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Journal of Pharmaceutical and Biological Sciences

Journal homepage: https://www.jpbs.in/

Review Article

Navigating the cellular pathways: Chaperone-mediated autophagy as a targeted approach for management of parkinson's disease

Pratiksha S Kawade[1], Shatrughna U Nagrik[2], Ganesh J Lamkhade[3], Ajay A Bhagwat[4], Rohit R Doke[1,*]

[1]*Dept. of Pharmacy, Jaihind College of Pharmacy, Narayangaon, Maharashtra, India*
[2]*Dept. of Pharmacy, Satyajeet College of Pharmacy, Mehkar, Maharashtra, India*
[3]*Dept. of Pharmacy, Samarth Institute of Pharmacy, Pune, Maharashtra, India*
[4]*Dept. of Pharmacy, Samarth College of Pharmacy, Belhe, Maharashtra, India*

ARTICLE INFO

Article history:
Received 10-05-2023
Accepted 25-06-2023
Available online 19-07-2023

Keywords:
Autophagy
Chaperone
synuclein
LAMP2A
Chaperonemediated autophagy α

ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative condition marked by the degeneration of dopaminergic neurons and the amassing of α-synuclein protein in Lewy bodies. Chaperone-mediated autophagy (CMA), a selective form of autophagy, has been implicated in the development of PD. Mutant GBA1, α-synuclein, UCHL1, VPS35, and LRRK2 are affected proteins in PD that impair the CMA process. CMA Dysfunction cause accumulation of PD-associated proteins such as α-synuclein and many other, including DJ-1, MEF2D, PARK7,etc resulting in mitochondrial dysfunctioning and apoptosis. The impact of gene mutations associated with PD on CMA has been observed, along with dysregulation of miRNAs targeting CMA components. Toxicant-induced PD models demonstrate that impaired CMA increases α-synuclein aggregates and neurotoxicity. Understanding the molecular mechanisms of CMA has identified potential therapeutic targets, including increasing LAMP2A levels. Several compounds and substances have shown promise in enhancing CMA and reducing α- synuclein aggregates, such as 6-aminonicotinamide, geldanamycin, metformin, and natural compounds like trehalose and caffeine. Pharmacological modulation of CMA, such as through retinoic acid derivatives, has demonstrated positive effects on reducing protein aggregates in neurodegenerative diseases. However, the specific effects of inhibiting CMA on macroautophagy remain uncertain. Overcoming challenges in studying CMA, such as developing suitable models and monitoring methods, is crucial for advancing our understanding of CMA's role in neurodegenerative diseases and developing effective therapeutic strategies. Overall, CMA emerges as a key player in the pathogenesis of PD, and targeting this selective autophagy pathway holds promise for developing novel therapies to combat neurodegenerative disorders.

1. Introduction

Parkinson's disease (PD) is the second most prevalent degenerative disorder impacting the nervous system. Based on estimates, it is projected that around 12 million individuals could have PD by 2040 worldwide[1] The substantia nigra pars compcata (SNpc) is the primarily region that affects, where dopamine-producing cells are located. Dopamine is an essential neurotransmitter that plays a critical role in the coordination and regulation of motor movement. The dopamine-producing cells in the SNpc significantly degenerate leading drastically reduction in dopamine level which further hampers the brain's communication and impairs the coordination of movements.[2]

* *Corresponding author*.
E-mail address: rohitdoke2853@gmail.com (R. R. Doke).

https://doi.org/10.18231/j.jpbs.2023.005

The precise underlying cause of Parkinson's disease remains incompletely comprehended at present. Although both genetic and environmental factors are believed to contribute. While most cases of Parkinson's disease occur sporadically with no known cause, a small percentage of cases are linked to specific genetic mutations. The clinical manifestations of PD encompass bradykinesia, rigidity, tremors and postural instability along with non-motor symptoms like depression, autonomic dysfunctions, sensory impairments, and disturbances in sleep.[3,4] These symptoms typically develop gradually and worsen over time. The diagnosis of PD relies on a combination of medical history, physical examination, and careful observation of symptoms. There are no definitive tests to confirm the presence of PD, so the diagnosis is primarily clinical. Nevertheless, neuroimaging methods can be employed to exclude alternative conditions that may mimic the symptoms of PD.

Although there is no cure for PD, there are various treatment options available to manage its symptoms. The mostly all common and effective treatment is medication aimed at raising dopamine activity in the SNpc. L-Dopa, a dopamine precursor, is the most commonly prescribed medication. Other medications, such as MAO-B inhibitors and dopamine agonists, are also used to slow down symptoms.[5] In advanced cases where medications become less effective, surgical interventions like deep brain stimulation (DBS) may be considered. DBS involves implanting electrodes into specific regions of the brain to help regulate brain abnormality and alleviate symptoms. Additionally, music-dance therapy, physical therapy, speech therapy and occupational therapy can be useful to cut down the symptoms and improving the quality of life for people with PD.[6]

While PD is a chronic and progressive condition, the rate of progression varies among individuals. The Current research endeavors seek to enhance comprehension of the fundamental mechanisms of the disease and foster the development of more efficacious treatments, and ultimately find a cure. The underlying neuropathological changes in PD involve the progressive loss of dopamine neurotransmitters in the SNpc and leads to form Lewy bodies, which primarily consist of clumps of α-synuclein protein fibrils within neuronal cell bodies.[7] The many previous investigations having evidence suggesting that the autophagy is major contributing player in the progression of PD. In 2004, the discovery that mutant α-synuclein hinders CMA provided the initial link between malfunctioning CMA and PD.[7]

2. CMA and Genetic Mutation in PD

The interaction between various genes interrelated to both PD and the CMA pathway has been observed. In the process of CMA, heat shock cognate 71 kDa protein (HSC70) chaperones identify proteins that are defective or impaired and possess KFERQ-like sequences. Subsequently, these chaperones facilitate the transfer of these proteins to lysosomes by communicating with lysosome-associated membrane protein type 2A (LAMP2A). (Figure 1).[8] The presence of the KFERQ motif in α-synuclein indicates its classification as a CMA substrate and enables its degradation through CMA. However, mutant α-synuclein with a more affinity for LAMP2A exhibits reduced efficiency in degradation by CMA.[9] Mutations such as AS30P and AS53T in α-synuclein hinder it's binding to LAMP2A, thereby interrupting the degradation efficiency of CMA for not only α-synuclein but also other CMA substrates.[10] Additionally, mutations in GBA1 and UCHL1 genes, which are associated with PD, also inhibit CMA activity by blocking LAMP2A.[11] GBA1 mutation, responsible for encoding β-glucocerebrosidase, a genetic risk factor for PD, results in mutant β-glucocerebrosidase binding to HSC70 and disrupting the lysosomal internalization through LAMP2A, consequently preventing CMA degradation of its substrates.[12] Moreover, decreased β-glucocerebrosidase affects all types of autophagy by inhibiting autophagy lysosomal reformation. Mutant UCHL1, linked to familial PD, interacts with LAMP2A and HSC70 during CMA. The I93M mutant UCHL1 enhances its interaction with LAMP2A. Similar to mutant α-synuclein and mutant GBA1, I93M UCHL1 inhibits CMA and leads to the accumulation of wild-type α-synuclein.[13] LRRK2, another PD-related protein found in Lewy bodies, impairs the formation of the translocation complex during CMA. While wild-type LRRK2 can undergo degradation through CMA in lysosomes, the G2019S mutant LRRK2 blocks CMA and leads to neuronal damage. G2019S LRRK2 inhibits the multimerization of LAMP2A on the lysosomal membrane, thereby blocking CMA and resulting in the accumulation of various CMA substrates, including α-synuclein[1516]. Mutant VPS35, identified in PD patients, affects the translocation pathway of LAMP2A from endosomes to the Golgi. Defects in LAMP2A caused by VPS35 mutations downregulate CMA and increase α-synuclein accumulation.[14] In summary, mutant α-synuclein, GBA1, UCHL1, LRRK2, and VPS35 have been identified as pathogenic proteins in PD that impair the CMA process. The activity of CMA appears to influence other PD-related proteins like PARK7/DJ-1 and MEF2D. PARK7, a familial PD protein involved in antioxidant defense and mitochondrial homeostasis, is regulated directly by CMA. Dysfunctional CMA leads to the accumulation of oxidatively damaged and dysfunctional PARK7, resulting in mitochondrial defects and impaired cell survival. MEF2D expression is linked with dopaminergic neuronal death in PD, with increased MEF2D levels found in α-synuclein transgenic mice and PD patients' brains. Notably, CMA helps maintain MEF2D

homeostasis, but impaired CMA contributes to MEF2D.[15]

Apart from the impact of gene mutations related to Parkinson's disease (PD) on chaperone-mediated autophagy (CMA), findings from PD models also underscore the significance of CMA in PD. Examination of post-mortem brains from PD patient's revealed reduced levels of HSC70 and LAMP2A in the SNpc and amygdala. In female PD patients with the LRRK2 mutation, compromised CMA, indicated by reduced LAMP2 levels, was observed.[16,17] Dysregulation of miRNAs, small RNA molecules, has been implicated in PD pathogenesis. 8 miRNAs were highly predicted to target the 3'UTR of LAMP2A or HSC70 and were noticeably more prevalent in PD brains, revealing a possible function for miRNAs associated with the suppression of CMA in PD.[18] Among these miRNAs, miR-320a selectively targets the 3'UTR of HSC70, reducing HSC70 protein and mRNA production in cells overexpressing α-synuclein, thereby promoting α-synuclein aggregation in PD. Neurotoxins and chemicals like 6-OHDA,MPTP, paraquat and rotenone, are commonly experimented to manipulate CMA components and substances, shedding light on the link among PD and CMA.[19] The exposure to natural toxicants dowunregulate CMA functioning and up regulate the levels of α-synuclein clusters by influencing LAMP2A and HSC70. The misfolded α-synuclein results in neuronal damage in Parkinsons models. These research findings on Neurotoxins -induced neurodegenartion offer evidence supporting the involvement of CMA in the progression of the disease.[20]

3. Therapeutic Targets for PD

Growing evidence suggests that chaperone-mediated autophagy responsible for PD progression, affecting neuron protection, protein regulation, and mitochondrial function. Understanding the molecular mechanisms behind CMA has led to the identification of potential therapeutic targets. One promising target is increasing the levels of LAMP2A, which has shown potential for PD treatment in both lab experiments and living organisms. Regulating CMA by manipulating the levels of HSC70 and LAMP2A through pharmacological means offers a potential therapeutic approach for PD. Early studies revealed that compounds like 6-aminonicotinamide and geldanamycin (GA) enhanced CMA through specialized screenings6-aminonicotinamide blocks the function of the enzyme glucose-6-phosphate dehydrogenase, causing oxidised cytoplasmic proteins to accumulate and increased CMA activity.[21] GA, an inhibitor of HSP90, enhances CMA by regulating the activity of LAMP2A and HSC70.[22] Additionally, other substances such as bortezomib, metformin, manganese, and natural bioactive such as silymarin, caffeine, trehalose, β-asarone, salvianolic acid B, dihydromyricetin, and mycophenolic acid are well known as CMA boosters. These substances have shown pharmacological effects By diminishing the buildup of α-synuclein clusters and enhancing motor functions.[18] However, it is important to note that these substances do not specifically target CMA and may have broader effects.

The impact of inhibiting CMA on the upregulation of macroautophagy remains uncertain, with conflicting evidence regarding its advantages and disadvantages. The signalling of retinoic acid receptor alpha has been found to influence the transcription of LAMP2A and stimulate CMA. All-trans retinoic acid, an activator of retinoic acid, specifically activates CMA without affecting macroautophagy.[23] Treatment with retinoic acid derivatives primarily activates CMA by increasing the levels of LAMP2A and Rab1, although the precise mechanism is not fully understood. Studies have demonstrated that treatment with retinoic acid derivatives reduces Tau aggregates and amyloid plaques, which are characteristic features of Alzheimer's disease.[24] Moreover, boosting CMA through retinoic acid derivatives has been shown to decrease α-synuclein aggregates in astrocytes from PD models and restore neuronal survival.

4. Conclusion

In recent decades, there has been an increasing amount of research dedicated to studying chaperone-mediated autophagy. This specific form of autophagy, which selectively targets proteins, has been linked to the maintenance of organ function and the development of various conditions, particularly aging and cancer. The recognition of α-synuclein as a substrate for CMA has provided a fundamental understanding of CMA's involvement in PD and rest of neurological conditions. Despite progress, the study of CMA in the central nervous system is still relatively new, and significant challenges remain. These challenges include the lack of suitable models and methods to monitor CMA in living organisms, the absence of animal models with CMA deficiencies, and the unclear mechanisms of CMA modulators. For the development of efficient treatment approaches, it is necessary to improve our understanding of the processes that control CMA, find pharmacological compounds that particularly promote CMA, and establish animal models to study the function of CMA in neurodegenerative conditions. Additionally, the review highlights the importance of further investigations to uncover the intricate interplay between CMA and other autophagic pathways, as well as the identification of novel pharmacological agents that can modulate CMA specifically. Overall, harnessing the potential of CMA as a targeted approach for PD management holds great promise and paves the way for the development of novel disease-modifying therapies in the future.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Author biography

Pratiksha S Kawade, Lecturer

Shatrughna U Nagrik, Assistant Professor

Ganesh J Lamkhade, Assistant Professor

Ajay A Bhagwat, Assistant Professor

Rohit R Doke, Assistant Professor

Cite this article: Kawade PS, Nagrik SU, Lamkhade GJ, Bhagwat AA, Doke RR. Navigating the cellular pathways: Chaperone-mediated autophagy as a targeted approach for management of parkinson's disease. *J Pharm Biol Sci* 2023;11(1):26-29.