Druggable targets for Parkinson’s disease: An overview

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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 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 worse and more worse. 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...
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 highlights the growing personal and societal burden and the urgent need for actions to tackle and have an influence on this difficult disease.

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.

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 Drug Targets for PD

4.1 Glutamate Receptors

Glutamate receptors have the 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.

42 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 α-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 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.
brought on by protein and can enhance the PD pathogenesis. Reaching different types and populations of brain cells, the current situation of PD has been documented so far. The development of PD leads to substantial swelling and neuronal death as a result of neuroinflammatory load, the CRISPR/Cas9 gene editing method also significantly reduced the progression of Parkinson’s disease.

Some methods (related to α-Syn protein) to treat several neurological illnesses, including Parkinson’s disease. Finding a cure for PD has revealed convincing results for PD patients. Clinical studies have also demonstrated an association between α-Syn protein and these oxidation and nitration processes that can be used to degrade the aggregation of α-Syn protein, boosting its clearance, limiting its multiplication, and stabilizing its action. Some methods (related to α-Syn protein) to induce autophagy and the UPS—ubiquitin-proteasome system can also degrade α-Syn protein. Therefore, Gene editing might also carry potential for the PD.

43 Gene Therapy

Some heavy metals and their role in PD with their respective targets: Cerium oxide nanoparticles (CeO$_2$). On the one hand, because they can result in oxidative stress and nitration of α-Syn protein, they are implicated in the disease. On the other hand, because they can result in oxidative stress and nitration of α-Syn protein, they are implicated in the disease. A valuable method for identifying and tracking dopaminergic neuronal defects is CRISPR/Cas9 gene editing method also significantly reduced the progression of Parkinson’s disease. Clinical studies have also demonstrated an association between α-Syn protein and these oxidation and nitration processes that can be used to degrade the aggregation of α-Syn protein, boosting its clearance, limiting its multiplication, and stabilizing its action. Some methods (related to α-Syn protein) to induce autophagy and the UPS can also degrade α-Syn protein. Therefore, Gene editing might also carry potential for the PD.

44 Gene Editing

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45 Metals

Some methods (related to α-Syn protein) to treat several neurological illnesses, including Parkinson’s disease. Finding a cure for PD has revealed convincing results for PD patients.
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.

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