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Pesticide-Associated Parkinson's Disease: Environmental Stress, Genetic Susceptibility, and Loss of Neuronal Resilience

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Abstract:
Parkinson's disease (PD) is a multifactorial neurodegenerative disorder shaped by environmental exposures, aging, and genetic predisposition. Pesticides are established as potentially modifiable environmental risk factors for PD, although the precise mechanisms linking exposure to neurodegeneration remain incompletely defined. This review synthesizes epidemiological evidence connecting pesticide exposure to PD and integrates recent advances regarding the molecular, genetic, gastrointestinal, and translational mechanisms underlying pesticide-induced neurotoxicity. Current research demonstrates that multiple pesticides disrupt interconnected biological pathways, including mitochondrial dysfunction, oxidative stress, impaired proteostasis, α-synuclein misfolding, lysosomal and autophagic dysfunction, neuroinflammation, and synaptic impairment. These disruptions may also alter the gut microbiota, compromise the intestinal barrier, and affect peripheral immune signaling, indicating a mechanistic relationship between environmental exposure and the gut–brain axis. Genetic variability in pesticide metabolism, mitochondrial quality control, α-synuclein regulation, lysosomal function, and antioxidant capacity may further modulate individual susceptibility. In conclusion, pesticide-associated PD is best conceptualized as a systems-level failure of neuronal resilience resulting from cumulative environmental exposures, genetic factors, aging, and gut–brain interactions. This framework supports integrated strategies for early detection, targeted prevention, and comprehensive neuroprotection.
Key Word*: Parkinson's disease, pesticides, environmental exposure, neurotoxicity, mitochondrial dysfunction, oxidative stress, α-synuclein, gut–brain axis, genetic susceptibility, probiotics, neuroprotection.*

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I. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder worldwide and represents an increasing public health concern as populations age. Clinically, PD is characterized by progressive motor impairments, including bradykinesia, rigidity, resting tremor, and postural instability, as well as a broad spectrum of non-motor symptoms that affect autonomic, gastrointestinal, cognitive, psychiatric, sleep, and sensory functions.[1-3] Neuropathologically, PD is defined by the degeneration of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of misfolded α-synuclein in vulnerable neurons. Recent evidence indicates that environmental factors significantly contribute to disease susceptibility and progression, thereby expanding upon the traditional view of PD as primarily resulting from intrinsic neuronal dysfunction.[4-6] The etiology of PD is multifactorial and cannot be attributed to a single genetic or environmental factor. Rather, disease risk emerges from prolonged interactions among aging, genetic predisposition, environmental exposures, metabolic factors, immune responses, and cellular mechanisms that maintain neuronal homeostasis.[7] This complexity is evident in the variability observed among individuals with comparable exposures. While some individuals experience long-term contact with neurotoxic chemicals without developing PD, others develop parkinsonism following similar exposures. Understanding this variability requires investigating the mechanisms by which environmental exposure leads to neurodegeneration in some individuals but not in others.[7-9]

Pesticides are a significant environmental concern due to their widespread use, biological activity, persistence in the environment, and capacity to disrupt cellular processes essential for neuronal survival.

Epidemiological studies involving agricultural workers, pesticide applicators, and residents of agricultural regions consistently demonstrate associations between pesticide exposure and elevated PD risk. Experimental research further indicates that various pesticides can induce molecular and cellular alterations relevant to PD, including mitochondrial dysfunction, oxidative stress, impaired protein degradation, neuroinflammation, and dopaminergic neuronal injury.[10-13] Pesticide-associated PD should not be conceptualized as resulting from exposure to a single class of toxicants or a single molecular target. Pesticides encompass a diverse array of compounds, including herbicides, insecticides, and fungicides, each with distinct primary mechanisms of action. Nevertheless, evidence indicates that multiple pesticides may converge on a limited set of biological pathways that govern neuronal vulnerability.[12,14,15] Mechanisms such as mitochondrial dysfunction, increased reactive oxygen species production, impaired proteostasis, lysosomal dysfunction, α-synuclein accumulation, microglial activation, and synaptic impairment are likely interconnected in mediating pesticide-induced neurotoxicity. This convergence of mechanisms is particularly pertinent to dopaminergic neurons. Nigrostriatal neurons possess intrinsic characteristics that heighten their susceptibility to environmental stress, including high energy requirements, extensive axonal projections, calcium-dependent pacemaking, dopamine-mediated oxidative reactions, and dependence on mitochondrial and proteostatic systems.[11,13,16] Consequently, environmental toxicants may not need to induce immediate or severe damage; rather, repeated minor insults can progressively diminish these neurons' capacity to manage metabolic and oxidative stress. This perspective reframes pesticide exposure as a chronic environmental stressor that incrementally challenges neuronal resilience, rather than as a singular neurotoxic event. In this context, resilience refers to the capacity of neurons and associated systems to preserve function and structure despite environmental, metabolic, inflammatory, and genetic stressors. Processes including mitochondrial quality control, antioxidant defenses, autophagy, lysosomal degradation, proteostasis, immune regulation, and synaptic maintenance collectively support this resilience.[17-19]Genetic background influences the threshold at which compensatory mechanisms become insufficient. Variants affecting pesticide metabolism, antioxidant responses, mitochondrial quality control, lysosomal function, α-synuclein biology, and immune regulation can modify the impact of environmental exposures. Thus, genetic susceptibility should be regarded as a modifier of the capacity to withstand cumulative environmental stress, rather than as a direct cause of PD.[19-21]

The gut–brain axis introduces an additional dimension to this model. The gastrointestinal tract serves as a critical interface between the body and environmental chemicals. Evidence indicates that pesticide exposure can alter the intestinal microbiota, compromise the intestinal barrier, affect microbial metabolism, and influence peripheral immune signaling.[11,22-24] These alterations may impact neuroinflammatory pathways and contribute to the milieu in which α-synuclein pathology and neuronal vulnerability develop. Although the causal role of microbiome changes in pesticide-associated PD is not yet fully established, the gut–brain axis remains a significant link between environmental exposure and central nervous system dysfunction. Diagnosis typically occurs after substantial neuronal dysfunction has developed, thereby limiting opportunities for preventive intervention. Biomarkers that identify pesticide exposure, biological responses to toxicants, and early neurodegenerative changes may provide a crucial translational bridge between environmental epidemiology and prevention. Pesticide metabolites, oxidative and mitochondrial biomarkers, inflammatory mediators, pathological α-synuclein, neurofilament light chain, and molecular neuroimaging constitute complementary approaches to reconstructing the trajectory from environmental exposure to neuronal injury.[25-28.] This integrated perspective carries direct therapeutic implications. If pesticide-associated neurodegeneration involves disruption of multiple systems, interventions targeting a single pathway are likely to provide limited benefit. Future strategies may require a combination of exposure reduction, mitochondrial protection, redox regulation, modulation of neuroinflammation, α-synuclein-targeted therapies, and interventions directed at the gut–brain axis. Although probiotics and other microbiome-based approaches show promise for modifying intestinal and systemic processes, current clinical evidence does not yet confirm their neuroprotective or disease-modifying effects.[12,14,18,29] Drawing on these considerations, this review synthesizes evidence from epidemiology, toxicology, molecular biology, genetics, gastrointestinal research to develop a systems-level framework for pesticide-associated PD. It is proposed that disease emerges when the cumulative environmental burden, genetic susceptibility, and age-related decline in cellular homeostasis collectively surpass the compensatory capacity of vulnerable neurons. This transition is termed the loss-of-neuronal-resilience threshold.[14,19,20]

Within this framework, pesticide-associated PD is conceptualized as the gradual failure of an interconnected biological system, rather than the consequence of a single toxic event. The central hypothesis posits that cumulative pesticide exposure, genetic susceptibility, aging, and peripheral–central signaling collectively diminish neuronal resilience until compensatory mechanisms are exhausted, resulting in irreversible dopaminergic neurodegeneration.[12,19,20]

II. Classes of Pesticides Associated with Parkinson's Disease

Pesticides are a diverse group of chemicals used to control insects, weeds, fungi, and other organisms that affect agriculture. Their chemical diversity complicates efforts to assess their roles in Parkinson's disease (PD), as individual compounds differ in structure, biological targets, persistence, metabolism, and routes of exposure. Evidence increasingly shows that the link between pesticides and PD goes beyond their agricultural use. Different compounds may affect common cellular pathways that regulate neuronal homeostasis, leading to similar patterns of mitochondrial dysfunction, oxidative stress, impaired proteostasis, neuroinflammation, and synaptic injury.[13,30-32] Table 1 summarizes the major pesticide classes investigated in relation to PD, representative compounds, and their principal biological and PD-relevant mechanisms.

Herbicides such as paraquat and glyphosate, and insecticides like rotenone, organophosphates, organochlorines, and pyrethroids, are among the most studied pesticides in relation to PD. Paraquat is notable for its ability to undergo redox cycling and generate reactive oxygen species (ROS), a feature particularly relevant to dopaminergic neurons, which are vulnerable to oxidative damage due to dopamine metabolism and high energy demands. Experimental models show that paraquat exposure leads to oxidative stress, mitochondrial changes, neuroinflammation, and dopaminergic neuronal injury. However, it remains uncertain how well these experimental results reflect the complexity of human PD.[16,33,34]

Rotenone offers a distinct but related example. Unlike paraquat, which causes toxicity through redox cycling, rotenone directly inhibits mitochondrial complex I. This inhibition disrupts electron transport, reduces ATP production, and increases ROS generation, making rotenone a common experimental model for environmental parkinsonism. Rotenone exposure can cause dopaminergic neuronal degeneration, α-synuclein accumulation, oxidative stress, and neuroinflammation. These findings are significant because mitochondrial complex I dysfunction is also seen in the substantia nigra of people with PD, suggesting a mechanistic link between environmental toxicology and disease pathology.[12,34]

Other pesticide classes may act on different primary molecular pathways but often lead to similar downstream effects. Organophosphate insecticides are known to inhibit acetylcholinesterase and disrupt cholinergic neurotransmission.[35-37] However, experimental and epidemiological studies show they may also cause oxidative stress, mitochondrial dysfunction, inflammatory signaling, and changes in cellular metabolism. Organochlorine pesticides are notable for their persistence and lipophilicity, which allow them to accumulate in biological tissues over time. Their ability to disrupt mitochondrial function, ion channel activity, oxidative balance, and neuronal signaling may further increase neuronal vulnerability with chronic exposure.[38,39]

Pyrethroids and other newer insecticides have been studied less extensively in relation to PD. However, experimental data suggests some compounds may affect ion channel function, redox balance, mitochondrial activity, and inflammatory pathways. The neurological effects of glyphosate are also under investigation. While the link between glyphosate and PD is less well established than that for other pesticides, experimental studies suggest potential effects on oxidative stress, mitochondrial function, and the intestinal microbiome. These findings should be interpreted with caution, as epidemiological evidence is mixed and experimental exposure levels may not reflect typical human exposures.[40-43]

Table 1. Pesticide classes and their potential relevance to PD

Pesticide class	Representative compounds	Biological effects	PD-relevant mechanisms
Herbicides	Paraquat	Redox cycling, ROS generation	Oxidative stress, mitochondrial dysfunction
Herbicides	Glyphosate	Oxidative and metabolic alterations	Mitochondrial stress, inflammation, gut microbiota
Insecticides	Rotenone	Complex I inhibition	Mitochondrial dysfunction, ROS, α-synuclein
Organophosphates	Chlorpyrifos and others	Cholinesterase inhibition	Oxidative stress, mitochondrial and inflammatory effects
Organochlorines	DDT-related compounds and others	Persistent bioaccumulation	Oxidative stress, mitochondrial and neuronal effects
Pyrethroids	Permethrin and others	Ion-channel modulation	Oxidative stress, mitochondrial dysfunction

The chemical diversity of pesticides suggests that pesticide-associated PD is unlikely to result from a single, compound-specific mechanism. In practice, people are often exposed to mixtures of chemicals rather than single agents. Agricultural workers may encounter several herbicides, insecticides, and fungicides simultaneously, while the general population may experience lower-level exposures through food, water, air, and residential environments. As a result, the biological effects of chronic pesticide exposure likely reflect the combined impact of multiple compounds acting on shared cellular pathways. Rather than their agricultural functions, their effects are most informative in the context of PD. Despite differences in primary molecular targets, multiple pesticide classes can disrupt mitochondrial function, elevate oxidative stress, impair protein and

organelle degradation, activate inflammatory pathways, and alter neuronal and gastrointestinal homeostasis. These convergent effects establish a crucial connection between epidemiological findings and the molecular mechanisms underlying neurodegeneration.[44,34]

Therefore, the main issue is not whether all pesticides linked to PD act through the same molecular targets. Instead, the key question is whether diverse environmental toxicants can collectively push vulnerable neuronal systems toward impaired homeostasis. This view supports the view that pesticide-associated PD is a convergent, system-level process in which various environmental factors may reduce neurons' ability to withstand metabolic, oxidative, inflammatory, and proteostatic stress.[12,15, 34]

This perspective is especially relevant to the selective vulnerability of nigrostriatal dopaminergic neurons. These neurons have extensive axonal projections, high energy demands, autonomous pacemaking activity, and biochemical features that increase oxidative burden. Environmental toxicants may therefore worsen existing physiological vulnerabilities rather than create entirely new pathological states. The mechanisms behind this interaction are discussed in the following sections.[46,47]

III. Molecular Mechanisms Underlying Pesticide-Induced Neurotoxicity

The association between pesticide exposure and Parkinson's disease (PD) is clarified when the molecular effects of these compounds are viewed as interconnected elements within a unified biological process. Rather than functioning independently, mitochondrial dysfunction, oxidative stress, impaired proteostasis, α-synuclein pathology, neuroinflammation, synaptic dysfunction, and gut–brain disturbances can reinforce one another, progressively diminishing vulnerable neurons' capacity to maintain homeostasis. This interconnectedness may account for the observation that diverse environmental chemicals can ultimately produce overlapping neurodegenerative features.[12,48-50]

Disruption of mitochondrial function is among the earliest and most consistent effects observed following exposure to various pesticides. Mitochondria are critical in neurons, supplying the energy necessary for maintaining membrane potentials, axonal transport, synaptic transmission, calcium homeostasis, and cellular repair. Certain pesticides, such as rotenone, directly inhibit components of the mitochondrial electron transport chain, while others may indirectly affect mitochondrial membrane potential, calcium regulation, mitochondrial dynamics, or quality-control mechanisms. The consequent reduction in oxidative phosphorylation compromises ATP availability and increases electron leakage and reactive oxygen species (ROS) production. Thus, mitochondrial dysfunction serves as an early point of convergence through which structurally diverse pesticides initiate neuronal stress.[12,34,51,52]

The elevation of ROS is particularly significant because oxidative stress is not solely a downstream effect of mitochondrial dysfunction; it can also exacerbate mitochondrial damage. Excessive ROS oxidize mitochondrial proteins, lipids, and DNA, further impairing electron transport and increasing the generation of reactive species. This establishes a self-reinforcing cycle in which mitochondrial dysfunction induces oxidative stress, which in turn further impairs mitochondrial function. In dopaminergic neurons, this process is intensified by dopamine metabolism, which generates reactive intermediates that modify proteins and cellular membranes. As a result, pesticide exposure may impose an oxidative burden on these neurons that surpasses the capacity of endogenous antioxidant defenses.[12, 53-56]

The progressive accumulation of oxidative damage significantly impacts protein homeostasis. Neurons rely on efficient mechanisms to recognize, repair, and remove damaged proteins due to their longevity and limited regenerative capacity. Persistent oxidative stress alters protein conformation and promotes the accumulation of dysfunctional proteins, while mitochondrial dysfunction reduces the energy available for proteostatic processes. Of particular interest is α-synuclein, whose misfolding and aggregation are central to PD pathology. Oxidative modifications can alter α-synuclein conformation and promote aggregation, while aggregated or misfolded species may disrupt mitochondrial function, vesicular trafficking, and synaptic processes. Thus, environmental stress and α-synuclein pathology may establish a pathological feedback loop in which each process reinforces the other.[49, 57-60]

The autophagy–lysosomal system serves as a critical mechanism linking these pathological processes. Autophagy and lysosomal degradation are essential for the removal of damaged proteins and organelles, including dysfunctional mitochondria. Pesticide exposure that disrupts autophagic flux or lysosomal activity leads to the accumulation of damaged mitochondria and misfolded proteins. This accumulation increases oxidative stress, while impaired α-synuclein degradation promotes its persistence and aggregation. Therefore, mitochondrial dysfunction, oxidative stress, α-synuclein accumulation, and impaired autophagy are interconnected components of a deteriorating proteostatic and metabolic system.[61-63]

This interplay is particularly relevant to genetic susceptibility. Variants that affect lysosomal function, mitochondrial quality control, α-synuclein biology, or antioxidant defenses can diminish the neuronal capacity to compensate for environmental stress. Individuals with a high biological reserve may effectively repair or eliminate pesticide-induced mitochondrial or oxidative disturbances. Conversely, genetic variations that impair

mitochondrial quality control or lysosomal function can amplify the biological impact of the same environmental exposure. This mechanistic framework helps explain why pesticide exposure increases PD risk without invariably causing disease in all exposed individuals.[19, 64,65]

Neuroinflammation constitutes an additional layer of interaction. Pesticide-induced cellular stress activates microglia via damaged mitochondria, oxidative products, altered neuronal signaling, and other danger-associated molecular signals. Activated microglia release cytokines, chemokines, ROS, and other mediators that modulate neuronal function. Inflammatory pathways, such as the NLRP3 inflammasome, are of particular interest because they may link mitochondrial dysfunction and cellular stress to sustained inflammatory signaling. Notably, this relationship is bidirectional: inflammatory mediators can further impair mitochondrial function and increase oxidative stress, establishing another positive feedback loop. Chronic environmental exposure may thus shift microglia from transient protective responses to a persistent inflammatory state that exacerbates neuronal vulnerability.[66-68]

Pesticide exposure may also impact the blood–brain barrier and synaptic compartments. Oxidative stress and systemic inflammation can compromise barrier integrity, increasing the interaction between circulating inflammatory mediators and neural tissue. Synapses, being highly energy-dependent, are particularly susceptible to mitochondrial dysfunction. Disruptions in ATP availability, calcium regulation, vesicular trafficking, and membrane integrity can impair neurotransmitter release and receptor function prior to irreversible neuronal degeneration. This suggests that synaptic dysfunction may serve as an intermediate stage between environmental exposure and neuronal death, offering a critical window for early detection and intervention.[58, 69-71]

These mechanisms may elucidate the selective vulnerability of nigrostriatal dopaminergic neurons. The substantia nigra contains neurons with extensive axonal arborization and high energetic demands. Their autonomous pacemaking activity imposes continuous metabolic requirements, while calcium handling and dopamine metabolism further increase oxidative stress.[72-75] These features may bring these neurons closer to the limits of their compensatory capacity. Consequently, pesticides may function less as uniquely selective toxins and more as environmental stressors that reveal pre-existing weaknesses in the biological systems maintaining neuronal homeostasis. Thus, selective vulnerability may primarily reflect differences in neuronal resilience rather than differences in exposure alone.[72-75]The gut–brain axis introduces an additional dimension to this process. The gastrointestinal tract serves as a critical interface between environmental chemicals and the organism, while the intestinal microbiome contributes to metabolism, maintenance of the epithelial barrier, immune regulation, and the production of neuroactive metabolites. Experimental evidence demonstrates that pesticide exposure can alter microbial composition and function, potentially resulting in dysbiosis, impaired intestinal barrier integrity, and changes in microbial metabolites. Increased intestinal permeability may facilitate systemic inflammatory signaling, and microbial alterations may influence immune pathways that impact brain homeostasis.[76-78] This relationship is particularly relevant to PD, as gastrointestinal abnormalities often occur during the prodromal phase, and alterations in the gut microbiome have been consistently reported in individuals with PD. However, the direction of causality remains unresolved. Dysbiosis may contribute to disease initiation or progression, result from disease-related physiological changes, or involve both processes. In the context of pesticide exposure, it is most plausible that environmental chemicals serve as additional stressors, modifying an already vulnerable gut–brain system. Therefore, pesticide-associated dysbiosis may not independently cause PD but could amplify systemic inflammation, alter α-synuclein-related pathways, and contribute to the progressive decline in neuronal resilience.[76,79,80]

Collectively, these mechanisms reveal an interconnected biological network rather than isolated toxicological effects. Mitochondrial dysfunction increases ROS production, which promotes protein and lipid damage. Impaired proteostasis facilitates α-synuclein accumulation, while damaged mitochondria and abnormal proteins activate inflammatory responses. Inflammation further compromises mitochondrial and synaptic function, and alterations in the gut microbiome may reinforce both systemic and central inflammatory signaling. Each disturbance thus has the potential to amplify the effects of the others.[81-83]This network perspective offers a coherent explanation for the prolonged and clinically heterogeneous course of pesticide-associated PD. Initial exposures may induce molecular alterations that remain subclinical, as cellular antioxidant, mitochondrial, lysosomal, and immune systems initially compensate for these disturbances. However, repeated exposure, aging, and genetic susceptibility can progressively diminish this compensatory capacity. When the accumulated biological burden surpasses the capacity of these systems, the process may shift from reversible cellular stress to persistent dysfunction.[84-86]

Pesticide-associated PD can thus be conceptualized as a progressive loss of neuronal resilience. In this framework, neuronal resilience refers to the capacity of neurons and their supporting biological systems to withstand environmental stress while maintaining metabolic, proteostatic, synaptic, and inflammatory homeostasis. Pesticide exposure incrementally challenges this capacity, while aging and genetic susceptibility

further reduce the available reserve. The critical transition arises when the cumulative burden of environmental and endogenous stress exceeds the system's compensatory capacity.[84,85,87]

Table 2. Molecular mechanisms linking pesticides to PD

Mechanism	Effect of pesticide exposure	Consequence for neuronal homeostasis	Potential link with PD
Mitochondrial dysfunction	mpaired electron transport	ATP deficit and ROS generation	Dopaminergic vulnerability
Oxidative stress	Increased ROS/RNS	Protein, lipid and DNA damage	Neuronal injury
Proteostatic dysfunction	Impaired protein degradation	Accumulation of damaged proteins	α-synuclein pathology
Autophagy/lysosomal dysfunction	Reduced clearance	Accumulation of proteins and organelles	α-synuclein accumulation
Neuroinflammation	Microglial activation	Chronic inflammatory signaling	Progressive neuronal damage
Synaptic dysfunction	Altered energy and vesicular processes	Impaired neurotransmission	Early neuronal dysfunction
Gut–brain alterations	Dysbiosis and barrier disruption	Systemic inflammatory signaling	Potential contribution to PD progression

IV. Genetic Susceptibility and Gene–Environment Interactions

Epidemiological evidence links pesticide exposure to an increased risk of Parkinson's disease (PD). Experimental studies show that pesticides disrupt mitochondrial function, oxidative balance, proteostasis, neuroinflammation, and the gut–brain axis. However, neither environmental exposure nor these molecular changes fully explain the variability in disease susceptibility. Some individuals remain unaffected despite prolonged exposure, while others develop PD after similar exposures. This suggests that genetic and cellular context significantly influence the biological impact of pesticide exposure.[88-90] The genetic architecture of PD includes both common variants with modest effects and rare variants that can significantly alter disease susceptibility. While genetic factors alone do not account for most PD cases, they can influence pathways relevant to environmental neurotoxicity. In pesticide exposure, genes involved in xenobiotic metabolism, mitochondrial quality control, oxidative stress responses, lysosomal degradation, α-synuclein homeostasis, and immune regulation are especially important, as they determine cellular responses to environmental stress.[91,92]

Genes responsible for metabolizing and detoxifying environmental chemicals play a key role. Enzymatic systems such as glutathione S-transferases, paraoxonase 1, and other xenobiotic-metabolizing pathways affect the biotransformation and elimination of toxic compounds. Genetic variation in these systems can change the internal dose tissues receive, even with similar external exposures. As a result, individuals in the same environment may experience different biologically effective exposures.[93] Differences in metabolism, detoxification, tissue distribution, and elimination can alter both the magnitude and duration of pesticide-induced cellular stress. Genetic variation in mitochondrial pathways is especially important because mitochondria are central to pesticide toxicity. Genes such as PINK1, PRKN, and DJ-1 regulate mitochondrial quality control, oxidative stress responses, and cellular protection. Deficiencies in these pathways reduce neurons' ability to remove dysfunctional mitochondria or respond to oxidative damage. In these cases, pesticide exposure adds further stress to an already compromised system. Genetic and environmental factors may therefore combine to produce a greater effect than either alone.[93-95]

The interaction between environmental exposure and SNCA, the gene encoding α-synuclein, is another key example. α-Synuclein is central to PD pathology, and genetic variation affecting its expression or regulation can influence disease risk. Environmental stressors that increase oxidative damage, impair protein degradation, or disrupt vesicular trafficking can further disrupt α-synuclein homeostasis. Individuals with genetic backgrounds favoring α-synuclein accumulation may be especially vulnerable to environmental conditions that increase proteostatic stress. GBA1, which encodes the lysosomal enzyme glucocerebrosidase, is a critical link between genetic susceptibility and environmental stress. Altered GBA1 function can impair lysosomal degradation and affect α-synuclein homeostasis. If pesticide exposure also increases oxidative stress or disrupts autophagy, this combination may further reduce neurons' ability to eliminate damaged proteins. This illustrates how environmental factors can amplify existing vulnerabilities without being sufficient to cause disease on their own.The interaction between genetic susceptibility and pesticide exposure is best understood in terms of

biological reserve. Genetic variants do not solely determine PD risk after exposure; instead, they influence the threshold of cellular stress that can be tolerated before compensatory mechanisms fail. Individuals with greater mitochondrial, proteostatic, antioxidant, or detoxification capacity may remain resilient despite significant exposure, while those with reduced reserve may reach the pathological threshold sooner.This interpretation aligns with the concept of the neuronal resilience threshold. Environmental exposure increases biological stress, while genetic background helps determine the capacity to absorb that stress. Aging further shifts this balance, as mitochondrial efficiency, proteostasis, antioxidant capacity, and immune regulation decline over time. PD may develop when the combined effects of environmental exposure and age-related cellular decline exceed the genetically determined capacity for compensation.[96-98]

Gene–environment interactions can also occur through epigenetic regulation. Environmental chemicals may influence DNA methylation, histone modifications, chromatin structure, and non-coding RNA networks. These changes can alter the expression of genes involved in inflammation, oxidative stress, metabolism, and neuronal survival without changing the DNA sequence. Epigenetic mechanisms thus provide a biological bridge by which environmental exposure can cause lasting changes in cellular function. The concept of gene–environment interaction calls for a revised epidemiological view of pesticide exposure. Rather than assuming a uniform increase in PD risk for all exposed individuals, future research should identify genetically and biologically defined subgroups with higher susceptibility. This approach may clarify inconsistencies in epidemiological studies and support individualized environmental risk assessment. Evidence supports a model where genetic susceptibility interacts with environmental exposure. Genetic variation can influence pesticide metabolism, mitochondrial quality control, antioxidant defenses, lysosomal function, α-synuclein homeostasis, and inflammatory responses, shaping how neurons tolerate cumulative environmental stress. Thus, genetic susceptibility may determine not only disease risk but also the resilience threshold at which environmental stress becomes biologically significant.[99-101]

V. From Environmental Exposure to Neurodegeneration: The Neuronal Resilience Threshold

The long latency and heterogeneous clinical presentation of PD suggest that the transition from environmental exposure to neurodegeneration is not an abrupt event. Instead, disease likely develops through a prolonged continuum in which molecular disturbances accumulate while compensatory mechanisms attempt to preserve neuronal function. This continuum provides a useful framework for integrating environmental exposure, genetic susceptibility, aging, and the molecular mechanisms described above. The process often begins with repeated exposure to pesticides via occupational, residential, dietary, or environmental routes. At this initial stage, exposure may not result in detectable neurological symptoms. Cellular systems responsible for detoxification, antioxidant defense, mitochondrial quality control, autophagy, and immune regulation can often compensate for the initial perturbation. As a result, individuals may remain clinically healthy despite measurable biological effects of environmental exposure. With repeated or prolonged exposure, however, molecular disturbances may accumulate. Mitochondrial function becomes less efficient, ROS production increases, damaged proteins accumulate, and inflammatory signaling becomes more persistent. In genetically susceptible individuals or in older adults with reduced cellular reserve, these alterations may become increasingly difficult to compensate for. The system therefore moves from adaptive stress toward maladaptive stress.[102-104]

The concept of a neuronal resilience threshold offers a framework for understanding this transition. Neuronal resilience is the capacity of a neuron and its surrounding biological systems to maintain functional stability despite metabolic, oxidative, inflammatory, and environmental challenges. This capacity is not fixed. It is influenced by genetic background, age, mitochondrial health, proteostatic capacity, immune regulation, metabolic status, and cumulative environmental exposure. During the early stages of exposure, the biological system may remain above the resilience threshold. Antioxidant responses neutralize ROS, damaged mitochondria are removed through mitophagy, misfolded proteins are degraded, and inflammatory responses resolve. However, progressive accumulation of environmental and endogenous stress may eventually exceed compensatory capacity. At this point, molecular disturbances begin to reinforce one another, producing a transition toward persistent cellular dysfunction. This transition may correspond to the biological phase of prodromal PD. Subtle abnormalities involving autonomic function, gastrointestinal physiology, sleep, olfaction, mood, and sensory processing may emerge before classical motor symptoms. Although these manifestations are not specific to pesticide-associated PD, their occurrence in an individual with substantial environmental exposure could indicate that the system has moved beyond simple exposure and into a state of biological vulnerability. As pathology progresses, synaptic dysfunction and impaired axonal transport may precede substantial neuronal death. This is particularly important because neurons may lose functional capacity before they are irreversibly lost. Consequently, the interval between environmental exposure and clinical diagnosis may contain a valuable window for intervention.[105-107]

Eventually, persistent mitochondrial dysfunction, oxidative stress, α-synuclein pathology, impaired lysosomal function, and chronic neuroinflammation may contribute to irreversible dopaminergic neuronal

degeneration. Once substantial neuronal loss has occurred, compensatory mechanisms may no longer be sufficient to restore normal circuit function, and the clinical manifestations of PD become increasingly apparent.[108]

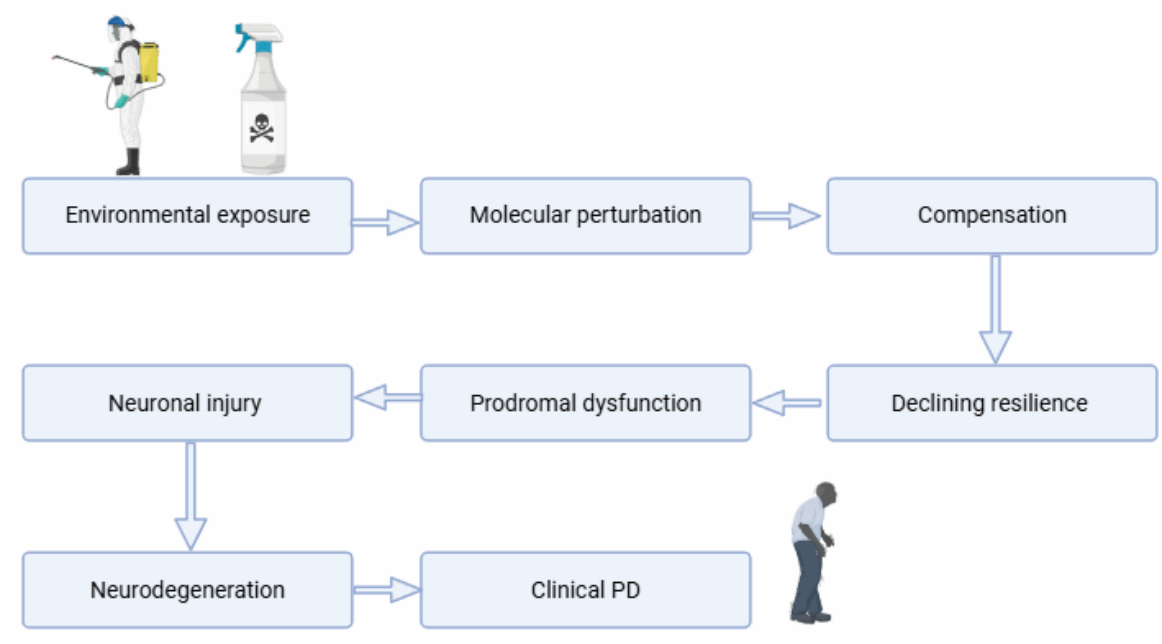

Figure 1. Proposed conceptual model linking environmental pesticide exposure, progressive loss of neuronal resilience, and Parkinson's disease development

This continuum has significant implications for environmental neurodegeneration research. The most informative biomarkers are likely those that identify individuals during the transition from exposure to biological dysfunction, rather than those that detect established PD. Likewise, the most effective preventive strategies may need to be implemented before the resilience threshold is irreversibly crossed.

VI. Conclusions

Parkinson's disease is now widely recognized as a multifactorial disorder involving complex interactions among environmental, genetic, metabolic, immune, and gastrointestinal factors over extended periods. In this context, pesticide exposure is a significant, potentially modifiable environmental risk factor. Epidemiological studies indicate an association between various pesticide classes and Parkinson's disease. Concurrently, experimental research demonstrates that chemically diverse pesticides can induce mitochondrial dysfunction, oxidative stress, impaired proteostasis, α-synuclein pathology, lysosomal dysfunction, neuroinflammation, synaptic impairment, and disturbances in gut–brain communication.

The central argument of this review is that these mechanisms should not be viewed as isolated pathways. Rather, they form an interconnected biological network through which cumulative environmental exposures progressively diminish vulnerable neurons' capacity to maintain homeostasis. Genetic susceptibility and aging further compromise this capacity, influencing the threshold of environmental stress that can be tolerated before compensatory mechanisms are overwhelmed.

From this perspective, pesticide-associated Parkinson's disease can be conceptualized as a progressive decline in neuronal resilience, rather than the result of a single toxic event. Environmental exposures elevate cellular stress, genetic background alters biological reserve, and aging incrementally reduces compensatory capacity. The interplay among mitochondrial, proteostatic, inflammatory, synaptic, and gut–brain mechanisms may ultimately drive vulnerable neurons beyond a critical threshold of resilience.

The primary challenge remains to determine whether the progression from environmental exposure to neurodegeneration can be interrupted prior to irreversible neuronal loss. Conceptualizing pesticide-associated Parkinson's disease in terms of neuronal resilience offers a valuable framework for addressing this challenge and developing a more integrated model that encompasses environmental risk, individual susceptibility, early detection, and precision prevention.

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