

Endoplasmic Reticulum Dysfunction and Parkinson's Disease

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Abstract. An key organelle that manages protein quality and controls cell homeostasis is the endoplasmic reticulum (ER). When the misfolded proteins is builduped, its stress is brought on, and next comes the unfolded protein response (UPR). Long-term stress can cause cell apoptosis. Protein folding is particularly sensitive to neuronal cells, Now, many evidence-based researches can clarify the points: the stress of the ER stress and the UPR are closely associated with a large number of the illnesses that is neurodegenerative, including the Parkinson's disease (PD) and others. These illnesses are characterized by protein misfolding and accumulation. Numerous people are affected by PD. Parkinson's disease (PD) is caused by many factors, and the stress of the endoplasmic reticulum is actually one of them. The treatment of UPR pathway can alleviate the stress effect of ER to a certain extent, reduce the death of the nerve cells, and thus play a positive role in the treatment of this disease. This article will state the two exception mechanisms in PD and explore the potential therapeutic strategies targeting endoplasmic reticulum stress.

Keywords: Endoplasmic Reticulum Stress, Unfolded Protein Response, Parkinson's Disease.

1. Introduction

The most prevalent neurodegenerative disorder is Parkinson's disease (PD), which is followed by Alzheimer's disease [1]. The main symptoms of PD are tremors, impaired balance, posture, and movement. Some studies on the pathology of PD indicate that PD may be related to mitochondrial dysfunction, may be associated with oxidative stress abnormalities, and may also be closely related to autophagy function impairment. PD usually has two main characteristics: Dopaminergic (DA) neurons, whose role is to control the areas related to movement and muscle in the brain, are being lost selectively; neurons in the aggregation of misfolded alpha-synuclein fibrils (alpha SYN) accumulation within the neurons, called lewy body (LBs) or as Louis neurites of dendrites and axons (LNs).

At present, the pathogenesis of PD is not completely clear, only 5-10% of Parkinson's disease cases are familial, some cases are caused by gene mutations. A protein found in brain samples from the PD patients, this protein is associated with the unfolded protein response (UPR). This result suggests that the development of disease is closely related to the stress of the endoplasmic reticulum.

The main roles of endoplasmic reticulum are lipid synthesis, protein synthesis, calcium storage and control of intracellular calcium balance. The main location for protein synthesis, post-translational modification, folding, and assembly is the ER. The ER is particularly sensitive to alterations in structural integrity, and these changes affect protein folding. If proteins are misfolded, these misfolded proteins are transferred to the cytoplasmic matrix for degradation.

ER stress occurs if too many misfolded proteins accumulate, causing ER overload. The UPR is a mechanism of action in eukaryotic cells, the purpose of this mechanism is to reduce the accumulation of misfolded proteins. On the contrary, if cells want to overcome ER stress, the balance between ER protein load and folding ability will be restored. The physiological activity of misfolded proteins changes, and the neurons are very sensitive to the misfolded proteins, so the abnormal aggregation of these proteins can lead to the different outcomes, such as the synaptic dysfunction or the apoptosis. Protein misfolding and buildup in the brain are the main contributors to the development of many neurodegenerative disorders. This article will review the affect of two exception mechanisms in the pathogenesis and treatment for the PD in order to provide more theoretical basis and evidence for the diagnosis and treatment of PD.

2. Relationship between between ERS and UPR

In the ER of eukaryotic cells, when protein misfolds and accumulates, the ER load increases, leading to ER stress. At this time, By delaying protein production and boosting the action of molecular chaperones, the cells stop the buildup of misfolded proteins. This is what has long been known as the UPR. UPR occurs by activating an intracellular signaling cascade.

Three proteins regulate the UPR: the PKR-like ER kinase (PERK), the inositol-requiring transmembrane kinase/endoribonuclease 1 α (IRE1 α), and the activating transcription factor 6 (ATF6). Normally these proteins bind to BiP and in this condition they are inactive. BiP may dissociates when ER stress happens. PERK induced ATF4 translation by phosphorylating the translation initiation factor eIF2, and ATF4 translation increased and up-regulated apoptosis-related genes, like the proapoptotic substance CHOP or GADD153. ATF4 can also direct the transcription of autophagy genes [2]. A collection of genes involved in the development and operation of autophagosomes are promoted in transcription by the eIF2 α kinase, the GCN2 and PERK, the ATF4 and CHOP. These results suggest a point: the PERK pathway is required for the process of the autophagy.

In ER, unfolded protein accumulation promotes IRE1 α oligomerization and autophosphorylation. IRE1 α can indirectly promote the transcription of UPR related genes by activating ribonucleolactase, which can lead to cell death and apoptosis under chronic stress [3].

UPR helps maintain ER stability, but the UPR changes from a pro-survival response to a pro-apoptotic response through three pathways: CHOP/GADD153, JNK, and caspase12, in the case of if ER stress is too severe or prolonged.

3. ERS and PD

3.1. Interaction between ERS and PD

The human PD brain has been shown to have an activated ER stress response. ER chaperone accumulation was found in Lewy bodies (LB), while in the postmortem PD DA neurons in the substantia nigra, the PERK/p-eIF2 α signaling was discovered that it is increased, confirming that in the vivo, ER stress activation is linked to PD pathology.

Protein misfolding causes changes in physiological function and activity. Neuronal cells are very sensitive to misfolded proteins, which may lead to neuronal apoptosis. Neuronal protein aggregates lose function, causing degenerative diseases to develop. Protein aggregation buildup leads to ER stress, then triggers the UPR. To begin, the adaptive response will alleviate ER stress while maintaining normal neuronal function. If ER stress persists, it initiates a cell death program that results in neuronal loss. ER protein imbalance is caused by a variety of molecular mechanisms, which results in neurodegeneration. In the PD patients, it have been found to contain the UPR markers, and neurons from the PD, also the Alzheimer's disease have been reported to express phosphorylated versions of PERK, BIP, eIF2 α , and IRE1 α . UPR activation defends dopaminergic (DA) neurons from harm in the early stages of PD. The expression of these ER stress markers is suppressed in the later phases, though, by significant DA neuronal loss or excessive stress-induced neuronal injury [4].

The presynaptic and the perinuclear regions of central nervous system contain a soluble protein called α -synuclein (α -SYN), This is essential for the release of neurotransmitters and the movement of synaptic vesicles. There are many reasons for neurodegenerative changes, may be involved in synaptic vesicle trafficking, could be related to intracellular protein transport, it may also be closely related to ERS caused by the changes of the ERAD process [5].

One of the most significant pathogenic elements of sporadic and hereditary PD is aggregated α -SYN. The aggregated neurotoxic form of α -SYN and its overexpression activate all three UPR branches, which causes prolonged apoptosis induced by ERS. The synergistic effect of ER stress induced by the α -SYN accumulation, also, the α -SYN neurotoxicity enhanced by the ER stress is essential for PD pathogenesis. Misfolded α -SYN propagates in cells through the associated neural circuits and damages neurons by causing the synaptic nucleus damage [6]. When attached to

misfolded proteins, α -SYN aggregates engage with BiP and start the UPR response. α -SYN accumulation, on the other hand, inhibiting ER-Golgi transport results in ER stress. α -SYN inhibits the activation of ATF6 induced by ER stress through ER-Golgi transport, it is arbitrate by the coat protein complex II (COPII), leading to its weakened cytoprotective effect and apoptosis.

Parkin, an E3 ubiquitin ligase involved in mitophagy regulation, promotes XBP-1 splicing and activates the UPR prophase survival response to shield cells from ER stress. The E3 ligase activity of Parkin, which is increased by ATF4 in response to ER or the stress of the mitochondrial, prevents the stress that is related to the mitochondrial malfunction and also the death of the cells. The accumulation of Parkin's substrate, the PAEL receptor causes ER stress and the cells' death.

It has been proved that the LRRK2 controls the number of lysosomal autophagy stages, which is involved in neuronal cell stability [7]. When LRRK2 is depleted, GRP78 is downregulated in response to ER stress brought on by 6-hydroxydopamine(6-OHDA). LRRK2 has a kinase role for catalyzing substrates as well as a GTPase function for GTP-GDP hydrolysis LRRK2 phosphorylates leucyl-tRNA synthetase (LRS), and it raises quantity of the improperly folded proteins, leads to ERS and incites cellular autophagy. Other research has found that LRRK2 regulates the ER-mitochondrial lineage via E3 ligase activation mediated by PERK, and that LRRK2 mutation increases sensitivity to ER stress while decreasing mitochondrial biogenesis [8]. Mutations in LRRK2 have been found to inhibit upregulation of BiP/GRP78 levels after the 6-OHDA treatment or expression of the α -SYN is over, increasing both in vivo and in vitro neuronal death. In that respect, the additional safeguards could be needed to protect the cellular environment from harmful consequences of ER stress, and modifications to these pathways may hasten the evolution of PD [9].

DJ-1 has a variety of functions, including antioxidant stress and chaperone properties. Cells can be shielded from oxidative stress damage by the DJ-1 protein, regulating the transcription of antioxidant genes, activating signaling pathways, preventing apoptosis caused by mitochondrial damage, and interacting with certain proteins. Early-onset Parkinson's disease with autosomal recessive variants is associated with DJ-1 mutations or deletions [10]. ERS can lead to upregulation of DJ-1 expression, and under basal and stress conditions. To control the ERS and also the UPR, DJ-1 binds to and stabilizes the mRNA of the ATF4.

However, some studies investigated the feasibility of saliva as a biomarker carrier for the PD diagnose by detecting the levels of α -SYN and DJ-1 in saliva of patients with primary PD(n=27) and the healthy controls (n=27). This result was that the levels of α -syn and DJ-1 in saliva were statistically different between PD and control group, and were not related to the severity of PD. The sensitivity was high, but the specificity was low. These results indicated that the detection of α -syn and DJ-1 in saliva could not be used alone in the screening of clinical PD, but could be used as a clinical auxiliary diagnostic method to identify PD [11].

3.2. Relationship between PD Neurotoxins with ERS and UPR

The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)/1-methyl-4-phenylpyridinium (MPP), the 6-OHDA, and also the rotenone are very common inducers for the Parkinson's disease that affect the ERS and the UPR. Common parkinsonism inducers include the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) / 1-methyl-4-phenylpyridine (MPP), the 6-OHDA, and the rotenone, which contribute to the progress of the PD by affecting the ER stress and the UPR.

MPP kills DA neurons by decreasing mitochondrial activity and elevating mitochondrial superoxide when it enters them through the dopamine transporter (DAT). In numerous cell models, MPP boosted the expression of the UPR genes, for example the ATF4 and the CHOP, these genes are critical for the IRE1 α and the PERK activation.

The 6-OHDA-induced PD mouse model is also a classic model in the field of PD research, which can simulate many pathological features and motor defects similar to PD. Through the formation of the mitochondrial and the cytosolic reactive oxygen species (ROS), the selective catecholaminergic neurotoxin 6-OHDA causes PD by killing DA neurons. In DA cells treated with 6-OHDA, it was discovered that GRP78 and CHOP expression levels were greater along with phosphorylated PERK

and eIF2. Rotenone increases the expression of ATF4 and CHOP, which in cell models have a role in activating IRE1 α and PERK.

IRE1 α of the UPR is activated in a rotenone mouse model of PD, the PERK branch is also activated. Different branches are more or less affected by the ER stress and the UPR caused by rotenone therapy [12]. Endoplasmic reticulum stress and UPR induced by rotenone promote autophagy, but inhibit autophagy through the decreasing lysosomal function, aggravating the dysregulation of cell homeostasis, and damaging DA neurons.

4. Treatment strategies

Because UPR activation may cause the pro-apoptotic processes, patients with PD can be treated with disrupting the buffering capacity of protein balance network. Because it lowers the expression of vital elements of the nervous system's synaptic mechanism, protein translation inhibition can be detrimental. Sustained eIF2 α phosphorylation has been shown to disrupt synapse protein synthesis in neurodegeneration models [13].

Parkinson's disease treatment may benefit from the gene therapy to lower the levels of the ER stress [14].

The chronic PERK activation has also been observed in the PD brain. The PERK inhibitor GSK2606414 targeting the PERK/eIF2 α pathway leads to a protective effect on the nervous system, increasing synaptic protein expression and reducing the DA neuronal loss [15]. Overexpression of the transcription factor XBP1 in substantia nigra (SNpc) can also have a protective effect on nerves. Helping proteins fold correctly is also an effective strategy aimed at restoring the cell's ability to fold. Targeting small molecule ER protein homeostasis is mainly through the PERK/ P-eIF2 α pathway targeting the transformation and decay process. GSK2606414, a PERK inhibitor, protects DA neurons and restores motor function in the mouse neurotoxin PD model by increasing DA and synaptic protein levels [16].

Inhibition of translational attenuation by GSK2606414 and the Integrated Stress Response inhibitor (ISRIB) can also protect the neurons in prion mice. In prion disease mice, the translational attenuator ISRIB was typically well tolerated and had no adverse consequences [17]. According to the study, ISRIB and the other PERK/ p-eIF2 α modulators that with non-toxic might be considered as the potential applications. Sarbutyral is a low-dose drug, it blocks p-eIF2 α through the growth arrest and the DNA damage inducing protein (GADD34) dephosphorylation, increased p-eIF2 α levels in a mouse model of mutant syn-over expression of PD, restored motor function, and reversed the phenotype.

Targeting ER proteins by IRE1 α to balance the alpha branch aims to regulate sXBP1 activation or to reduce ER loading of misfolded proteins by RIDD. In a PD animal model with neurotoxins, sXBP1 overexpression was found to be neuroprotective. Additionally, sXBP1 can enhance the expression of the brain-derived neurotrophic factor (BDNF), synaptic plasticity, and cognition in vivo [18]. Not only the in vitro studies, but also the in vivo the midbrain astrocyt-derived neurotrophic factor (MANF) and CDNF shows the protective effects, which is a parathyrogenic form of the CDNF. These neurotrophins are found in the ER lumen and have been shown to DA neurons and other cell types' ER stress should be reduced [19]. According to research, MANF interacts directly with IRE1 α , has a low affinity for competing with BiP for IRE1 α interaction, along with PERK and ATF6. The interaction between Manf and Ire1 is required for MANF survival activity in DA neurons [18]. Because ATF6 has been shown to participate in neuroprotection in the PD neurotoxin mouse model, cesapins shows significant potential for the treatment of PD, together with the recently identified ATF6 specific activators, compounds 147 and 263, and ATF6 selective inhibitor [20].

MANF has been shown in some studies to improve motor behavior and increase the number of the DA neurons in the substantia nigra (SN) in a neurotoxic rat model of the PD. On a contrary, MANF mutants, however, can not shield neuronal activity. Recent data have shown that binding of MANF to cell-surface neuropilin reduces inflammation and apoptosis by inhibiting NF- κ B signaling [21].

MANF and CDNF, unlike many GFs with primarily neuroprotective properties, also have neurorepair effects in DA neurons. Importantly, MANF and CDNF lowered ER stress and inflammation in addition to their effects on neurorepair. In addition, CDNF reduced α -SYN aggregation in neurons. CDNF directly interacts with α syn, reduces the phosphorylation of Ser129 α -SYN and alleviates motor dysfunction stimulated by α -SYN fibrils.

At the same time, an increasing number of professionals and academics are dedicated to the study of traditional Chinese medicine's ability to treat Parkinson's disease. Curcumin is a natural polyphenol component in turmeric and a neuroprotective agent. Curcumin has an antioxidant effect, which can accelerate the clearance of ROS to inhibit cell apoptosis, thereby promoting cell survival. And reduce inflammation by regulating autophagy and inhibiting neuroinflammation α -SYN aggregation. At the same time, curcumin has low toxicity and high safety. It has broad application prospects in the clinical treatment and prevention of PD [22].

5. Discussion

Due to it controls the homeostasis of the protein, the ER is a very crucial material in the pathophysiology of the neurodegenerative disorders. The pathogenesis of the PD is heavily influenced by ER stress. Some proteins misfolded and accumulate can activate the UPR response, resulting in neuronal and synaptic dysfunction, apoptosis, or autophagy, particularly in the context of DA neuronal death and α -SYN toxicity. The abnormal expression of some genes is also the cause of PD.

Therefore, the ERS should be intervened in a timely manner to make it appropriate without excessive stimulation, which not only helps the folding of terminal and staggered proteins correctly, but also does not cause autophagy or apoptosis due to excessive stress; It can provide many new ideas and prospects for the prevention and also the treatment for the PD. From this point of view, genetic or pharmacologic approaches that target the UPR pathway to restore ER function may treat or prevent the occurrence of neurodegenerative diseases such as PD.

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