

Druggable targets for Parkinson's disease: An overview

Mridul Biswas and Mukta Gupta*

School of Pharmaceutical Sciences, Lovely Professional University, Punjab, India

*Corresponding author: mukta.16541@lpu.co.in gupta2k@yahoo.com

Abstract. One of the most crippling conditions affecting the brain and its progression causes neurodegeneration is Parkinson's disease (PD). The disease is characterized by accumulation of α -synuclein having Lewy bodies and further loss of dopaminergic neuron in substantia nigra, ultimately causing reduced ability of voluntary movements. The main symptoms of PD include tremor, bradykinesia and rigidity. Though, various symptomatic treatment options are available targeting both motor and non-motor signs but none of them claim to improve quality of life of PD patients. Recent studies indicated the identification of targets for PD such as glutamate receptors, α -Syn, c-Abl, molecular chaperones, GPR109A and metals have been and some drugs targeting these targets are already there in market. The effectiveness of these pharmacological targets in treating PD has to be confirmed by a larger-scale trial. Effective PD therapy may also target pathways mediated by autophagy. Gene therapy and gene editing all have strong therapeutic effects and provide fresh PD medication targets. Additionally, the therapy of PD is more effective when a multi-target response is used. Further, research should be conducted to validate and explore new targets for treatment of PD.

Keywords: Gene therapy; Levodopa; Molecular chaperones; Parkinson's disease; Symptomatic treatments

1 Introduction

Parkinson's disease (PD) is a neurodegenerative disease that belongs to synucleinopathy (a class of neurodegenerative conditions marked by an aberrant buildup of soluble α -synuclein in glial and neuronal cells), which gradually develops, and there's not any good a technique for early detection and treatment. PD is a brain disorder that causes uncontrollable movements or unintended, such as stiffness, shaking and difficulty with balance and coordination. Over time, this disease becomes worsen and more worsen. Many people have difficulties in walking as well as talking as this disease progresses. Mental behavior changes, depression, sleep problems, fatigue and memory difficulties are some common problems in PD. Mostly PD can occur at elderly age and some of the researches also show that elderly men have been more in PD than elderly women. PD can be inherited or can be from genetic mutations. Parkinson's symptoms and indicators can include tremor, bradykinesia, tight muscles, poor posture and balance, loss of automatic motions, changes in speech and

writing, and tremor. Druggable targets have been used to assess the potential for pharmacological activity on a novel, predicted protein from the genome. GPCR families, protein kinases, and several enzymes are notable instances of this. [1-2].

2 Prevalence

There are 1-2 cases of PD for every 1000 people, however; PD prevalence rises with age and affects 1% of those over the age of 60. More people worldwide are becoming disabled and dying from Parkinson's disease (PD) than from any other neurological condition. In the last 25 years, PD prevalence has doubled. According to 2019 estimates, there were approximately 8.5 million people worldwide who had PD. According to estimates, PD caused 329 000 deaths in 2019, a rise of over 100% since 2000, and 5.8 million disability-adjusted life years, an increase of 81% since 2000. The rise in Estimates of PD prevalence highlight the growing personal and societal burden and the urgent need for actions to tackle and have an influence on this difficult disease[3].

3 Symptoms

Lewy bodies containing α -Syn and dopaminergic neuron loss in the substantia nigra, which manifests as lessened facilitation of voluntary movements, are the primary neuropathological findings. As PD worsens, Lewy body disease spreads to the cortex and neocortex. The three primary signs of Parkinson's disease are tremor, rigidity, and bradykinesia. Postural instability is no longer included as a fourth characteristic in the diagnostic criteria, which also describe supporting criteria, absolute exclusion criteria, and red flags [4].

In PD, non-motor symptoms are receiving more attention, and both motor and non-motor symptoms are now considered supportive criteria. In most situations, the cause of PD is unknown. There are known genetic risk factors, such as uncommon monogenetic causes in populations without selection. In 5–10% of patients, a genetic component can be detected. There are several environmental factors linked to an increased risk of PD. According to studies on corpses, a significant number of people do not have their Parkinson's disease clinical diagnosis verified during autopsies. The accuracy of the clinician's diagnosis of PD is anticipated to increase with the revised diagnostic criteria. In the near future, it's likely that growing awareness of the genetic and environmental PD risk factors may reveal the disease's underlying cause[4].

4 Drug Targets for PD

4.1 Glutamate Receptors

Glutamate receptors have ability of controlled neural transmission in basal ganglia in our brain. The targets of PD treatment can be also studied/identified with this ability of Glutamate receptors. By postponing the neurodegenerative processes, compounds that act against these receptors can slow the progression of PD. Neuroprotection is a function of amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. Additionally, levodopa-induced dyskinesias (Uncontrolled, involuntary movements of the face, arms or legs) can be effectively treated with its antagonist Perampanel. (mGluRs) Metabotropic glutamate receptors pharmacological modulation can regulate neurotransmission can help in delay PD. Some drugs that target glutamate receptors like antagonists of mGluR5, Motor dysfunctions can be treated, and activators of group II mGluRs and group II mGluR4 can prevent neurodegeneration that can help in delay progression of PD [5-6].

4.2 Alpha-synuclein(α -Syn)

The α -Syn protein is usually insoluble in blood, and in PD it gets accumulated and enhances the PD progression. The SNCA gene also encodes the -Syn protein. Further, it has been observed that the accumulation ultimately causes the LBD (disease associated with abnormal deposits of a protein). The α -Syn protein despite having the appropriate mechanism, experiences point mutations, triplications, and duplications of α -Syn protein in PD is still unknown. Oligomerization (a chemical procedure that, through a limited amount of polymerization, transforms monomers into macromolecular complexes) of α -Syn form toxic add on which multiplies from one to another cell. Multiple α -Syn oligomers cause damage to specific areas of the brain in PD [7- 9].

The development of α -Syn protein's harmful effects can be prevented in four ways that have been identified and documented so far i.e.; reducing α -Syn aggregation, boosting its clearance, limiting its multiplication, and stabilizing its current situation. The aggregation of α -Syn protein has been recorded to extend to the cell types and cell populations in brain. And two key mechanisms—autophagy and the (UPS) ubiquitin-proteasome system—have been implicated in reaching different types and populations of brain cells. UPS also degrades the proteins so thus it can also degrade α -Syn protein and can enhance the PD pathogenesis. Using both inherent and learned immunity, By reducing inflammation brought on by α -Syn protein and proteotoxic processes, the clearance of pathogenic aggregates can be increased [10-14].

Some methods (related to α -Syn protein) to induce progress slowly of PD are by immunotherapy aggregation of the α -Syn can be suppressed, Motor impairments can be restored by preventing the creation of the α -Syn axonal, Antibodies that prevent C terminal truncation can reduce α -Syn protein cell-to-cell proliferation, Oxidation and nitration are further processes that can be used to degrade the aggregation of α -Syn protein of α -Syn protein and these oxidation and nitration of α -Syn protein can also block oligomerization. Some of these methods are still in validation process but apart from that all the above methods have already showed lesser aggregation of α -Syn protein in PD patients[15].

43 GeneTherapy

Disease-modifying and non-disease-modifying transgene levels in gene therapy has revealed convincing results for PD treatment in both animals and people. Some of the factors that halts the progression of PD at preclinical level are cerebral dopamine neurotrophic factor, Growth derived neurotrophic factor, brain- derived neurotrophic factor, and nurturing. Mutations in mitochondrial genes are also to blame for the development of Parkinson's disease. A potential gene treatment for Parkinson's disease (PD) involves targeting certain mitochondrial genes, such as Parkin and Pink1, which result in decreased activity of the electron transport system, abnormal mitochondrial dynamics, impaired mitochondrial permeability, and altered membrane potential. Clinical studies have also demonstrated an association between α -Syn buildup and decreased miR-7 levels. The gene therapy that substitutes for miR-7 activity also slows the onset of PD [16-19].

44 Gene Editing

The clustered regularly interspaced short palindromic repeats (CRISPR) technology is particularly useful for discovering fresh PD research pathways and gene-gene interactions. In addition to greatly reducing oxidative stress and neuroinflammatory load, the CRISPR-Cas9 gene editing method also significantly reduced the progression of Parkinson's disease (PD). A valuable method for identifying and tracking dopaminergic neuronal defects is CRISPR/Cas9-mediated gene editing. It may also be useful for creating knockout cell lines that may be used to more thoroughly study illness. Therefore, Gene editing might also carry potential treatment for the PD [20-23].

45 Metals

Researchers discovered connections between metals and PD.[24-26] On the one hand, because they can result in neuronal death through oxidative stress, metals, particularly heavy metals, are typically viewed as neurotoxins.[27] For instance, both copper and iron can lead to oxidative stress and harm neurocytes, Both the both the periphery and the central nervous systems experience substantial swelling and neuronal death as a result of lead exposure, PD patients have considerably more aluminum than controls in their substantia nigra, Cerium has been shown to have a detrimental impact on DNA methylation, i.e., cerium is likely to cause PD.[28] Cerium oxide nanoparticles (CeO₂ NPs), a different cerium chemical, have shown promising results and may be able to treat several neurological illnesses, including Parkinson's disease.[29] People are reasonably knowledgeable on the pathophysiology of various metals.[30] On the other hand, current research has revealed that metals can control epigenetics in Parkinson's disease. Finding a cure for PD maybe aided by understanding the functions that metals play in the epigenetics of the disease[31].

Table 1 Some heavy metals and their role in PD with their respective targets [2]

Metals	Targets	Action
--------	---------	--------

4 Conclusions

Recently, several pharmacological targets that can be used to treat PD have been discovered. Some examples of new therapeutic targets in PD include c-Abl, GPR109A, glutamate receptors,

molecular chaperones, and α -Syn. A larger-scale trial is required to confirm whether these pharmaceutical targets are useful in treating PD. Effective PD therapy may also target pathways mediated by autophagy. Gene therapy and gene editing all have strong therapeutic effects and provide fresh PD medication targets. Additionally, the therapy of PD is more effective when a multi-target response is used. Further, research should be conducted to validate and explore new targets for treatment of PD.

Iron	Ceruloplasmin and Glutamate receptors	Iron encourages oxidative damage and the development of a-synuclein intracellular clumps.
Mercury	Mitochondria	loss of dopamine receptors, degradation of tubulin, axons, and glutathione, as well as a rise in amyloid levels that favour a-synuclein aggregation
Zinc	Autophagy-lysosomal pathway	When PARK9 is lost, intracellular zinc levels become dyshomeostatic, which in turn causes lysosomal dysfunction and the build up of alpha-synuclein.
Manganese	Basal ganglia	Dopaminergic, glutamatergic, and GABAergic transmission impairment, along with mitochondrial dysfunction, oxidative stress, and prominent neuroinflammation are all present in this condition.
Lead	Nervous system	Calcium homeostasis interruption, oxidative stress and mitochondria dysfunctioning.
Aluminium	Monoamine oxidase B	Calcineurin B activates the unfolded protein response to protect the brain following injury. the neuroscience of disease
Copper	Brain, Mitochondria and Cytochrome	DNA damage, increased ROS production, and mitochondrial malfunction

5 References

- [1] Giasson BIGalvin JELe, and VM-YTrojanowski JQ.“The cellular and molecular pathology of Parkinson's disease.” In: Clark CM, Trojanowski JQ, eds. Neurodegenerative Dementias: Clinical Features and Pathological Mechanisms. New York, NY, McGraw- Hill Co, 2000, 219-228.
- [2] Clayton DFGeorge JM.“Synucleins in synaptic plasticity and neurodegenerative disorders.” Journal of Neuroscience Research 58 (1999): 120-129.
- [3] <https://www.who.int/news-room/fact-sheets/detail/parkinson-disease>
- [4] <https://pubmed.ncbi.nlm.nih.gov/28150045/#:~:text=Epidemiology%20of%20Parkinson%27s%20disease.%20The%20main%20neuropathological%20finding,body%20pathology%20spreads%20to%20neocortical%20and%20cortical%20regions>
- [5] Johnson KA, Conn PJ, and Niswender CM. “Glutamate receptors as therapeutic targets for Parkinson’s disease.” CNS Neurological Disorder Drug Targets 8(2009) :475–491.
- [6] Freudenberg F, Celikel T, and Reif A. “The role of α -amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) receptors in depression: central mediators of pathophysiology and antidepressant activity.” Neuroscience Biobehavariial Review 52(2015):193–206.
- [7] Stefanis L. “ α -Synuclein in Parkinson’s disease.”Cold Spring Harbal Perspective Medicine 2(2012) :a009399.
- [8] Konno T, Ross OA, Puschmann A, Dickson DW, and Wszolek ZK. “Autosomal dominant Parkinson’s disease caused by SNCA duplications.” Parkinsonism Relative Disorder 22(2016) :S1–S6.

- [9] Xu L, and Pu J. “Alpha-synuclein in Parkinson’s disease: from pathogenetic dysfunction to potential clinical application.” *Parkinsonism Disease* 2016 (2016):1720621.
- [10] Lashuel HA, Overk CR, Oueslati A, and Masliah E. “The many faces of α -synuclein: from structure and toxicity to therapeutic target.” *Nat Review Neuroscience* 14 (2013) :38–48.
- [11] Zhang G, Xia Y, Wan F, Ma K, Guo X, Kou L, Yin S, Han C, Liu L, Huang J, Xiong N, and Wang T. “New perspectives on roles of alpha-synuclein in Parkinson’s disease.” *Frontier Aging Neuroscience* 10 (2018):370.
- [12] Dennissen FJ, Kholod N, and van Leeuwen FW. “The ubiquitin proteasome system in neurodegenerative diseases: culprit, accomplice or victim.” *Progressive Neurobiology* 96 (2012):190–207.
- [13] Ciechanover A, and Kwon YT. “Degradation of misfolded proteins in neurodegenerative diseases: therapeutic targets and strategies.” *Experimeta Molecular Medicine* 47 (2015):e147.
- [14] Allen Reish HE, and Standaert DG. “Role of α -synuclein in inducing innate and adaptive immunity in Parkinson disease.” *Journal of Parkinsonism Disease* 5(2015) :1–19.
- [15] Games D, Valera E, Spencer B, Rockenstein E, Mante M, Adame A, Patrick C, Ubhi K, Nuber S, Sacayon P, Zago W, Seubert P, Barbour R, Schenk D, and Masliah E. “Reducing C- terminal-truncated alpha-synuclein by immunotherapy attenuates neurodegeneration and propagation in Parkinson’s disease-like models.” *Journal of Neuroscience* 34 (2014) :9441–9454.
- [16] Axelsen TM, and Woldbye DPD. “Gene therapy for Parkinson’s disease, an update.” *Journal of Parkinsons Disease* 8 (2018) :195–215.
- [17] Huttunen HJ, and Saarna M. “CDNF protein therapy in Parkinson’s disease. “ *Cell Transplantation* 28 (2019) :349–366.
- [18] Choong CJ, and Mochizuki H. “Gene therapy targeting mitochondrial pathway in Parkinson’s disease.” *Journal of Neural Transmission* 124 (2017):193–207.
- [19] Titze-de-Almeida R, and Titze-de-Almeida SS. “miR-7 replacement therapy in Parkinson’s disease.” *Current Gene Therapy* 18 (2018) :143–153.
- [20] Luo J, Padhi P, Jin H, Anantharam V, Zenitsky G, Wang Q, Willette AA, Kanthasamy A, and Kanthasamy AG. “Utilization of the CRISPR-Cas9 gene editing system to dissect neuroinflammatory and neuropharmacological mechanisms in Parkinson’s disease.” *Journal of Neuroimmune Pharmacology* 14 (2019) :595–607.
- [21] Maiti P, Manna J, and Dunbar GL. “Current understanding of the molecular mechanisms in Parkinson’s disease: Targets for potential treatments.” *Translational Neurodegeneration* 6 (2017):28.
- [22] Caobi A, Dutta RK, Garbinski LD, Esteban-Lopez M, Ceyhan Y, Andre M, Manevski M, Ojha CR, Lapierre J, Tiwari S, Parira T, and El-Hage N. “The Impact of CRISPR-Cas9 on age- related disorders: from pathology to therapy.” *Aging Disease*. 11(2020) :895–915.
- [23] Überbacher C, Obergasteiger J, Volta M, Venezia S, Müller S, Pesce I, Pizzi S, Lamonaca G, Picard A, Cattelan G, Malpeli G, Zoli M, Beccano-Kelly D, Flynn R, Wade- Martins R, Pramstaller PP, Hicks AA, and Cowley SA, Corti C. “Application of CRISPR/Cas9 editing and digital droplet PCR in human iPSCs to generate novel knock-in reporter lines to visualize dopaminergic neurons.” *Stem Cell Research*. 41 (2019) :101656.
- [24] Wei X, Cai M and Jin L. “The Function of the Metals in Regulating Epigenetics During Parkinson’s Disease.” *Frontier Genetics* 11 (2021) :616083.

- [25] Monnet-Tschudi, F, Zurich, MG, Boschat, C, Corbaz, A, and Honegger, P. "Involvement of environmental mercury and lead in the etiology of neurodegenerative diseases." *Review of Environmental Health* 21 (2006): 105–118.
- [26] Altschuler, E. "Aluminum-containing antacids as a cause of idiopathic Parkinson's disease." *Medical Hypotheses* 53 (1999): 22–23.
- [27] 27Khamparia, A., Saini, G., Gupta, D., Khanna, A., Tiwari, S. and de Albuquerque, V.H.C., 2020. Seasonal crops disease prediction and classification using deep convolutional encoder network. *Circuits, Systems, and Signal Processing*, 39, pp.818-836.
- [28] 28Bahadure, N.B., Ray, A.K. and Thethi, H.P., 2018. Comparative approach of MRI-based brain tumor segmentation and classification using genetic algorithm. *Journal of digital imaging*, 31, pp.477-489.
- [29] 29 Kumar, V., Singh, S., Singh, J. and Upadhyay, N., 2015. Potential of plant growth promoting traits by bacteria isolated from heavy metal contaminated soils. *Bulletin of environmental contamination and toxicology*, 94, pp.807-814.
- [30] 30 Prabhakar, P.K., Kumar, A. and Doble, M., 2014. Combination therapy: a new strategy to manage diabetes and its complications. *Phytomedicine*, 21(2), pp.123-130.
- [31] 31Khamparia, A., Gupta, D., de Albuquerque, V.H.C., Sangaiyah, A.K. and Jhaveri, R.H., 2020. Internet of health things-driven deep learning system for detection and classification of cervical cells using transfer learning. *The Journal of Supercomputing*, 76, pp.8590-8608.