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A Review on Targeting A-Synuclein Aggregation for Parkinson's Disease Modification

I. B. Shelke[1]; S. S. Wanjari[2]; A. R. Jaiswal[3]

[1;2;3]Bhausaheb Mulak College of Pharmacy

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Abstract:Global Burden of Disease Study and other major global health - surveillance efforts show that parkinson's disease (PD) has seen a sharp rise in prevelance over recent decades. In 1990, there were roughly 3.15 million people living with PD worldwide; by 2021, that number had increased to about 11.77 million - a rise of ~ 27.4%.The age - standardized prevalence rate increased from around 86 per 100,000 in 1990 to about 139 per 100,000 in 2021. According to 2019 estimates , over 8.5 million individuals globally had PD ; the disease burden - in terms of disability and mortality - also risen substantially. As of 2019, PD contributed to approximately 5.8 million disability adjusting life years and the number of ths attributed to PD was about 329,000 - reflecting more than 100% increase in PD- related deaths since 2000.Parkinson's disease is one of the most common neurodegenerative disorders, affecting more than seven million people worldwide. It is primarily caused by the progressive degeneration of dopamine-producing neurons in specific regions of the brain, which results in a variety of motor symptoms such as tremor, rigidity, and slowed movement, along with several non-motor complications. The condition is complex and influenced by both genetic susceptibility and environmental factors that contribute to its development and prevalence in different populations. A key pathological feature of the disease is the formation of abnormal protein aggregates known as Lewy bodies within brain cells. Early diagnosis of Parkinson's disease can be challenging because initial symptoms are often subtle and may appear years before the typical motor signs become evident. Effective management therefore requires improved diagnostic criteria, recognition of different disease subtypes, and the use of individualized treatment strategies to address the diverse clinical presentations and progression patterns of the disorder.

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I. INTRODUCTION

This review merges the current knowledge on a-synuclein biology, highlights the molecular events that drives its pathological aggregation , and examines the therapeutic landscape aimed at modulating these processes. By integrating mechanistic insights with emerging translationals strategies , this work aims to clarify the potential and limitations of a-synuclein - focused interventions and define the future directions necessary for achieving meaningful disease modifcation in Parkinson's disease.

As per the understanding of Parkinson's disease has deepened, it has become increasingly evident that the formation and accumulation of misfolded a-synuclein plays a central role in both the onset and progression of the disorder. The presence of a-synuclein - a rich Lewy bodies and Lewy neurites in affected brain regions, together with genetic evidence implicating *SNCA* mutations and multiplications , places a- synuclein pathology at the core of PD pathogenesis . These discoveries have shifted scientifc and clinical attention from purely dopaminergic mechanisms toward broader molecular pathways involving protein misfolding , aggregation, impaired clearance , and prion-like propagation. Consequently, targeting a-synuclein aggregation has emerged as promising avenue for developing disease-modifying therapies capable of slowing altering the course of PD.

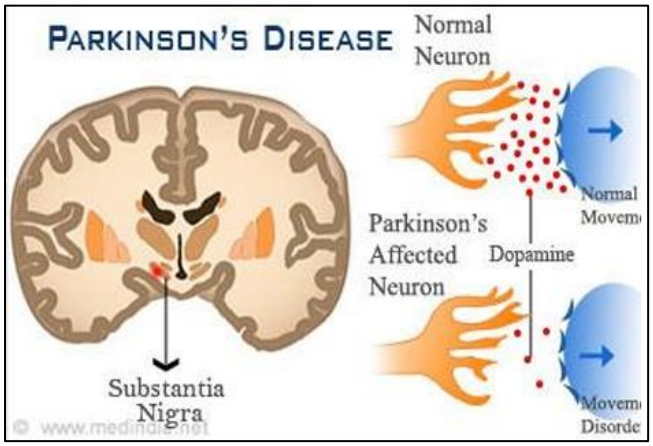

Fig 1 Dopamine Transmission

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Parkinson's disease is a well-defined clinical syndrome characterized by progressive neurodegeneration and a wide variety of causes and clinical manifestations. The global prevalence of Parkinson's disease has been increasing rapidly, showing trends similar to a pandemic, although it is not caused by an infectious agent. A small proportion of cases (about 3–5%) arise from single-gene mutations associated with known Parkinson's disease genes, while numerous genetic risk variants contribute significantly to the susceptibility of non-monogenic forms of the disease. Certain factors, such as a family history of Parkinson's disease or tremor, chronic constipation, and being a non-smoker, are also associated with an increased likelihood of developing the disorder. Diagnosis is mainly clinical and is based on the presence of bradykinesia together with either resting tremor, rigidity, or both, while additional tests are generally used only when the presentation is atypical. Besides the characteristic motor symptoms, patients often experience a range of non-motor features. The disorder may be preceded by a prolonged prodromal phase during which early symptoms appear before the classical signs become evident. Management focuses on improving quality of life through individualized treatment strategies. Levodopa remains the most widely used first-line medication for symptomatic relief, and optimal care usually involves a multidisciplinary approach along with various non-pharmacological therapies. Although no current treatment can halt or reverse disease progression, ongoing research into genetic mechanisms and neuronal degeneration is leading to the development of potential disease-modifying therapies aimed at improving future management of Parkinson's disease.

➢ *Disease:*

Parkinson's disease (PD) is a chronic , progressive neurodegenerative disorder and the second most prevalent neurological disease after Alzeimer's disease. It primarily affects older adults, though early onset cases also occur. Clinically , PD is defined by a constellation of motor symptoms - resting tremor, bradykinesia, muscular rigidity, and postural instability - arising largely from the degeneration of dopaminergic neurons in the substantia nigra pars compacta. The resulting loss of dopamine in the nigrostriatal pathway disrupts basal ganglia circuitry, impairing the precision and fluidity of voluntary movement.

Among the various molecular and cellular abnormalities implicated in PD, misfolding and aggregation of a-synuclein (a-syn) has emerged as a central pathogenic hallmark. A-Syn is a 40 amino - acid, instrinsically disordered presynaptic protein thought to play essential roles in synaptic vesicle trafficking, neurotransmitter release, and membrane dynamics. Under physiological conditions, a-Syn exists in dynamic equilibrium between monomeric, oligomeric, and membrane-bound forms, enabling it to support synaptic function.

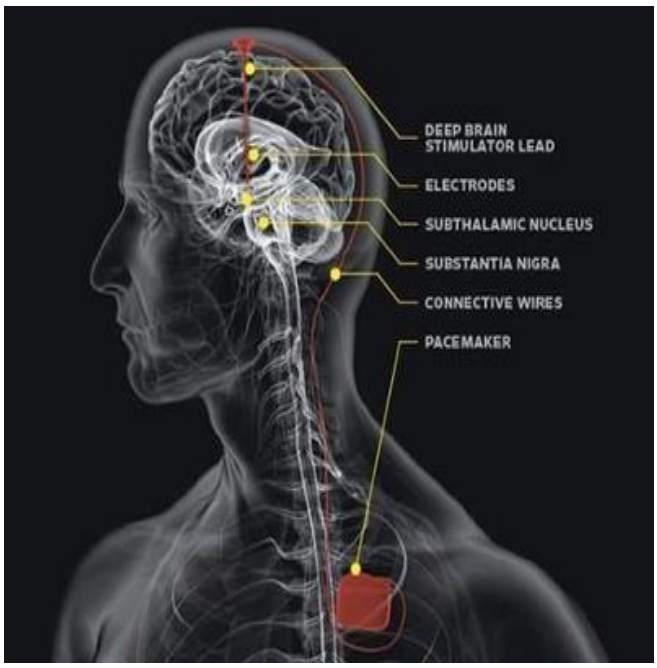

Fig 2 Diagram of Brain

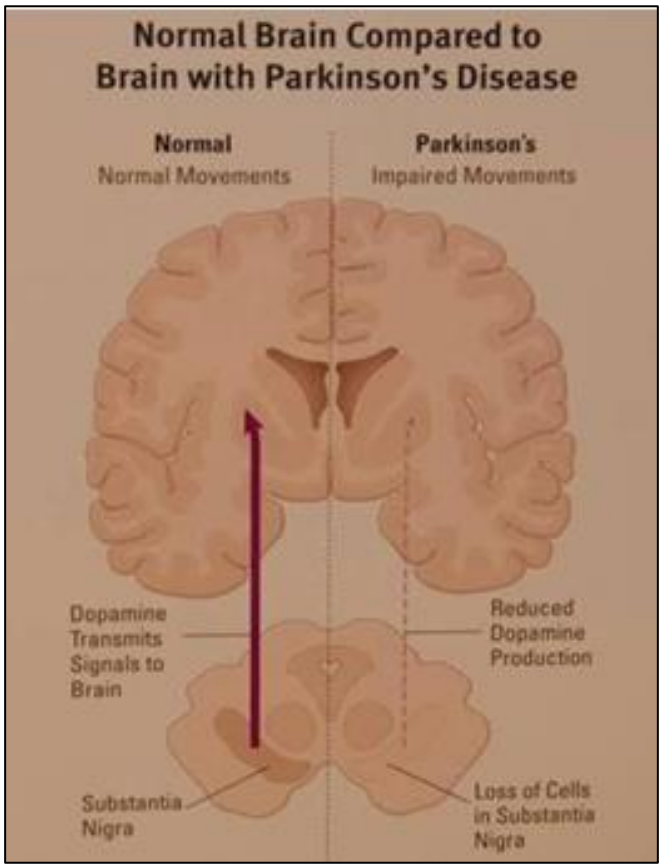

Fig 3 Comparison of Normal Brain with Parkinson's Disease Brain

➢ *How is Parkinson's Disease Brain Different from Normal Brain?*

- Significant loss of dopamine due to degeneration of neurons in the substantia nigra.
- Appearance of substantia nigra pale because many dopamine- producing neurons are lost.

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- Basal ganglia works smooth and coordinated in normal brain whereas in parkinson's is imbalanced .Overactive inhibitory signals cause slowed and stiff movements.
- Lewy bodies are absent in normal however in parkinson's are present and also contributes to neuronal damage.
- Tremors, rigidity, bradykinesia and postural instability can be seen.

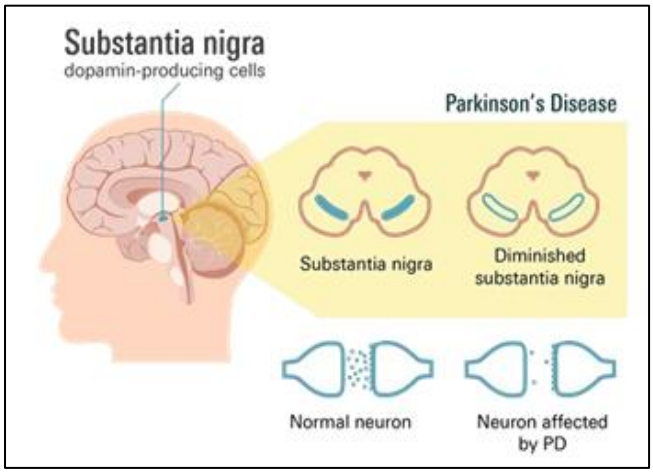

Fig 4 Substantia Nigra

Symptoms and causes of parkinsons are dependent on various factors such as Degree of Dopamine Loss, Brain region affected, Stage of the disease, Individual variability, Presence of Lewy Bodies.

Fig 5 Symptoms of Parkinsonism

➢ *General Parkinsons Symptoms may Include:*

- *Motor Symptoms (Cardinal Features)*

✓ Tremors - usually resting tremors ('pill-rolling')
✓ Bradykinesia - slowness of movements
✓ Rigidity - stiffness in limbs (lead-pipe or cogwheel rigidity)
✓ Postural instability - imbalance, frequent falls in later stages

- *Other Motor Symptoms*

✓ Reduced arm swing while walking
✓ Mask-like facial expression
✓ Difficulty initiating movements
✓ Soft or low voice

- Non-Motor Symptoms

✓ Loss of smell
✓ Sleep problems
✓ Mood changes
✓ Constipation
✓ Urinary issues
✓ Cognitive decline or memory loss
✓ Autonomic dysfunction

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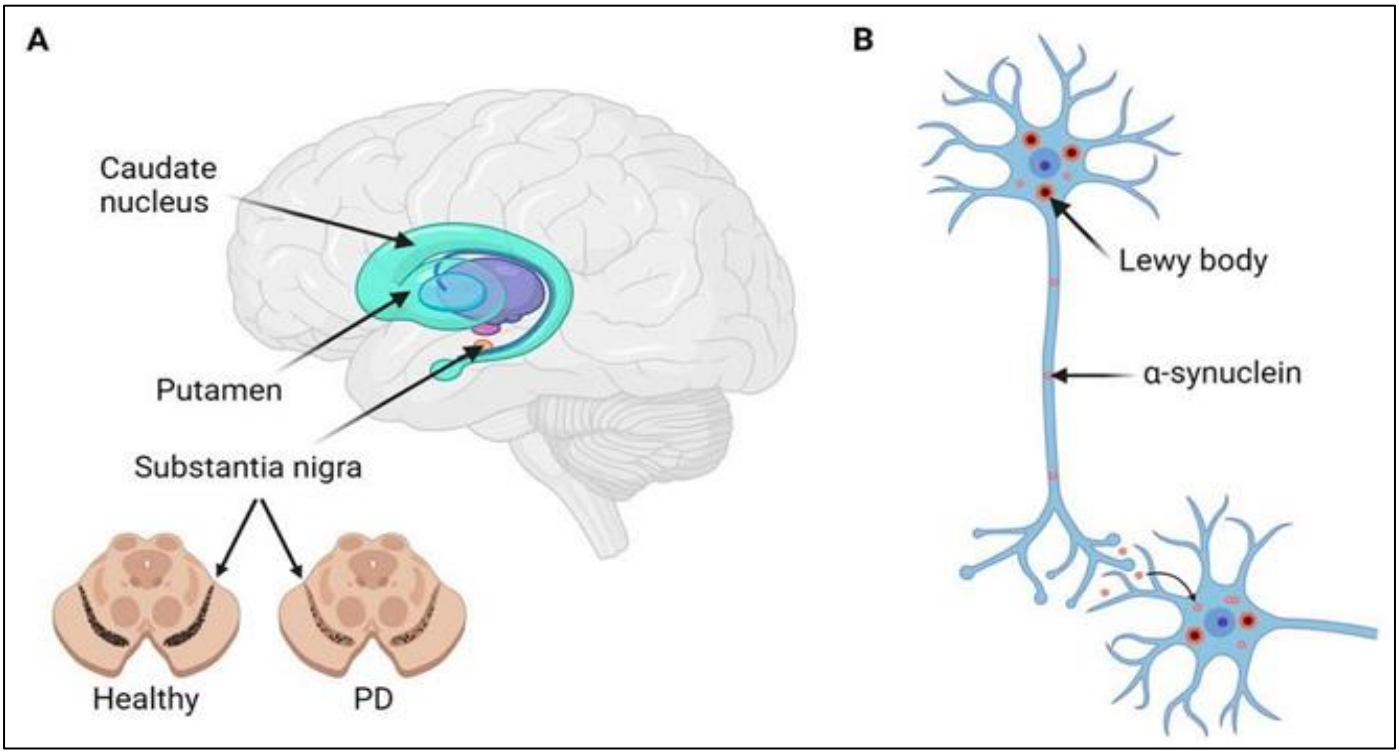

Fig 6 Comparison of Basal Ganglia

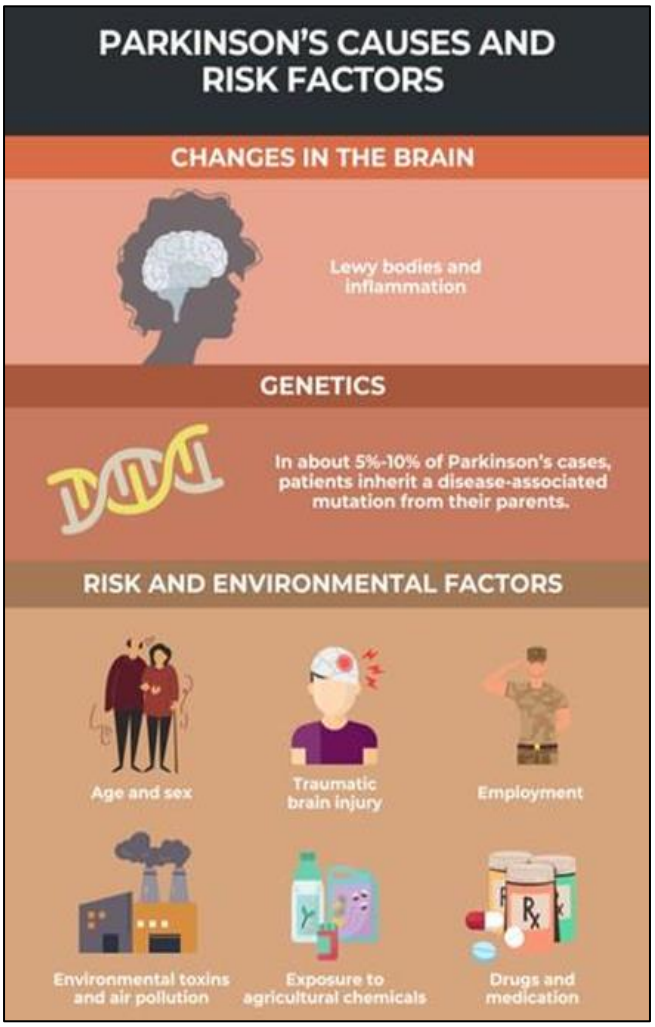

Fig 7 Causes and Risk Factors of Parkinsonism

- *Parkinson's are Mainly Caused by Degeneration of Dopamine-Producing Neurons in Substantia Nigra of the Brain.*
- Primary Cause: Loss of dopamine affects the basal ganglia which leads to impaired movement control.
- Underlying Pathological Features : Accumulation of a-synuclein protein forming lewy bodies inside neurons.
- Genetic Factors: Mutation in genes likes LRRK2, PARK7, PINK1, SNCA.
- Environmental factors: exposure to pesticides, heavy metals, rural living.
- Lifestyle-related risks: ageing,male sex.

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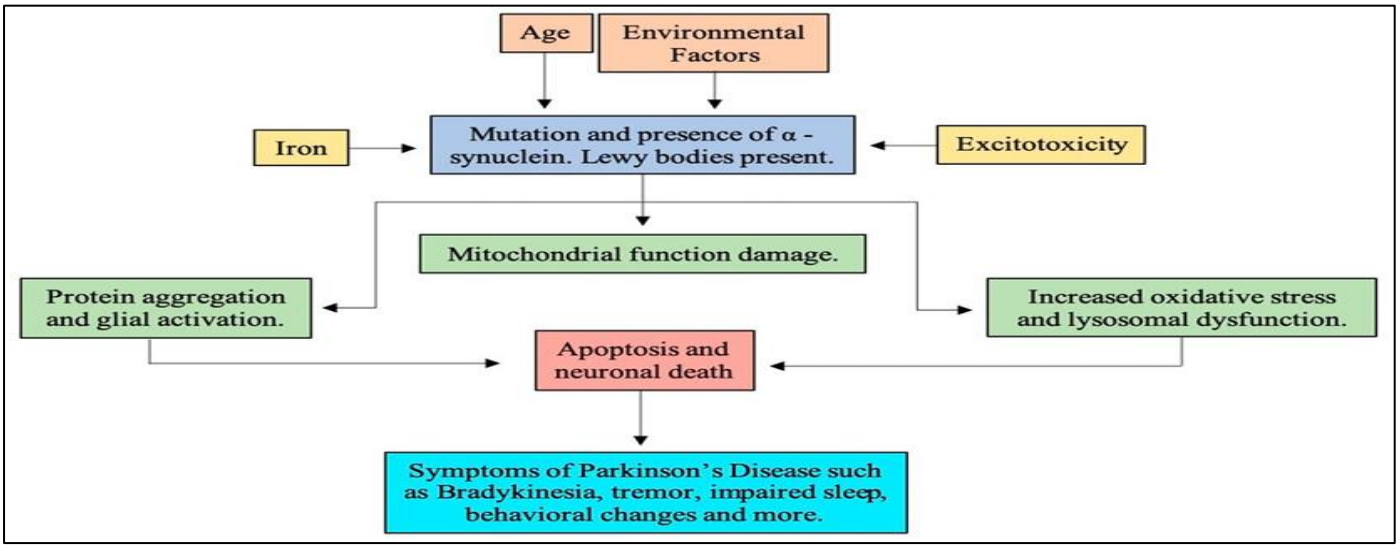


Fig 8 Pathophysiology of Parkinsonism

➢ *Pathophysiology of Parkinson's Disease*

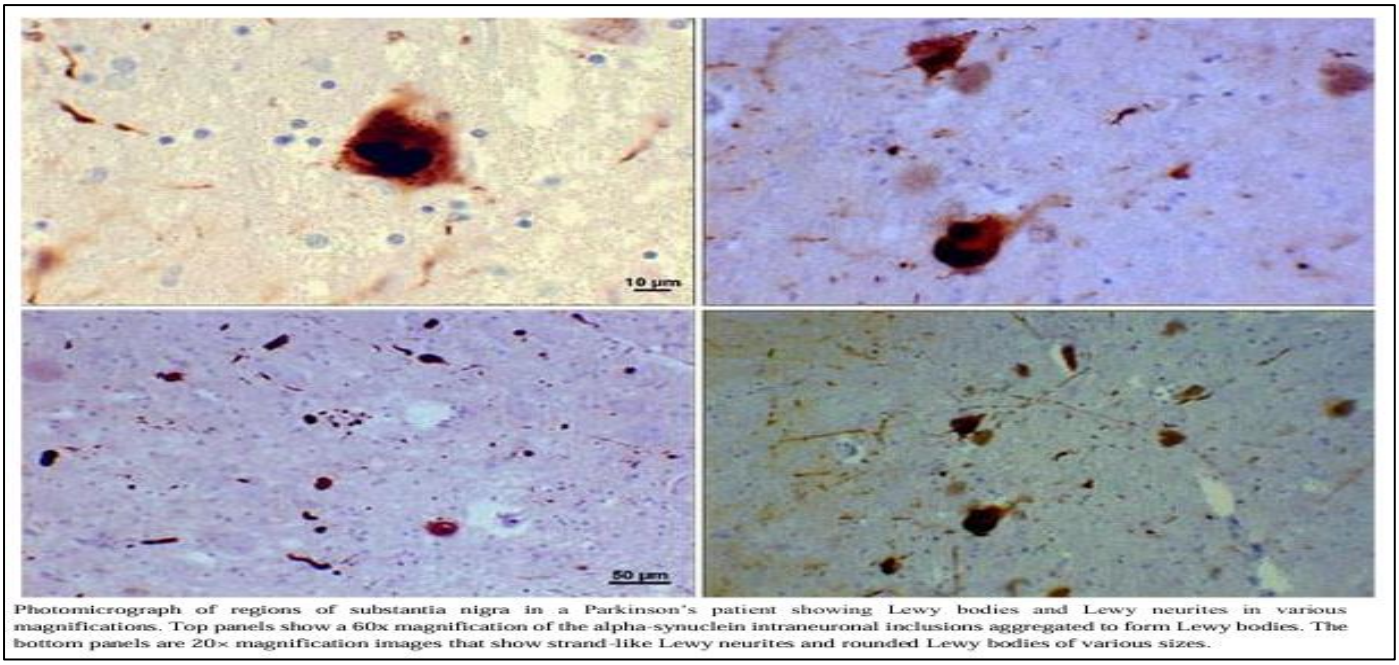
Physiologically, the symptoms of parkinson's disease arise primarily from progressive loss of multiple neurotransmitter systems, with dopaminergic degeneration being the most significant contributor. As dopamine producing neurons deteriorate, particularly within the substantia nigra pars compacta, motor and non-motor symptoms become increasingly pronounced.

This leads to marked reduction of dopamine in the striatum and subsequent disruption of basal ganglia circuits that control movement. This dopamine depletion results in an imbalance between the direct and indirect pathways, producing hallmark motor symptoms. A central pathological feature of the diease abnormal accumulation of misfolded a-synuclein protein, which aggregate to form Lewy bodies and contribute to neuronal dysfunction and death. Additional mechanisms- including mitochondrial impairement, oxidative stress , impaired protein degradation, and chronic neuroinflammation - further accelerate neurodegeneration. As pathology spreads to other brain regions in a pattern described by Braak's staging, non motor symptoms emerge, reflecting the multisystem neurodegenerative nature of the disorder.

➢ *Lewy Bodies and Alpha-Synuclein*

Lewy bodies are abnormal aggregates and inclusions of protein that develop inside nerve cells in people with Parkinson's disease. The aggregations containing misfolded protein. A large number of molecules have been identified in Lewy bodies but a protein called alpha-synuclein is the main component.

- *Lewy Bodies (Alpha-Synuclein Inclusion)*



Photomicrograph of regions of substantia nigra in a Parkinson's patient showing Lewy bodies and Lewy neurites in various magnifications. Top panels show a 60x magnification of the alpha-synuclein intraneuronal inclusions aggregated to form Lewy bodies. The bottom panels are 20× magnification images that show strand-like Lewy neurites and rounded Lewy bodies of various sizes.

Fig 9 Lewy Bodies

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➢ *Role of Dopamine*

Dopamine, like other neurotransmitters, transmits chemical messages from one nerve cell to another across the synapse, a space between the presynaptic cell and the postsynaptic receptor. Dopamine is secreted into the synapse from membrane storage vesicles in the presynaptic membrane. It crosses the synapse and binds to the postsynaptic membrane, where it activates dopamine receptors. Unused dopamine remaining in the synapse is absorbed back into the presynaptic cell; once back in the presynaptic cell, the excess dopamine is repackaged into storage vesicles and released once more into the synapse.

Within the synapse, as dopamine travels from one cell to another, it can be broken down and rendered inactive by two enzymes, MAO (monoamine oxidase) and COMT (catechol-O-methyl transferase). One therapeutic strategy introduces a MAO inhibitor into the synapse, which interrupts the action of the MAO enzyme and prevents the breakdown of dopamine. This allows more dopamine to remain in the synapse and increases the likelihood that it will bind to the postsynaptic membrane.

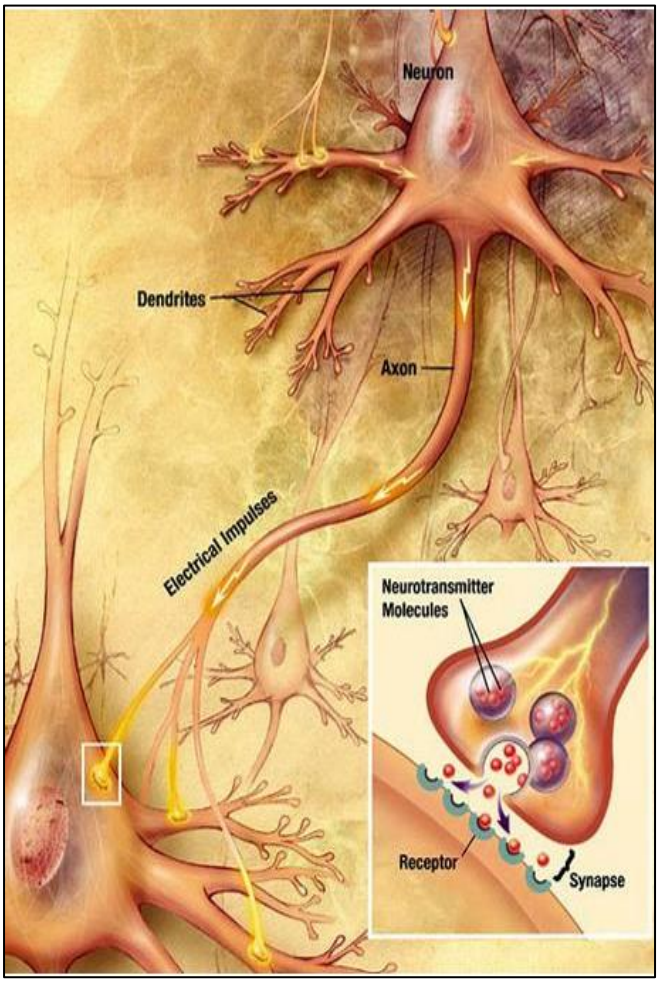

Fig 10 Chemical Synaptic Transmission

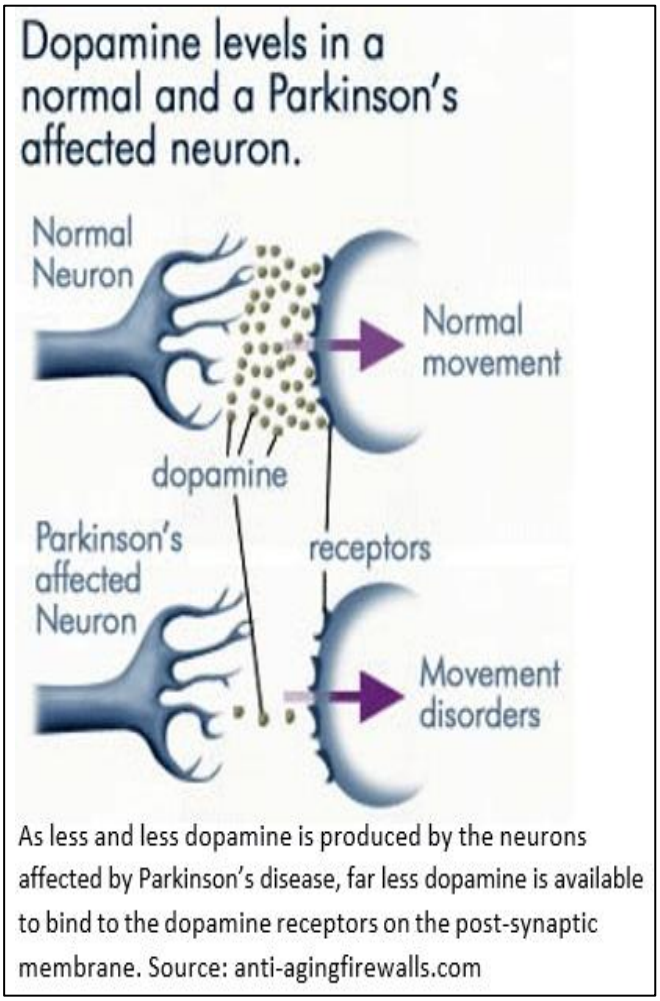

Fig 11 Comparison of Dopamine Level

As less and less dopamine is produced by the neurons affected by Parkinson's disease, far less dopamine is available to bind to the dopamine receptors on the post-synaptic membrane. Source: anti-agingfirewalls.com

Although dopamine cell loss cannot be measured directly, measurements in neurologically normal people and in nonhuman primates reveal a slow progressive loss of dopamine with age. In Parkinson's disease the loss occurs at a much greater rate and both biochemical measures and imaging studies suggest there is a significant decrease in dopamine by the time motor symptoms appear. In this view, Parkinson's disease is an accelerated version of the cell death seen with normal aging (Cookson, 2009).

➢ *Alpha-Synuclein (A-Syn)*

Alpha-synuclein (α-syn) is a small protein encoded by the SNCA gene (the gene that provides instructions for α-syn). It is amply expressed in the nervous system and exists in a natively unfolded state under normal physiological conditions (however its conformation changes depending on its environment and interactions with binding partners).

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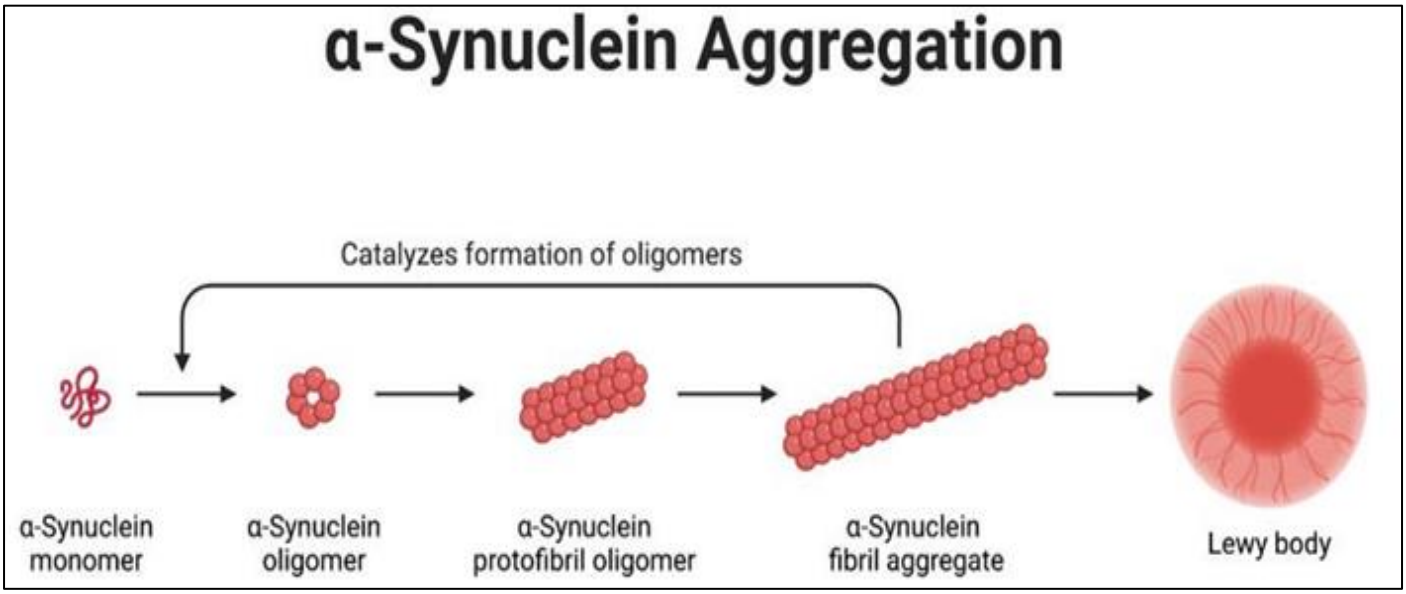

Fig 12 Alpha-Synuclein Aggregation

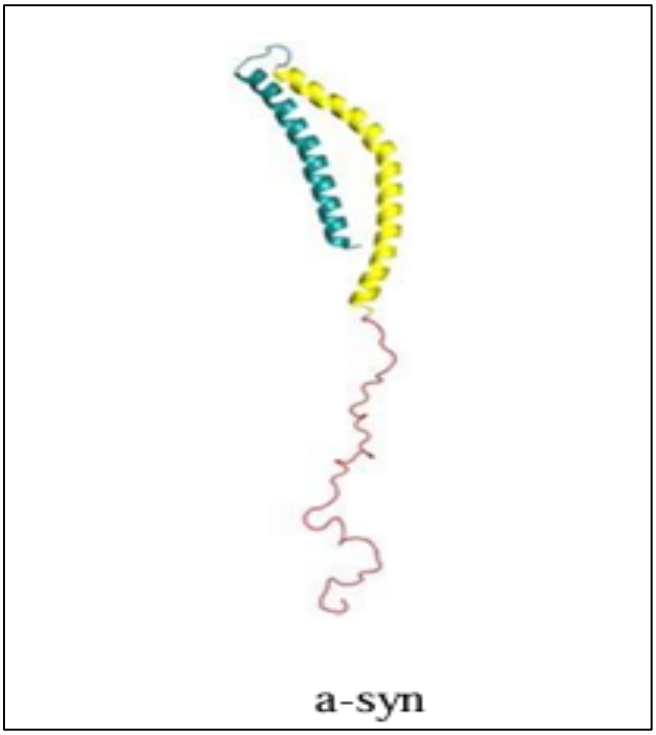

Fig 13 A-Syn

Alpha-synuclein aggregation is a process where the a-syn misfold and clumps together, which is a key feature of neurodegenerative diseases like PD and dementia with lewy bodies.

➢ *What Happens During Aggregation:*

- Misfolding and clumping: The a-syn protein, which is normally found in neurons, begins to misfold and form aggregates.
- Formation of Lewy bodies: These aggregates accumulates in the brain to form structures called Lewy bodies., which are the central hallmark of several neurodegenerative diseases.
- Cellular dysfunction: The aggregates impair cellular function, such as mitochondrial and lysosomal function, and disrupt neurotransmission, leading to neuronal damage and loss.
- Propagation between cells: The aggregated forms of a-syn can be released from neurons and taken up by other cells, spreading the pathology through the nervous system in "prion-like" manner.

Alpha-synuclein is a small neuronal protein composed of 140 amino acids and encoded by the SNCA gene. It is mainly found in the presynaptic terminals of neurons in the brain, where it plays an important role in regulating synaptic vesicles and controlling the release of neurotransmitters, particularly dopamine. Under normal conditions, alpha-synuclein exists as a soluble and unfolded protein that helps maintain synaptic function and plasticity. However, when the protein misfolds, it can aggregate to form insoluble fibrils that accumulate inside neurons as structures called Lewy bodies. The abnormal deposition of alpha-synuclein is strongly associated with several neurodegenerative disorders, including Parkinson's disease, Dementia with Lewy bodies, and Multiple system atrophy. These conditions are collectively known as synucleinopathies.

Alpha-synuclein is a protein that is highly concentrated in the brain, although smaller amounts are also present in tissues such as the heart, skeletal muscles, and other organs. In the brain, it is mainly located at the presynaptic terminals of neurons, particularly within axons. At these sites, the protein interacts with phospholipids and several other proteins involved in neuronal activity. Presynaptic terminals contain synaptic vesicles that store neurotransmitters, and alpha- synuclein plays an important role in regulating the release of these neurotransmitters, which is essential for normal communication between nerve cells.

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In Parkinson's disease and other synuclein-related disorders, abnormal and insoluble forms of alpha-synuclein accumulate within neurons, forming intracellular inclusions known as Lewy bodies. Mutations in the SNCA gene are associated with inherited forms of Parkinson's disease. During disease progression, the protein can undergo structural changes through a process called seeded nucleation, forming cross-β sheet structures typical of amyloid fibrils. Human alpha-synuclein is composed of 140 amino acids. A specific segment of this protein, called the non-amyloid-β component (NAC), was first identified in amyloid-rich brain extracts linked to Alzheimer's disease and was later found to originate from a precursor protein known as NACP. Further research revealed that NACP corresponds to the human counterpart of synuclein originally discovered in the electric ray genus Torpedo, which led to the protein being named human alpha- synuclein.

II. TREATMENTS

The treatment of Parkinson's disease focuses on improving motor and non- motor symptoms through a combination of pharmacological and non-pharmacological approaches. Levodopa, usually administered with carbidopa, remains the most effective therapy for motor symptoms by replenishing brain dopamine levels, while dopamine agonists, MAO-B inhibitors, and COMT inhibitors provide additional or alternative symptomatic control. Other medications such as anticholinergics and amantadine help manage tremor and levodopa-induced dyskinesias. For patients with advanced disease and significant motor fluctuations, deep brain stimulation of the subthalamic nucleus or globus pallidus offers substantial benefit. Rehabilitation strategies—including physiotherapy, speech therapy, and occupational therapy—play an essential role in maintaining mobility, communication, and daily functioning. Emerging treatments such as gene therapy, stem cell–based interventions, and α-synuclein-targeted therapies are under investigation for their potential to modify disease progression. Overall, treatment is individualized to optimize symptom control and enhance quality of life.

III. CONCLUSION

Targeting a-syn aggregation represents one of the most promising and biologically rational strategies for developing disease--modifying therapies in parkinson's disease. As evidence increasingly supports the central role of misfolded a-syn in initiating and propagating neurodegeneration, interventions aimed at reducing its accumulation, blocking its aggregation, or preventing its cell-to-cell transmission have gained significant scientific momentum.

Although several therapeutic approaches- including small-molecule inhibitors, immunotherapies, gene based strategies, and enhancers of protein clearance pathways- have shown encouraging results in preclinical studies, clinical translation remains challenging due to the complexity of a-syn biology and disease heterogeneity. Continued refinement of therapeutic targets, improved biomarker development, and early patient stratification will be critical for advancing these strategies into effective disease-modifying treatments. Overall, targeting α-synuclein aggregation holds substantial potential, and ongoing research may ultimately lead to interventions capable of slowing or altering the course of Parkinson's disease.

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