Understanding the Multifactorial Origins of α-Synuclein Misfolding in Parkinson's Disease

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Abstract

Parkinson's disease is often known for its motor symptoms like tremors, stiffness and slowed movement. However, these signs show up late long after the damage to cells and molecules has started. A key part of this problem is a protein called α-synuclein. This protein works fine under normal conditions but can change into a wrong shape, which starts a series of problems for neurons.

Methodologically, relevant research was reviewed by searching scientific studies in databases like PubMed and Scopus, focusing on work that explored how things like oxidative stress, mitochondrial problems, environmental toxins, and aging contribute to Parkinson's disease.

The main aim of this literature review is to evaluate the molecular and environmental factors that contribute to α-synuclein misfolding in Parkinson's disease and to explain how their combined, cumulative effects cross a critical threshold to initiate the disease. A **Threshold Crossing Model** is suggested where many stressors together make the cell unstable and eventually α-synuclein changes shape much. Finding this point of change might help us find a way to detect and treat the disease early rather than looking for one cause.

Introduction

Parkinson's disease is often seen as a movement disorder. Movement problems are often a late manifestation of the disease that has been going on for decades.

Long before people start to notice tremors or stiffness brain cells are slowly. The proteins inside these cells start to behave strangely. Research suggests that the disease process may start 15–20 years before symptoms are diagnosed (Postuma et al., 2015) [1].

Some early signs are:

- Olfactory dysfunction, including reduced odorant detection, is commonly reported
- REM sleep disturbances are frequently observed
- Gastrointestinal dysfunction, including chronic digestive irregularities, is often present

These early signs show that something is going wrong in the body long before doctors can diagnose the disease.

The main problem in Parkinson's disease is a protein called α-synuclein. This protein can get misfolded depending on where it's in the cell, which is normally helpful but also makes it vulnerable.

When α-synuclein is under stress it can change into a shape that clumps together and forms Lewy bodies (Goedert, 2001) [2]. These clumps, the small ones called oligomers are very toxic to brain cells. Scientists are still trying to figure out what causes α-synuclein to misfold.

Some possible contributors are:

• Exposure to chemicals like pesticides

• Problems with the cells energy system

• Stress and damage to proteins

• Problems in other parts of the body like the gut

No single one of these factors fully explains why the disease starts. Most researchers think that it takes a combination of stresses over time to cause α-synuclein to become unstable. PD is a condition and α-synuclein plays a key role in it. The disease process involves α-synuclein misfolding and α-synuclein is a protein to study. Understanding α-synuclein is essential, to understand Parkinson's disease.

However, there are multiple research gaps that must be addressed to further deepen our understanding of the disease etiology and its long preclinical progression.

• Scientists still do not fully understand what initiates α-synuclein misfolding at the molecular level

• The relative contribution and interaction of environmental factors (such as pesticides), mitochondrial dysfunction, and genetic susceptibility in triggering disease onset remain unclear

• The mechanisms by which cumulative stressors interact over time to cross a critical threshold and initiate Parkinson's disease are not yet well defined

Methodology

This review synthesized literature that directly addresses mechanisms of α-synuclein instability. Main sources included PubMed, Google Scholar, and ResearchGate, with keywords such as -

Keywords: α-synuclein misfolding, Parkinson's disease initiation, and mitochondrial dysfunction.

Approximately ninety studies were analysed, emphasizing studies published primarily between 2000 and 2024, including peer-reviewed human and experimental (animal and cellular) research. The studies primarily emphasized -

- Mechanistic insights over descriptive observations
- Experimental, genetic, and epidemiological evidence
- Cross-validation of findings to identify consistent patterns

Key observations included:

- Oxidative stress is commonly observed but its causative role varies by model
- Genetic studies explain susceptibility rather than initiation
- Environmental correlations exist but outcomes are not uniform

Molecular Basis of α-Synuclein Misfolding

α-synuclein is intrinsically disordered, able to adopt multiple conformations depending on cellular context (Goedert, 2001) [2]. This structural plasticity enables normal synaptic function but also predisposes it to misfolding under stress.

The misfolding progression typically follows:

- Monomeric instability
- Oligomer formation
- Protofibril development
- Aggregation into fibrils and Lewy bodies

Crucially, misfolded α-synuclein can propagate pathology by acting as a template for nearby proteins, amplifying the misfolding cascade (Brundin & Melki, 2017) [3].

Mechanisms of Propagation

Once misfolding initiates, α-synuclein spreads across connected neural regions:

- Peripheral origins such as the gut or olfactory pathways
- Brainstem involvement
- Extension to midbrain and cortical areas

Mechanisms facilitating this spread include:

- Release via extracellular vesicles
- Direct neuron-to-neuron transfer
- Uptake through endocytosis

This propagation mirrors the Braak staging model (Braak et al., 2003) [4], highlighting the stepwise involvement of the nervous system.

Candidate Triggers of Misfolding

Environmental Exposure

Pesticide exposure really increases the risk of Parkinson's Disease, by two times or even more (Goldman, 2014) [5].

Pesticides do some things to our bodies. Here is what they do:

Mitochondrial inhibition: They stop mitochondrial complex I from working.

Oxidative stress induction: They make more reactive oxygen species, which is not good for the health of human beings.

Proteostatic disruption: They cause stress at the protein level in our bodies, which is also bad for Parkinson's Disease. Pesticide exposure has been significantly associated with increased Parkinson's disease.

Oxidative Stress

Research on reactive oxygen species (ROS) shows that their levels are elevated across many experimental studies. When cells experience oxidative stress, ROS can chemically modify α-synuclein, increasing its tendency to misfold.

For example, processes such as dopamine oxidation and nitration of specific amino acid residues can alter the structure and stability of the protein.

Persistent ROS accumulation is particularly problematic because it is consistently observed across different models. Elevated ROS levels have been consistently observed across multiple experimental modelsThis oxidative stress environment promotes α-synuclein misfolding and aggregation, contributing to neuronal damage. (Abramov et al., 2020) [6]

Dysfunction of the Mitochondria

Mitochondria are central to neuronal survival, and their dysfunction contributes significantly to disease pathogenesis:

Less ATP production makes it harder for processes that depend on energy, like keeping ion gradients and checking the quality of proteins. High levels of ROS from broken mitochondria make oxidative damage worse. Weakened cellular resilience makes neurones more sensitive to environmental and internal triggers, which makes it easier for α-synuclein to misfold and clump together.

Genetics

Genetic variations mostly influence susceptibility, shaping baseline vulnerability rather than directly triggering disease (Kalia & Lang, 2015) [7].

Table 1: Comparative Support for Proposed Triggers

Risk Factor / Biomarker	Effect Size / Risk Metric	Metric Type
Pesticide exposure (ever vs never)	1.62	sRR
Pesticide exposure OR (general)	3.07	OR
Pesticide OR (occupational; highest subgroup)	3.82	OR
Genetic heritability (% of total PD risk)	16–36	Percentage

Gut-Brain Axis and Peripheral Initiation

Emerging evidence points to the gut as a starting point:
• The gut microbiota is different in people with Parkinson's disease, with studies showing reduced SCFA-producing bacteria such as *Prevotella* and increased pro-inflammatory taxa like *Enterobacteriaceae* compared to controls
• There is more inflammation in the gut, along with increased intestinal permeability that may allow bacterial products to trigger immune activation and α-synuclein aggregation in enteric neurons
• The Vagus nerve may help transport proteins (Sampson et al., 2016) [8], potentially through prion-like propagation of misfolded α-synuclein via retrograde axonal transport from the gut to brainstem regions

This suggests that misfolding of proteins in the gut may happen before problems, in the brain. We still need to figure out the exact causes.

Neuroinflammation

Inflammation contributes to α-synuclein instability but with complex timing:

- Microglial activation
- Cytokine release
- Increased neuronal vulnerability

Inflammation may act both as a trigger and as a response to early pathology.

Table 2: Mechanistic Interactions

Process	Linked Effect	Possible Outcome
Mitochondrial damage	Increased ROS	Protein instability
Microbiome alteration	Inflammation	Peripheral misfolding
Aging	Reduced clearance	Protein accumulation

Discussion

Evidence points away from a single trigger. Instead, PD initiation appears multi-factorial, with gradual accumulation of stress across cellular systems.

Key observations include:

- Environmental toxins are strongly associated but inconsistently causal
- Oxidative stress is a consistent lab finding but rarely primary
- Peripheral involvement, especially the gut, is increasingly supported

These observations underscore the **threshold-crossing model**, in which cumulative stressors destabilize the system until α-synuclein misfolding is triggered.

Table 3: Relative Contribution of Factors Across Disease Stages

Factor	Early Role	Later Role
Environmental	Strong	Strong
Genetic	Moderate	Moderate
Aging	Moderate	Strong
Inflammation	Unclear	Strong

Proposed Threshold-Crossing Model

The alpha synuclein misfolding process is something that the threshold crossing model helps us understand. This model looks at how alpha synuclein misfolding starts by considering environmental, cellular and age-related factors. It does not look for one thing that causes alpha synuclein misfolding. Instead, it looks at how all these factors add up and cause the system to become unstable.

This approach is consistent with earlier frameworks such as the “multiple hit hypothesis” , which similarly proposes that Parkinson’s disease arises from the cumulative effect of several interacting risk factors rather than a single trigger, thereby positioning the threshold crossing model as a more dynamic extension of existing ideas.

The threshold crossing model has two parts: **pre threshold accumulation and post threshold propagation.**

I. In the ***pre threshold accumulation phase*** many risk factors work together to make the neurons unstable. These include:

A) Baseline vulnerability, which's the genetic background of a person.

Specific genetic variants, like mutations in the SNCA or GBA genes do not directly cause α-synuclein misfolding. They do affect how stable the protein is and how well the cell can handle stress.

- These genetic variants set a threshold. This means that some people may reach a point where they get sick with stress than others.
- Some genetic variants also affect how well the cell can clear out proteins, how well it can protect itself and how well its mitochondria work.

B) Environmental exposures, like being around pesticides, herbicides, heavy metals or industrial toxins.

- Being around these things can cause stress to the neurons.
- This stress can stop the mitochondria from working create reactive oxygen species and make alpha synuclein more likely to misfold.
- If someone is exposed to these things times it can slowly weaken the cells defences and bring the system closer to the threshold.

C) Dysfunction of Mitochondria and Oxidative stress.

- When the mitochondria do not work right, they do not make energy for the cell. The cell requires energy to function properly.
- This can cause the cell to make harmful molecules known as reactive oxygen species (ROS). These bad things can change the alpha synuclein protein. When this happens the alpha synuclein protein is more likely to get all messed up.
- The cell can also get damaged because of something called stress. This can hurt the lipids and membranes in the cell. When this happens, it is more likely that the messed up alpha synuclein protein will cause problems, for the cell and the mitochondria and the alpha synuclein protein will not work right.

D). Decline of protein clearance.

- As people get older their cells get worse at removing misfolded proteins.
- The cells also get oxidative damage, which means that even small stressors can push the system closer to instability.
- Age related inflammation also makes the cell more sensitive to stress making it easier for alpha synuclein misfolding to occur.

II. In the ***post threshold propagation*** phase alpha synuclein misfolding becomes a self-reinforcing process.

A) The alpha synuclein protein starts to misfold.

The α-synuclein protein is usually fine. Sometimes it starts to get misfolded in a certain way. This new shape makes it more likely to stick with other alpha synuclein proteins and form clusters.

- When the alpha synuclein protein gets misfolded it becomes very stable. It can build up fast. The misfolded alpha synuclein proteins can accumulate quickly because they are so stable.

B) The misfolded alpha synuclein starts to aggregate.

- The alpha synuclein that is not folded correctly serves as a kind of model for proteins, which then also become misfolded.
- The process of alpha synuclein coming together. Forming clumps begins in places like the enteric nervous system or the pathways that are responsible, for smell and then alpha synuclein spreads to other parts of the brain.

C) The misfolding process becomes self-sustaining.

- Once the aggregation of alpha synuclein reaches a point it becomes independent of the initial triggers.
- The misfolded alpha synuclein can be transmitted from one neuron to another allowing the pathology to spread throughout the brain.
- The accumulation of Lewy bodies and oligomers makes the mitochondria work even worse causes oxidative stress and increases inflammation creating a cycle that is hard to stop.

The threshold crossing model helps us understand why people get alpha synuclein misfolding at times and why it progresses at different rates.

Integrative Insights

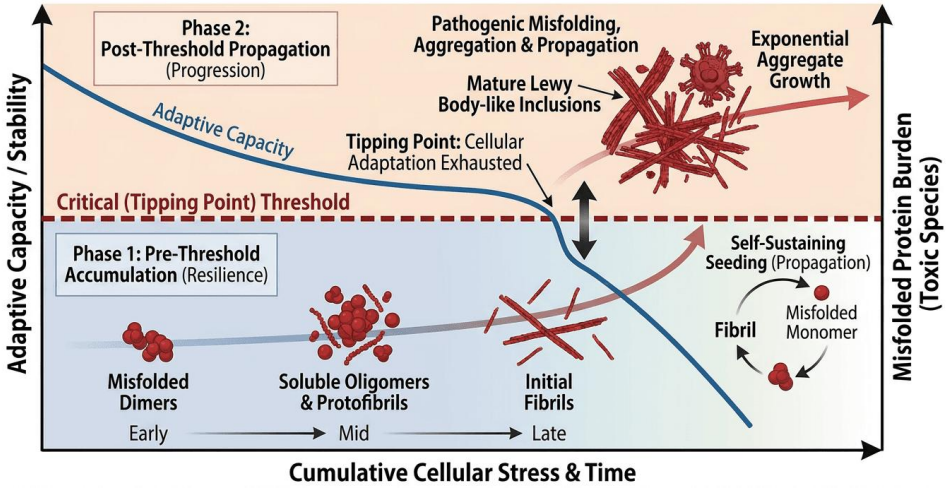
• The model shows that people with genetic resilience may not get sick even if they are exposed to environmental stressors.

• It also shows that people, with susceptibility may get sick with very little stress.

• The model suggests that we should look at all the factors that contribute to alpha synuclein misfolding than just looking for one cause.

• From a treatment perspective the model suggests that we should try to reduce stress improve protein clearance and reduce oxidative damage to prevent or delay alpha synuclein misfolding.

Figure 1: Threshold Crossing Model of α-Synuclein Misfolding



Conclusion

The search for a single factor responsible for α-synuclein misfolding is unlikely to fully explain Parkinson's disease. Instead, PD appears to arise from a combination of interacting biological and environmental influences that gradually destabilise cellular function over time. Factors such as environmental toxin exposure, mitochondrial dysfunction leading to reduced cellular energy production, oxidative stress from reactive oxygen species, and the natural ageing process collectively contribute to neuronal vulnerability.

Over time, these stresses accumulate and reduce the cell's ability to maintain protein homeostasis, eventually pushing the system beyond a critical threshold where α-synuclein misfolding and aggregation become more likely, ultimately contributing to neurodegeneration.

Focusing on the **threshold-crossing process** rather than isolated causes offers a more actionable framework for early detection, prevention, and targeted interventions.

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