. Mitochondrial sirtuins regulate energy metabolism and mitochondrial function and respond to cellular stress by releasing antioxidants. Especially,sirtuin-3 oxidized nicotinamide adenine dinucleotide deacetylase plays a vital role in maintaining the integrity and mitochondria biogenesis. Sirtuin-3 bind and deacetylate PTEN-induced kinase 1and E3 ubiquitin-protein ligase to promote mitophagy. We hypothesized that Sirtuin-3 activation might protect dopaminergic neurons in the Parkinson's disease animal model. In this review, we focused on the availability of current treatment and their failure in Parkinson's disease; meanwhile, we discussed the importance of mitochondria and Sirtuin-3 activation as potential ways to delay neurodegeneration.

Keywords: Oxidative Stress, Neuro degeneration, Sirtuin 3 enzyme, Mitophagy, Mitochondrial biogenesis, Parkinson's disease

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INTRODUCTION

Parkinson's disease (PD) is a slowly progressive neurodegenerative and hypokinetic movement disorder, with bradykinesia, muscular rigidity, resting tremors, and involuntary body movements. PD is a fast-growing neurodegenerative disease, nearly 1.5- 2% of people over 55 years even children and young adults can also be affected. Global burden in 2005 will be expected to double in 2030, in the western world due to an increase in an aging population. The pathological condition of PD is the loss of dopaminergic neurons (DA) in the substantial nigral pars compacta(SNPC) with the formation of Lewy bodies. Throughout the etiologic range, both hereditary and environmental causes are assumed to have a significant part in the development of PD; there has been no specific evidence supporting a particular reason for PD. However, six distinct genes have produced familial PD in the last ten years. They support the idea that PD has consistent pathogenetic mechanisms. Especially, mutations in alpha-synuclein, parkin, UCHL1, DJ1, PINK1, and LRRK2 may assume for causing PD, with a Mendelian inheritance pattern. Modifying mitochondrial proteins DJ1 and PINK1 and the accumulation of alpha-synuclein and parkin enhance mitochondrial damage. These same mitochondrial proteins and environmental toxins are involved in the occurrence of oxidative stress and proteasomal dysfunction. Therefore, these are common themes for the beginning of PD. These are better targets for research focused on developing treatments that will modify the course of PD [1,2]. Current PD treatment is focused on improving dopamine levels in the brain but has no stimulating effect on progressive neurodegeneration. Present ongoing studies focus on minimizing the pathology of PD by preventing further neurodegeneration. In the current scenario, literature evidence proves that SIRTUINS-3 activation shows a positive outcome for PD therapies [3,4].

First-line Drugs for PD

Levodopa with carbidopa (decarboxylase inhibitor) is used as a first-line anti-Parkinson's drug. Levodopa, a metabolic precursor to dopamine benefits asymptomatic relief by dopamine replacement due to DA loss but does not affect neurodegeneration. However, levodopa cannot cross the blood-brain barrier because it is rapidly metabolized to dopamine by the peripheral enzyme decarboxylase and causes severe nausea and vomiting, so peripheral decarboxylase enzyme inhibitors such as carbidopa or benserazide are used commonly fixed in combination with levodopa [5].

Alternative First-line Treatment for PD

Dopamine agonists such as Ropinirole, and Pramipexole may be an alternative first-line treatment for movement disorders in

PD, especially in 40 patients on dopamine agonists may also experience motor disturbance, more sleepiness, edema, and hallucinations compared to levodopa treatment; in clinical studies, dopamine agonists have been linked with increased dropout rates. Dopamine agonists and levodopa have been linked to developing motor control problems, and these potential side effects should be under observation [6]. Monoamine oxidase inhibitors (MAO inhibitors) like Selegiline is an MAO inhibitor used to inhibit the catabolism of dopamine and may be beneficial to PD patients with initial motor symptoms of PD. Selegiline is used alone or combined with levodopa, a decarboxylase inhibitor, to reduce symptoms in patients with advanced PD and for patients with postural hypotension selegiline and levodopa combination must be used under extreme supervision or may be avoided [7]. Amantadine is mild dopamine and glutaminergic agonist that can have a dual effect on early-onset PD, but it cannot be used as a first-line medication. Evidence from randomized controlled studies has concluded to control dyskinesia amantadine and levodopa combination are generally used. Amantadine is expected to have a minor impact that lasts less than eight months [8].When patients with severe PD develop end-of-dose degeneration that cannot be managed by the existing medication regimen, thus catechol-o-methyl-transferase(COMT) inhibitors may be used as adjunctive treatment with levodopa and dopa-decarboxylase inhibitors. COMT inhibitors act by inhibiting by transforming catechol's and dopamine into degradation products [9].Anti-muscarinic medicines show less effect compared to dopaminergic treatments. They rescue medicine-induced Parkinson's symptoms in patients treated with antipsychotics but are generally not used in patients with PD. However, benztropine may use to treat levodopa-resistance tremors in younger patients. Antimuscarinic medicines are not suitable for older patients due to the association between cognitive impairment and sedation. Researchers have concluded that there is an association between dementia with anti-cholinergic treatment in aged and PD patients; this reason firmly stands to oppose the usage of anti-cholinergic drugs to treat motor complications of PD [10].

Limitations of Parkinson's disease therapy

Up-to-date treatment for PD is not clear available drugs can only alleviate the disease symptoms but has no response to disease progression. The most successful pharmacological therapy for PD is levodopa, and its long-term usage shows severe adverse effects such as dyskinesia, motor fluctuations, and hallucinations. To treat motor disturbances, long-acting levodopa formulations like liquid levodopa or the addition of dopamine agonists or catechol-o-methyl transferase (COMT) inhibitors are commonly used. Olanzapine, clozapine, and ondansetron are the drugs that may reduce levodopa-induced psychiatric complications. Meanwhile, better symptomatic therapies such as neurodegenerative, gene therapies, and cell-based treatment are in clinical trials. A significant majority of patients with long-term PD have no option other than surgery since they cannot treat their symptoms with current pharmaceutical options. The favored surgical techniques are pallidotomy and deep brain stimulation (DBS) of the Globus pallidum pars interna and the subthalamic nucleus. Appropriate patient selection becomes a critical factor in attaining the best surgical outcomes [11,12].

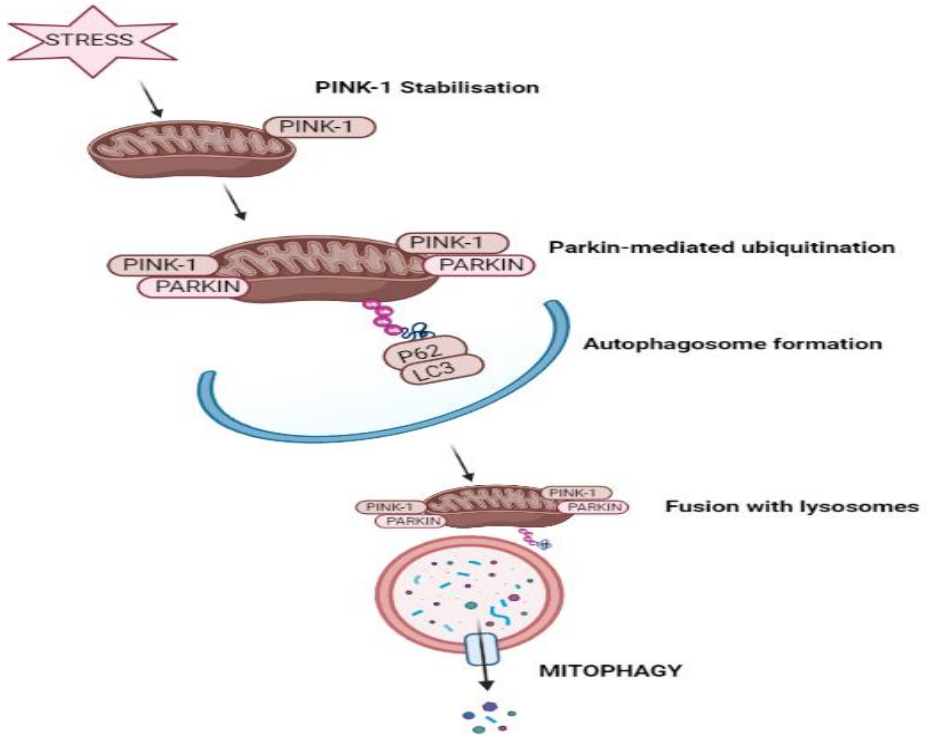
Role of mitochondrial function in Parkinson's disease

Mitochondria are commonly referred to as "Powerhouses of the cell" because of their critical role in the generation of adenosine triphosphate (ATP) through the oxidative phosphorylation process (OXPHOS), which is essential for neuronal signaling and ionic gradient maintenance in neurons. Mitochondria has a more significant role in neuroprotection and neurodegeneration. It is the primary source of superoxide produced through electrons permeability at complexes I and II of the electron transport chain (ETC) due to the failure of mitochondrial complexes. On the other hand, mitochondria are outfitted with superoxide dismutase 1 (SOD1) and 2 (SOD2) to avoid superoxide's potentially damaging effects. Superoxide is reduced to hydrogen peroxide by SOD1 and 2 activity in the mitochondrial matrix, respectively. Excessive Reactive oxygen species (ROS) is an essential point to emphasize some diseases like PD. Excessive mitochondrial ROS/superoxide has been linked to autophagy, hypoxia, and immunology by activating toll-like receptors. The lowest levels of ROS, which do not cause oxidative stress in cells, are considered essential defense mechanisms in Mito hormesis. Adaptive responses are triggered due to this process, which prepares and protects the cells from future shocks [13,14].Mitochondria are essential for cellular function and maintaining mitochondrial quality.

The balance of fission and fusion is one way that mitochondria maintain a healthy network and mitochondria population. Mitochondria is exceptionally crucial in neurons; mitochondrial quality is controlled by GTPase proteins like optic atrophy1 (OPA1), dynamin-related protein 1 (Drp1), and mitochondrial fusion1(Mfn1) and mitochondrial fusion 2(Mfn2) through fission and fusion process. During fission, Drp1 eventually controls the breaking of the mitochondrial outer membrane to produce two daughter organelles. During fusion, the function of OPA1, Mfn1, and Mfn2, both on the outer and inner membranes of mitochondria, coordinately fuse with neighboring mitochondria [15]. Mitophagy is a process in which unhealthy mitochondria cannot undergo the fusion process, thus targeted for mitochondrial degradation. Mitophagy involves the encapsulation of mitochondria

in double-membrane autophagosomes these subsequently bind to lysosomes, destroying their internal contents. Several research studies are looking at mitophagy control for neurodegenerative disorders. However, there are still many unsolved challenges. Phosphatase and TENsin homolog (PTEN)-induced putative kinase 1 (PINK1) and Parkin pathways are commonly known as mitophagy pathways. Autosomal mutations and risk alleles have been linked to hereditary and idiopathic PD; in normal conditions, presenilin's-associated rhomboid-like protein cleaved PINK1 in the mitochondrial membrane and degraded by ubiquitin proteosomes. In mitochondrial failure, PINK1 cannot leave and become stable on the mitochondrial membrane and it undergoes phosphorylation with several proteins like ubiquitin and parkin, leading to the complete activation of parkin for promoting mitophagy [16,17].

Figure 1: An unhealthy mitochondria PINK-1 gets stable on membranes of mitochondria and phosphorylates Parkin protein and recruit to the peripheral membrane of mitochondria and many other membranes protein-like ubiquitin is bounded to adaptors such as P62, LC3-II for the formation of autophagosomes. Later on, unhealthy mitochondria undergo degradation by the action of lysosomes [18].

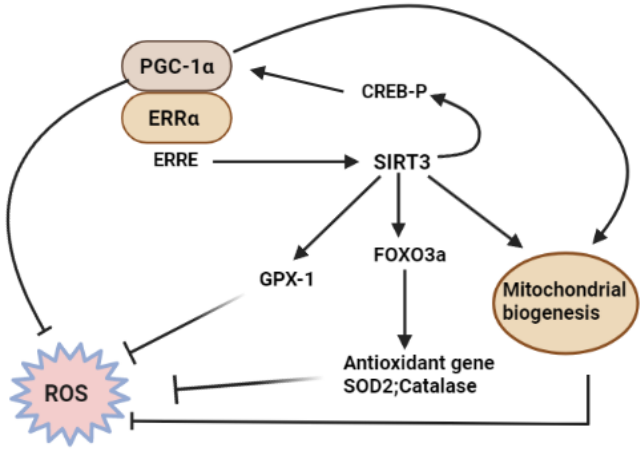


Role of Sirtuins in Mitochondria

Sirtuins are a group of enzymes related to the sirtuin silent information regulator 2 (Sir2) family within mitochondria and about seven sirtuins are found in human mitochondria based on the functions they classified as class 3 histone deacetylase (HDAC). Sirtuins are discovered as deacetylate histone proteins with the help of NAD+, and sirtuins are also expressed in most histone absence prokaryotes. Sirtuins of multiple species gather enzymes in four classes through phylogenetic analysis; in this classification, class1consists of SIRT 1-3, class2 consists of SIRT4, class 3 includes SIRT5, and class 5 consists of SIRT6 and SIRT7. Sirtuins are present at different positions of the mitochondrial cell, such as SIRT1,6&7are said to be nuclear sirtuins, and SIRT3,4&5 are known as mitochondrial sirtuins. According to scientific studies SIRT1, SIRT3 and SIRT5 are responsible for ROS scavengers. SIRT2, SIRT6, and SIRT7 regulate essential cytoprotective genes against oxidative stress. Moreover, SIRT3 is of particular importance in mitochondrial biogenesis in neurological disorders [19,20].

Sirtuin 3

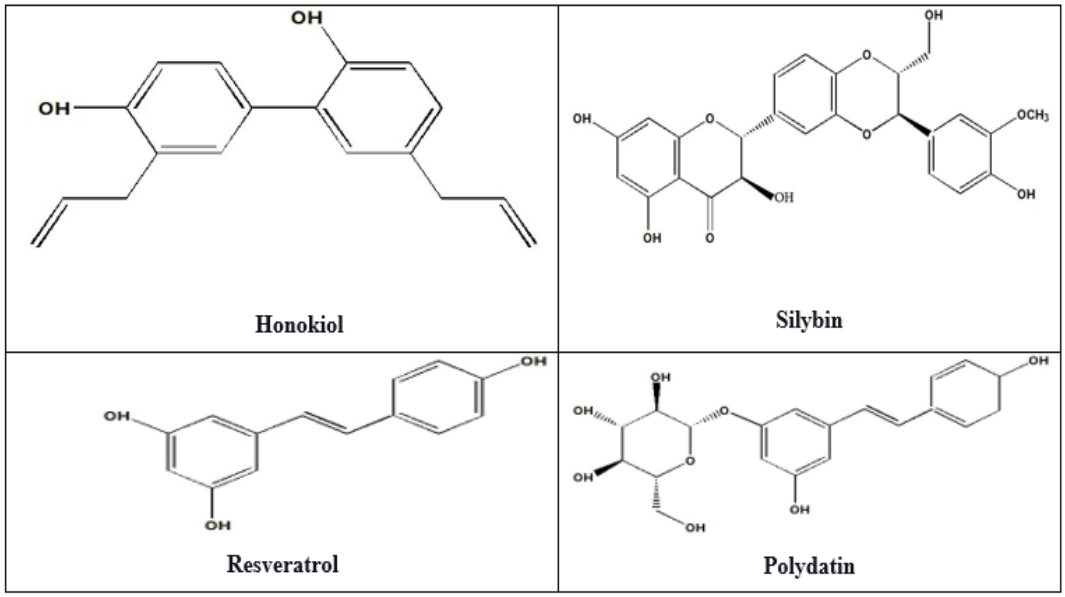
Figure 2: SIRT3 decreases ROS level and improves mitochondrial biogenesis by activating different pathways such as PGC-1α, which co-activates ERRα and controls SIRT3 expansion; it promotes GPX-1, FOXO3a for detoxification of ROS[24].



Sirtuin 3 (SIRT3) is an NAD+-dependent protein deacetylase enzyme that belongs to the Sir2 family. This protein family consists of seven members (SIRT1-SIRT7), each with its own set of enzymatic targets and cellular location. Sirtuins overexpansion

has been seen in caloric restriction and plays a vital role in diabetics, neurodegeneration, cancers, and aging diseases [21,22]. SIRT3 is commonly known as mitochondrial sirtuin for its mitochondrial function, and its activation extends its lifespan. In caloric restriction conditions, SIRT3 is activated and shows the oxidation of fatty acids; regulation of the urea cycle and many other metabolic pathways is observed in mice [23].In recent studies, many SIRT3 substrates have been discovered to increase mitochondrial biogenesis, reduction of ROS, and detoxification.SIRT3 enhances the activity of peroxisome proliferator activator receptor gamma coactivator 1– alpha (PGC-1α), a master regulator of mitochondrial biogenesis, and SIRT3 shows neuroprotection by binding with an estrogen-related receptor [24], and also it undergoes deacetylation to activate OPA1 for mitochondrial dynamism in stress conditions. Activation of SIRT3 has many consequences on mitochondrial metabolism and activates isocitrate dehydrogenase enzyme (IDH2) in a citric acid cycle, and using NADP+ promotes the generation of antioxidants.SIRT3 activates glutamate dehydrogenase (GDH), leading to increasing levels of NADPH which convert oxidized glutathione (GSSG) to reduced glutathione in the presence of glutathione reductase (GSR) enzyme, which acts as a cofactor by glutathione peroxidase (GPX) for detoxification of ROS [25].

Figure 3: Sirtuin 3 Activators



Overexpansion of SIRT3 enhances superoxide dismutase SOD2 and catalase antioxidant proteins by activation of FOXO3a transcription factor for detoxification of ROS.FOXO3a depends on gene expression because of its dependence on NAD+ or nicotinamide riboside, and SIRT3 has a direct link with metabolic activity in the cell. SIRT3-lacking mice show a low level of fatty acid oxidation in the liver; it proves that SIRT3 controls the metabolic process [26].The long-chain acyl-CoA dehydrogenase enzyme (LCAD) is deacetylated and activated by SIRT3, which plays an essential role in fatty acid oxidation in mitochondria. Researchers prove that SIRT3 is released from ATP synthase due to the loss of mitochondrial membrane potential; this expansion of SIRT3 promotes deacetylation of matrix proteins which leads to fatty acid metabolism [27].

Role of Sirtun3 in Parkinson's disease

In PD, mitochondria are affected by various aspects such as mitochondrial dynamics, metabolism, morphology, mitophagy, and biogenesis. Interestingly many proteins essential for maintaining mitochondria physiology were observed altered in PD animal models and patients; they are the primary targets for SIRT3 deacetylase activity, and SIRT3 overexpansion exerts dopaminergic neurons [28]. Many research studies prove that administration of 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine(MPTP), which further converts into MPP+, selectively damages dopaminergic neurons by affecting mitochondrial metabolism and decreases SIRT3, PGC-1α activity in the midbrain of mice and human neuroblastoma cell lines[29]also shows an impact on two main mitochondrial enzymes known as citrate synthase and isocitrate dehydrogenase. According to this report, SIRT3 activation has dopaminergic neurons' protective activity by increasing mitochondrial enzymes [30]. In PD, dopaminergic neurons are destroyed by mitochondrial dysfunction due to the downregulation of PGC-1α levels, which plays a vital role in mitochondrial biogenesis. PGC-1α reduction in mice shows an accumulation of α- synuclein protein leads to Lewy bodies formation, and overexpression of PGC-1α decreases α- synuclein toxicity [31]. The alteration of the fusion and fission process in PD mitochondria has been reported in recent studies that SIRT3 controls mitochondrial dynamism through the deacetylation of enzymes for activation; Meanwhile, SIRT3 deacetylatesOPA1, which is essential for the

mitochondrial fusion and fluctuations of OPA1 levels has been reported in many PD animal models leads to Parkinson and dementia [32].SIRT3 activates Lon protease in the mitochondrial matrix, which has a prominent role in the degradation of misfolded and accumulated proteins. Lon protease has a significant role in regulating PINK-1 in mitochondria; thus, the quality of mitochondria is maintained. On this basis, it has been concluded that SIRT3 activation protects mitochondria in PD [33].

Sirtuin 3 Activators

Honokiol is a compound extracted from leaves, seeds, and barks of magnolia species trees that have pharmacological SIRT3 activation and shows an expression of SOD2 that leads to scavenging of ROS observed in SH-SY5Y cell line and mice model [34]. Silybin is a secondary metabolite extracted from *Silybummarianum* that shows antioxidant and anti-inflammatory activity through SIRT3activation. In cisplatin-induced kidney damage in mice, demonstrated that silybin markedly reduces cellular apoptosis and improves cell regeneration in a SIRT3-dependent manner [35]. Resveratrol is a natural phenol produced by plants in response to bacterial and fungal infections. Recent studies suggest that resveratrol attenuated triptolide (a toxic Chinese herb) induced cardiotoxicity through activating SIRT3 by its antioxidant properties [36]. Polydatin is a major resveratrol derivative that has been proved toSIRT3 activator. Jie Wu et al., 2019 have demonstrated the potent activity of Polydatin against lipopolysaccharide-induced endothelial barrier disruption through SIRT3 activation [37].

CONCLUSION

The summarized data suggested the failure of currently available drugs to rescue degenerative neurons of PD. It has been discussed about the emerging solution to slowdown the neurodegeneration process by mitochondrial function, and activation of SIRT3 shows attenuation of oxidative stress and disease progression. Interestingly many neuronal diseases are common due to the loss of SIRT3 activity, especially *invitro* and *invivo* PD models. Hence this evidence strongly suggests loss of SIRT3 activity is one of the reasons for PD.SIRT3 can regulate mitochondrial quality control with deacetylatingPINK1 and Parkin to promote mitophagy. It might be beneficial to activate SIRT3 for mitochondrial biogenesis, especially in neurodegeneration; SIRT3 activators such as Silybin and Honokiol have been proved to show neuroprotective activity, but more effective and potent activators with anti-PD capability may be further identified to benefit neurodegenerative disorders and improve PD patient's quality of life.

Conflicts of interest

The authors have no conflict of interest.

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