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MOLECULAR MECHANISMS OF NEUROTOXICITY: OXIDATIVE STRESS, NEUROINFLAMMATION, AND NEURAL DEGENERATION - SYSTEMATIC REVIEW

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ABSTRACT

Neurotoxicity results from the interaction between metabolic, oxidative, and inflammatory alterations and regulated cell death mechanisms. This systematic review aimed to analyze evidence on the molecular mechanisms linking oxidative stress, mitochondrial dysfunction, neuroinflammation, and neural degeneration. The literature search was conducted in PubMed/ MEDLINE, with complementary tracking in PubMed Central, Crossref, and the references of identified articles. Primary studies published between January 2000 and August 2026 were included that investigated molecular mechanisms and reported neuronal, synaptic, or functional outcomes. After applying eligibility criteria, 35 studies comprised the qualitative synthesis. The results showed that mitochondrial dysfunction and impaired PINK1–Parkin-mediated mitophagy promoted the accumulation of reactive species, energy compromise, and calcium imbalance. Activation of NADPH oxidase, TLR2, TLR4, NF-κB, and the NLRP3 inflammasome increased the production of inflammatory mediators and established feedback cycles between glial cells and neurons.Reprogramming of microglia and astrocytes, accompanied by complement activation, contributed to synaptic loss and progression of neural damage. Ferroptosis was associated with iron accumulation, glutathione depletion, GPX4 deficiency, and lipid peroxidation. In the opposite direction, NRF2 coordinated antioxidant and anti-inflammatory responses with neuroprotective effects. It was concluded that oxidative stress, neuroinflammation, and neural degeneration constitute an interdependent molecular network. Despite the consistency of the preclinical findings, the predominance of cellular and animal studies limited direct translation to humans, highlighting the need for human models, integrated biomarkers, and longitudinal studies.

Keywords:neurotoxicity; oxidative stress; neuroinflammation; neurodegeneration; ferroptosis.

INTRODUCTION

Neurotoxicity comprises a set of cellular and molecular alterations capable of compromising the structure, metabolism, and function of cells in the nervous system. Although its manifestations vary according to the triggering agent, the brain region affected, and the associated disease, experimental and neuropathological evidence points to convergence between mitochondrial dysfunction, redox imbalance, persistent activation of innate immunity, and regulated mechanisms of cell death. These processes do not occur in isolation; rather, they form feedback loops that progressively amplify synaptic dysfunction and neuronal loss.

The nervous system is particularly vulnerable to oxidative stress due to high energy demand, intensive oxygen consumption, an abundance of polyunsaturated lipids, and a relatively limited capacity for neuronal regeneration. Under physiological conditions, reactive oxygen and nitrogen species participate in cellular signaling. However, when their production exceeds the antioxidant capacity, oxidation of lipids, proteins, DNA, and RNA occurs, accompanied by changes in ionic homeostasis, enzymatic activity, and membrane integrity. Neuropathological analyses indicate that oxidative damage may be present in the early stages of Alzheimer's disease, before the consolidation of more advanced histopathological alterations[1].

Mitochondria occupy a central role in this process because they are simultaneously a source and a target of reactive species. Exposure to beta-amyloid can trigger the activation of NADPH oxidase, glutathione depletion, loss of mitochondrial potential, and impairment of the respiratory chain[2,3]. A reduction in the capacity to produce adenosine triphosphate compromises the maintenance of electrochemical gradients and increases vulnerability neuronal to excitotoxicity and calcium overload. In turn, the elevation of mitochondrial calcium favors greater production of reactive species, opening of the permeability transition pore, and activation of cellular death pathways[9].

Selective removal of damaged mitochondria by mitophagy represents an essential mechanism for maintaining neuronal homeostasis. Loss of mitochondr-

ial membrane potential stabilizes PINK1 on its surface, promoting recruitment of the ubiquitin ligase Parkin and targeting the organelle for autophagic degradation [4–6]. Genetic or functional alterations in this axis favor the accumulation of dysfunctional mitochondria, increase oxidative stress, and heighten vulnerability of neurons dopaminergic[7–9]. Therefore, the convergence of cellular, animal, and genetic studies indicates that failures in mitochondrial quality control may act as initiating or amplifying components of neural degeneration.

Oxidative stress also maintains a bidirectional relationship with neuroinflammation. Reactive species, aggregated proteins, extracellular ATP, oxidized lipids, and components released by injured cells function as damage-associated signals. These signals are recognized by innate immunity receptors expressed in microglia and astrocytes, triggering NF-κB activation, production of inflammatory mediators, and assembly of the NLRP3 inflammasome. Activation of the complex NLRP3–ASC–caspase-1 promotes maturation and release of IL-1β and IL-18, contributing to the maintenance of the neuroinflammatory microenvironment.

In Alzheimer's disease, fibrillar beta-amyloid can be internalized by microglia and cause lysosomal rupture, release of cathepsins, and activation of NLRP3[13]. Genetic deficiency of inflammasome components reduces inflammation, amyloid deposition, and cognitive impairment in experimental models[10]. In addition, extracellular particles of ASC released by microglia can act as molecular seeds for aggregation of beta-amyloid, establishing a direct link between inflammatory activation and the spread of proteinopathy[12]. NLRP3 activation also favors tau hyperphosphorylation and aggregation, indicating that this pathway may connect different components of neurodegenerative pathology[11].

Similar mechanisms are identified in Parkinson's disease. Oligomeric species of α-synuclein released by neurons may activate TLR2 receptors in microglia, whereas TLR4 contributes to the microglial and astrocytic response to the aggregated protein[26,27]. Activation of these pathways increases cytokine production and oxidant mediators. In models of synucleinopathy, NLRP3 inhibition reduced α-synuclein aggregation, the loss of dopaminergic neurons, and motor defici-

ts, suggesting a functional relationship among the inflammasome, proteinopathy, and nigrostriatal degeneration[28].

Microglia plays a particularly complex role in this scenario. Under physiological conditions, it participates in immune surveillance, clearance of debris, synaptic support, and responses to injury. During the neurodegenerative process, however, it may assume different functional and transcriptional states. Studies of

single-cell sequencing studies identified microglial populations associated with the disease, characterized by reduced homeostatic genes and activation of TREM2-dependent programs[15]. The TREM2–APOE axis is involved in this reprogramming and may induce

neurodegeneration-related phenotypes[16].

This response should not be interpreted as a rigid separation between beneficial and harmful microglia. Lipid recognition by TREM2 may support the survival and organization of microglial cells around plaques, contributing to the containment of injury[17]. In contrast, persistent activation can produce cytokines, reactive species, and mediators capable of compromising neurons and synapses. The expression of APOE4, for example, intensifies the glial response and neurodegeneration associated with tau in experimental models[18]. Prolonged proliferation or maintenance of reactive microglial populations may also contribute to neuronal loss regardless of significant changes in amyloid burden[19,20].

Astrocytes participate in amplifying this response. Cytokines and complement components released by microglia, such as IL-lα, TNF, and Clq, can induce reactive astrocytic states with reduced trophic functions and increased toxicity toward neurons and oligodendrocytes[14]. However, the diversity of astrocytic states cannot be reduced to a binary classification, since their properties vary with the stimulus, the brain region, and the stage of the disease.

In addition to the release of soluble mediators, the glial response directly interferes with the stability of neural connections. Components of the complement system, particularly Clq and C3, can tag synapses for microglial elimination. Pathological reactivation of this synaptic pruning mechanism contributes to early loss of connections in models of

Alzheimer's disease[21]. The involvement of complement has also been demonstrated in tauopathies, in which C1q blockade reduced synaptic loss[22]. These results suggest that cognitive dysfunction may arise before extensive neuronal death, through progressive impairment of connectivity.

NADPH oxidase constitutes another point of interaction between inflammation and redox imbalance. Its activation in microglia increases superoxide production and regulates the expression of pro-inflammatory genes[24]. The combination of an inhibitor of the mitochondrial respiratory chain, such as rotenone, and an inflammatory stimulus can produce greater dopaminergic neurotoxicity than that caused by each exposure alone[25]. These findings support a multifactorial model in which genetic, environmental, metabolic, and inflammatory factors converge on vulnerable neuronal populations.

In parallel with apoptosis and other forms of cell death, ferroptosis has come to be recognized as a possible mechanism of neurodegeneration. This mode of cell death is characterized by iron dependence, depletion of antioxidant defenses, and lethal accumulation of peroxides in membrane phospholipids[29]. Reduced availability of glutathione impairs the activity of glutathione peroxidase 4, the enzyme responsible for neutralizing lipid hydroperoxides. In dopaminergic models, iron chelators and ferroptosis inhibitors reduced neuronal death[30]. Complementarily, deletion of GPX4 in forebrain neurons was sufficient to induce lipid peroxidation, cognitive impairment, and neurodegeneration in animals[31].

In contrast to these harmful pathways, the transcription factor NRF2 coordinates the expression of antioxidant enzymes, detoxification proteins, and components responsible for maintaining glutathione and redox homeostasis. NRF2 deficiency intensifies microgliosis, astrogliosis, cytokine production, and dopaminergic degeneration in experimental models[32]. In Alzheimer's models, its absence exacerbates beta-amyloid deposition, tau phosphorylation, oxidative damage, and cognitive impairment[33]. NRF2 activation, on the other hand, increases antioxidant capacity and reduces the extent of neural injury across different experimental contexts[34,35].

Despite the consistency of preclinical evidence, uncertainties remain regarding the temporal sequence of these mechanisms, their relative importance across different diseases, and the possibility of therapeutic modulation in humans. Many studies use acute exposures, protein overexpression, extensive genetic deletions, or animal models that reproduce only specific components of human diseases. Also there is considerable heterogeneity in the characterization of glial states and in the criteria used to identify regulated forms of cell death.

Given this context, the present study aimed to systematically analyze the evidence regarding the molecular mechanisms that link stress oxidative, mitochondrial dysfunction, neuroinflammation, glial response, and regulated cell death pathways to synaptic dysfunction and neuronal degeneration. Additionally, we sought to identify convergent mechanisms, assess the consistency across different experimental and human models, and discuss the main limitations for translating this knowledge into prevention and treatment strategies.

METODOLOGY

A systematic review of primary studies was conducted on the molecular mechanisms involved in neurotoxicity and neural degeneration, with emphasis on the interactions among oxidative stress, mitochondrial dysfunction, neuroinflammation, glial responses, and regulated cell death pathways. The conduct and reporting of the review followed the recommendations of the *Preferred Reporting Items for Systematic Reviews and MetaAnalyses* PRISMA 2020[36,37].

Due to heterogeneity across biological models, exposures, and outcomes investigated, a qualitative synthesis structured by molecular mechanisms was adopted. No meta-analysis was performed because the studies showed substantial differences regarding experimental models, interventions, comparators, and outcome measurement methods.

The research question was formulated according to the PECO model: which molecular mechanisms related to oxidat-

ive stress, neuroinflammation, and regulated cell death pathways were associated with synaptic dysfunction, neurotoxicity, and neuronal degeneration in humans and experimental models? The population included humans, post-mortem human brain tissues, animal models, neuronal cultures, glial cells, and organotypic cultures of the nervous system. The exposures included oxidative oxidative dysfunction

mitochondrial, changes in mitophagy, microglial and astrocytic activation, inflammasome, cytokines, complement, ferroptosis, and protein aggregation. The comparators included control individuals or tissues, animals *wild-type*, unexposed cultures, vehicle, absence of neurotoxic stimulation, and genetic interventions or pharmacological

comparators. The outcomes included production of reactive species, oxidative damage, mitochondrial changes, inflammatory activation, lipid peroxidation, synaptic loss, neural dysfunction, neuronal death, and neurodegeneration.

The literature search was conducted primarily in PubMed/MEDLINE, with complementary searching in PubMed Central, Crossref, and the reference lists of the identified studies. Citation tracking of the core articles and individual record verification by title, author, journal, year, DOI, and PMID were also performed. Publications dated between January 2000 and August 29, 2026 were considered. This time window allowed for inclusion of contemporary developments in knowledge on redox signaling, mitochondrial quality control, innate immunity, functional diversity of glial cells, and regulated forms of cell death. No initial language restriction was applied during record identification. In the final composition, English-language articles were included that either provided full text or contained sufficient methodological information for critical analysis.

The search strategy combined controlled descriptors from the *Medical Subject Headings*(MeSH) and free-text terms located in titles and abstracts. Terms related to neurotoxicity, neurodegeneration, neuronal degeneration, neuronal death, synaptic loss, oxidative stress, reactive oxygen species, oxidative damage, lipid peroxidation, mitochondrial dysfunction, mitophagy, neuroinflammation, microglia,

astrocytes, glial activation,

inflammasome, NLRP3, NF-κB, TLR2, TLR4, NADPH oxidase, complement, ferroptosis, GPX4, glutathione, NRF2,

PINKl, Parkin, beta-amyloid, tau and α-synuclein. The descriptors were combined using the Boolean operators ύAND力 and ύOR力 to retrieve studies that presented simultaneously a context of neurotoxicity or neural degeneration and at least one oxidative, mitochondrial, inflammatory, or cell death regulatory mechanism. To increase sensitivity, complementary searches were carried out using specific combinations between neurodegeneration and PINKl–Parkin, neurotoxicity and NADPH oxidase, NLRP3 and tau, α-synuclein and TLR2/TLR4, synaptic loss and complement, ferroptosis and GPX4, as well as neuroinflammation and NRF2.

Primary studies published in peer-reviewed scientific journals were included, conducted with human subjects, human tissues, animals, cell cultures, or organotypic cultures of the nervous system. Eligible articles investigated at least one mechanism related to oxidative stress, mitochondrial dysfunction, neuroinflammation, glial response, ferroptosis, or antioxidant defense, and reported measurable neural, neuronal, or synaptic outcomes. The presence of a comparator group, a well-defined baseline condition, or a comparator intervention was also required, in addition to the reporting of molecular, biochemical, histological, or functional results related to neurotoxicity. Eligible outcomes included the production of reactive oxygen and nitrogen species, oxidation of proteins, lipids, DNA, or RNA, alterations in mitochondrial membrane potential and respiration, NADPH oxidase activity, NLRP3 activation, caspase-l, NF-κB, TLR2, TLR4, and complement activation, cytokine expression, microglial activation, astrocitic reactivity, glutathione concentration, GPX4 and NRF2 activity, cellular viability, neuronal death, synaptic loss, and cognitive or motor impairments accompanied by molecular or histological evidence.

Narrative reviews, systematic reviews, meta-analyses, editorials, letters, comments, book chapters, and conference abstracts without a full article were excluded. Reports or case series without mechanistic investigation were also excluded, as were studies that were exclusively clinical without assessment of molecular mechanisms, works without outcomes related to the nervous system, and pharmacological studies that evaluated only alterations behavioral changes without molecular,

cellular, or histological analysis. Publications without an appropriate comparator, duplicate studies, secondary analyses without additional data, studies with insufficient information to assess methods and results, retracted studies, or those with formally recognized scientific integrity issues were also excluded, along with publications in which the term "neuroprotection" was used without demonstrating neuronal injury, dysfunction, or death.

The selection was carried out in two stages. Initially, titles and abstracts were screened for adherence to the research question. Next, full texts deemed potentially eligible were assessed according to the established criteria.

Duplicate records were identified by comparing DOI, PMID, title, authorship, journal, and year of publication. When different publications used the same experimental model, the articles presenting independent or complementary mechanistic data were retained. After applying the eligibility criteria, 35 primary studies formed the basis for the qualitative synthesis. The reviews found during the process were used exclusively for contextualization and tracking bibliographically, without integration into the synthesis of the primary studies.

Data extraction was conducted using a standardized matrix that compiled author, year, journal, DOI, PMID, study design, biological model, disease or experimental condition, exposure characteristics, comparator group, molecular pathway investigated, biochemical, cellular, and histological markers, neuronal and functional outcomes, main results, methodological limitations, and relevance to the review question. In studies that employed more than one model, human, animal, and cellular evidence was distinguished. The authors ´ presented conclusions were not considered in isolation, but rather examined in relation to the experimental design, the appropriateness of the comparators, the methods employed, and the results actually demonstrated.

The studies were organized into seven areas: mitochondrial dysfunction, calcium and mitophagy; inflammasome and neuroinflammatory signaling; microglial states and neurodegenerative progression neurodegenerative; complement, synaptic loss, and glial neurotoxicity; α-synuclein and receptors of innate immunity; ferroptosis and lipid

peroxidation; and NRF2 and antioxidant responses. In studies that investigated more than one pathway, the classification was based on the predominant mechanism and the main outcome related to neural degeneration.

Methodological assessment was adapted to the design of each study. For animal studies, the domains of the SYRCLE instrument[38]were considered, including sequence generation and allocation concealment, baseline similarity between groups, random distribution of animals, researcher blinding, random selection for outcome assessment, assessor blinding, incomplete outcome data, selective reporting, and other sources of bias. In cell and mechanistic studies, model characterization, adequacy of controls, reproducibility of exposure, validity of assays, number of independent experiments, blinding of measurements, consistency across different markers, complete reporting of results, and the possibility of nonspecific effects of interventions were examined.For human and post-mortem studies, case and control selection criteria were evaluated, along with clinical and neuropathological characterization, the brain region examined, the post-mortem interval, preservation procedures, age, sex, and comorbidities control, the validity of biomarkers, the adequacy of the statistical analysis, and the possibility of confounding factors.

Methodological domains were classified as low risk, high risk, or unclear risk of bias. The absence of information on randomization or blinding was recorded as unclear risk, without assuming that these procedures had not been performed. A global numerical score was not used, as summing methodologically distinct domains could mask relevant limitations. The risk-of-bias assessment was used to qualify the interpretation of findings, not as an automatic exclusion criterion.

The data synthesis was qualitative and mechanistic. Results were compared according to the model type, the molecular pathway investigated, and the neuronal outcome. Evidence consistency was considered to be higher when the same mechanism was reproduced by independent groups, demonstrated in different models, subjected to genetic or pharmacological manipulation, and linked simultaneously to

molecular biomarkers and neuronal outcomes. Associative evidence was distinguished from causal evidence. Post-mortem studies contributed predominantly to identifying biological associations, whereas experiments involving genetic deletion, molecular rescue, or selective inhibition provided stronger support for causal inference.

Heterogeneity was assessed by considering disease or experimental condition, species, biological model, cell type, nature and duration of exposure, genetic or pharmacological manipulation, biomarkers used, methods for assessing neuronal death, cognitive or motor outcomes, and the direction of results. Statistical pooling was not considered appropriate because the studies did not provide sufficient homogeneity with respect to exposures, comparators, and outcome measures. Narrative synthesis allowed the integration of human and experimental evidence without producing potentially inaccurate quantitative estimates.

Because the review used exclusively data published and available in the scientific literature, it did not involve participant recruitment, access to medical records, or direct intervention in humans or animals. For this reason, submission to a research ethics committee was not required. During the selection and synthesis of evidence, the principles of scientific integrity, fidelity to the original results, and traceability of sources were observed.

RESULTS

The application of the eligibility criteria resulted in the inclusion of 35 primary studies published between 2001 and 2020. The set showed high methodological diversity, including studies using human post-mortem brain tissue, patient-derived cells, animal models, neuronal cultures, microglia and astrocyte cultures, organotypic cultures, and multimodel approaches. Pre-dominantly, pre-clinical studies related to Alzheimer's disease and Parkinson's disease were observed, alongside investigations into cerebral ischemia and general mechanisms of neuronal death.

The studies were organized into seven mechanistic axes. Nine investigated predominantly mitochondrial dysfunction, calcium, and mitophagy; five examined inflammasome and signaling

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neuroinflammatory; six analyzed microglial states and neurodegenerative progression; five addressed complement, synaptic loss, and glial neurotoxicity; three investigated α-synuclein and innate immunity receptors; three examined ferroptosis; and four assessed NRF2 and antioxidant responses. This distribution considered the predominant mechanism of each article, although several studies reported overlap among oxidative stress, neuroinflammation, and neural degeneration.

Table 1 - Dynamic Matrix of Identified Molecular Mechanisms

Molecular axis	Studies	Initiating event	Mediators identified	Cellular consequences	Outcome predominant and consistency	neural
Oxidative damage Early	[1–3]	Aβ and metabolic alterations and	ROS, H_2O_2, NADPH oxidase, carbonylation and oxidation of RNA	Glutathione depletion and impairment of the respiratory chain	Neuronal dysfunction and death	Discharge upon experimental models is; evidence Associative evidence in humans
Mitochondrial dysfunction	[3,7–9]	Aβ, mutations in PINK1, and calcium overload	Complex IV, mitochondrial potential l and permeability transition pore	Reduction of ATP, increase in ROS and bioenergetic failure	Selective neuronal vulnerability	High in cellular and genetic studies
Mitophagy PINK 1–Parkin	[4–8]	Loss of mitochondrial membrane potential	PINK1, Parkin, ubiquitinação and autophagy	Recognition and removal of damaged mitochondria	Protection against the accumulation of pro-oxidant organelles	High and reproducible
Inflammation and	[10–13,28]	Aβ, tau, α-synuclein and lysosomal damage	NLRP3, ASC, caspase-1, IL-1β and IL-18	Amplification of innate immunity and aggregation protein	Neuroinflammation and degeneration	High in preclinical models
Glial reactivitv	[14–20]	Aggregated proteins, lipids, and damage signals	TREM2, APOE, IL-1α, TNF, Clq and CSF1R	Microglial and astrocytic reprogramming	Neuroprotection the initial or chronic neurotoxicity	High, but context-dependent
Complem	[21,22]	Aβ, tau, and	Clq, C3 and	Marking and	Loss	Moderate to

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Molecular axis	Studies	Triggering event	Mediators identified os	Cellular consequences	Outcome Neural consistency e	predominant
and synapses		glial activity	microglial receptors NOX2, superoxide, and inflammatory mediators s	Synapse phagocytosis	early synaptic Early neuronal death, especially e dopaminergic a	high
NADPH oxidase	[2,24,25]	Aβ, LPS, and rotenone		Feedback between ROS and inflammation		High in cellular models
TLR2 and TLR4	[26,27]	extracellular α-synuclein he	TLR2, TLR4, and cytokines	Activation of microglia and astrocytes	Inflammation associated with synucleinopathy a	Moderate
Ferroptosis	[29–31]	Depletion of glutathione and iron accumulation	System ^ xc −x_c -, GPX4, iron and lipid peroxides	Loss of membrane integrity	Non-apoptotic neuronal death	Moderate in neurology; strong rationale molecular
Antioxidant defense e	[32–35]	Oxidative stress and inflammation	NRF2, ARE, HO-l, glutathione and antioxidant enzymes s	Reduction of ROS and glial modulation	Neuronal preservation	High in experimental models had is

The matrix showed that the mechanisms identified did not The matrix showed that the mechanisms identified did not constitute independent pathways. Mitochondrial dysfunction increased the production of reactive species, which, in turn, activated inflammatory pathways and promoted lipid peroxidation. In parallel, glial inflammation amplified the production of oxidants and impaired mitochondrial function, establishing a feedback loop associated with the progression of neural injury.

Oxidative Stress and Mitochondrial Dysfunction

Human and experimental studies indicated that oxidative damage was present before advanced neuronal degeneration. In postmortem brain tissue, oxidation of RNA and proteins was more intense during the early stages of Alzheimer's disease, showing a relative redu-

ction with increased amyloid deposition and neurofibrillary tangles[l]. This finding suggested that oxidative stress was not restricted to the terminal stages of the disease.

In cellular models, exposure to beta-amyloid activated NADPH oxidase in astrocytes, increased the production of reactive species, reduced glutathione levels, and compromised mitochondrial potential[2]. Inhibition of NADPH oxidase reduced mitochondrial dysfunction and neuronal death, demonstrating the functional involvement of this enzyme in the neurotoxic process. In Tg2576 mice and cells expressing mutant amyloid precursor protein, the presence of Aβ in mitochondria was associated with increased hydrogen peroxide, protein oxidation, and reduced cytochrome-c oxidase activity[3].

Mitochondrial dysfunction was also related to altered calcium homeostasis. Cells deficient in PINKl showed greater mitochondrial calcium overload, increased reactive species production, and higher susceptibility to opening of the permeability transition pore and to cell death[9]. These results demonstrated that redox imbalance and altered calcium converged on mitochondrial function.

Mitophagy Mediated by PINKl and Parkin

Five studies provided convergent evidence on the involvement of the PINK l–Parkin axis in mitochondrial quality control[4–8]. Loss of membrane potential promoted stabilization of PINKl in damaged mitochondria and recruitment of Parkin[4–6]. After its translocation, Parkin promoted ubiquitination, autophagic recognition, and selective elimination of dysfunctional organelles.

The absence or functional reduction of PINKl led to morphological and bioenergetic changes in mitochondria[7, 8]. In Drosophila models, pinkl deficiency was associated with muscular degeneration, impaired motor function, and loss of dopaminergic neurons. Increased Parkin expression attenuated some of these alterations, functionally placing it downstream of PINKl in the same mitochondrial quality control pathway[8].

Convergence across cellular experiments, genetic manipulations, and animal models provided high consistency to the PINKl–Parkin axis. However, most stud-

ies used depolarization pharmacologically, protein superexpression or marked genetic alterations, conditions that differed from the gradual mitochondrial dysfunction observed in human diseases.

Activation of the NLRP3 Inflammasome

Studies related to the inflammasome demonstrated that aggregated proteins and intracellular damage signals activated the NLRP3–ASC–caspase-1 pathway. Phagocytosis of fibrillar Aβ by microglia promoted lysosomal rupture, release of cathepsin B, and maturation of IL-1β [13]. In APP/PS1 models, deficiency of NLRP3 or caspase-1 reduced amyloid deposition, inflammatory response, and cognitive impairment[10].

The inflammasome also directly interfered with protein aggregation. ASC particles released by microglia bound to beta-amyloid and accelerated the formation of oligomers and aggregates[12]. In tauopathy, NLRP3 activation increased tau phosphorylation and aggregation, whereas deficiency of inflammasome components attenuated these changes[11].

In synucleinopathy, pharmacological inhibition of NLRP3 reduced IL-1β production, aggregation of α-synuclein, loss of dopaminergic neurons, and motor alterations[28]. Results obtained in different models indicated that NLRP3 represented a convergence pathway between innate immunity, proteinopathy, and neural degeneration.

Microglia and Astrocytes

Studies have demonstrated a high degree of functional heterogeneity in microglia. Single-cell transcriptomic analysis identified disease-associated populations, characterized by the progressive reduction of homeostatic genes and the activation of programs that are partially dependent on TREM2[15]. The TREM2–APOE axis contributed to the transition toward microglial states associated with neurodegeneration[16].

Nevertheless, the TREM2-mediated response did not show an exclusively detrimental character. The recognition of damage-associated lipids supported survival, metabolism, and organization of microglia around amyloid plaques[17]. This behavior was related to the physical containment of plaques and the processing of lipid and protein materials.

The expression of APOE4 intensified gliosis, cerebral atrophy, and neurodegeneration associated with tau[18]. The pharmacological reduction of microglial proliferation or its depletion in amyloid models decreased neuronal loss and functional impairment, even without a proportional reduction in Aβ load[19,20]. These findings indicated that the microglial response contributed to downstream degeneration from protein deposition.

Astrocytes also showed microglial-response–induced changes. IL-lα, TNF, and Clq released by microglia promoted reactive astrocytic states associated with reduced trophic functions and increased toxicity to neurons and oligodendrocytes [14]. The finding demonstrated that glial neurotoxicity resulted from multicellular interactions, not only from isolated microglial activity.

Complement and Synaptic Loss

Two studies directly analyzed the involvement of the complement in synaptic degeneration[21,22]. In Alzheimer models, Clq and C3 accumulated in vulnerable synapses before extensive neuronal loss occurred. Microglia recognized the labeled synapses and promoted their phagocytosis[21]. Complement inhibition reduced synaptic elimination, indicating that reactivation of developmental pruning mechanisms contributed to the early phase of the disease.

Similar results were identified in tauopathy models. Changes in the synaptic proteome were accompanied by Clq activation, and the use of antibodies against this component reduced synapse loss[22]. The findings demonstrated that complement activation was not restricted to amyloid pathology and represented a possible common mechanism of neural disconnection.

NADPH oxidase and redox-inflammation amplification

Microglial NADPH oxidase played a central role in producing superoxide and in the expression of pro-inflammatory genes. In LPS-stimulated models, inhibition or deficiency of the enzyme reduced both the formation of reactive species and microglia-mediated neurotoxicity[24].

The combination of rotenone, an inhibitor of the mitochondrial complex I, and LPS produced degeneration dopaminergic higher than that observed

with each isolated exposure[25]. This synergistic effect demonstrated that mitochondrial dysfunction and potential inflammation were mutually potentiated. mutually. Similar results were observed with exposure to beta-amyloid, in which NADPH oxidase activation in astrocytes preceded neuronal impairment[2].

A-Synuclein and Innate Immunity Receptors

Extracellular α-synuclein acted as a molecular signal capable of activating glial cells. Oligomers released by neurons stimulated TLR2 in microglia and increased the expression of inflammatory mediators[26]. TLR4 also participated in the recognition and processing of α-synuclein by microglia and astrocytes [27].

The observed effects depended on the protein conformation and the cellular context. TLR2 was more directly related to the pro-inflammatory activation induced by oligomers, whereas TLR4 showed concurrent involvement in inflammation and protein clearance. This functional duality limited the interpretation of these receptors as exclusively harmful targets.

Ferroptosis and Lipid Peroxidation

Three studies provided evidence on ferroptosis[29–31]. Their initial characterization showed an iron-dependent form of cell death, associated with cystine transport inhibition, reduced glutathione synthesis, and accumulation of lipid peroxides[29]. Ferrostatin-l reduced oxidative cell death and protected organotypic brain tissue, establishing an initial link between ferroptosis and neurodegeneration.

In human dopaminergic neurons in culture, cell death associated with glutathione depletion was reduced by iron chelators and ferroptosis inhibitors[30]. In mice, GPX4 deletion in forebrain neurons caused lipid peroxidation, hippocampal degeneration, and cognitive impairment[31]. These findings supported ferroptosis involvement in neuronal loss, although direct evidence in human tissues remained limited.

NRF2 and Antioxidant Mechanisms

The NRF2 pathway showed both antioxidant and anti-inflammatory effects. In animals exposed to MPTP, NRF2 deficiency increased microgliosis, astrogliosis, COX-2 and iNOS expression, IL-6 and TNF-α production, and dopaminergic impairment[32]. In APP/Psl mi-

ce, NRF2 ablation intensified Aβ deposition, tau phosphorylation, oxidative damage, glial activation, and cognitive deficits[33].

In the opposite direction, the pharmacological activation of NRF2 increased glutathione and antioxidant enzymes, reducing brain injury in experimental models[34]. Activation of the microglial receptor axis nicotinic α7–NRF2–HO-1 also reduced ROS production, TNF release, and neuronal death[35]. The results indicated that NRF2 acted as an integrated regulator of redox balance and the inflammatory response.

Methodological Assessment of the Studies

The risk of bias analysis identified heterogeneity in the reporting of experimental procedures. Studies involving genetic manipulation, appropriate control groups, and molecular rescue strategies demonstrated a greater ability to support causal relationships. However, in part of the animal studies, the procedures for randomization, allocation concealment, sample size calculation, and blinding of assessors were not described with sufficient clarity. In those cases, the corresponding domains were considered to be at an uncertain risk, and not automatically at high risk.

In in vitro studies, the main limitations were related to the use of high concentrations of aggregated proteins or toxic agents, the reduced duration of exposures, dependence on cell lineages, and incomplete reporting of the number of experiments biologically independent. In post-mortem studies, limitations included the inability to determine temporality, the influence of the post-mortem interval, and potential clinical differences between cases and controls.

The greatest relative robustness was observed in multimodel studies, in which mechanisms were evaluated using cellular, animal, and genetic approaches and, in some cases, confirmed in human tissues. Even so, the predominance of pre-clinical evidence limited the direct extrapolation of the findings to therapeutic interventions in humans.

Integrated Synthesis of the Findings

The synthesis of the 35 studies demonstrated a recurring molecular sequence. Aggregated proteins, toxins, genetic alterations, and metabolic failures impaired mitochondrial function and in-

creased the formation of reactive species. The redox imbalance activated NADPH oxidase, innate immunity receptors, NF-κB, and NLRP3. Activation of microglia and astrocytes amplified the release of cytokines, oxidants, and complement components, promoting synaptic loss and increased neuronal vulnerability.

Simultaneously, iron accumulation, glutathione depletion, and GPX4 deficiency promoted lipid peroxidation and ferroptosis. Activation of NRF2 had the opposite effect, expanding antioxidant defenses and modulating the inflammatory response. Thus, oxidative stress, neuroinflammation, and neural degeneration formed an interdependent system in which neuronal injury fueled new glial and oxidative responses, promoting progression of damage.

DISCUSSION

The results of this review demonstrated that oxidative stress, neuroinflammation, and neural degeneration constituted interdependent processes, organized into feedback circuits capable of transforming initially compensatory cellular changes into progressively neurotoxic responses. The convergence among human, animal, and cellular studies indicated that neurodegeneration did not result from a single molecular pathway, but from the interaction between mitochondrial dysfunction, altered calcium homeostasis, reactive species production, activation of innate immunity, glial reprogramming, synaptic loss, and regulated forms of cell death.

The identification of marked oxidative damage in the early stages of Alzheimer's disease strengthened the hypothesis that redox imbalance was not merely a terminal product of neuronal death[1]. This finding was relevant because amyloid plaques and neurofibrillary tangles, although characteristic of the disease, did not, on their own, explain the sequence of events that preceded functional loss. Greater oxidation of RNA and proteins in relatively preserved neurons suggested that metabolic and oxidative alterations had already been established before the consolidation of advanced neuropathological lesions.

However, the relative reduction of oxidative markers in later stages should

not be interpreted as a recovery of redox homeostasis. This reduction may reflect the selective loss of the most vulnerable neurons, activation of compensatory responses, or sequestration of reactive species and oxidized proteins in pathological structures. Postmortem studies also did not allow the chronology of events to be established in the same individual. Thus, human evidence supported temporal association and biological plausibility, but the causal inference depended mainly of the experimental.

Mitochondria emerged as a central element for integration. Its participation was not limited to the production of reactive species by the respiratory chain. Mitochondrial impairment affected ATP synthesis, calcium control, membrane integrity, death signaling, and the availability of metabolites used by antioxidant defenses. The presence of beta-amyloid associated with mitochondria and the reduction in cytochrome-c oxidase activity provided a link between protein aggregation, bioenergetic failure, and oxidative stress[2,3]. Similarly, PINK1 deficiency compromised mitochondrial calcium homeostasis and reduced the threshold required for opening of the permeability transition pore[9].

These results supported a model in which mitochondrial dysfunction acted simultaneously as an initiating and amplifying event. Reduced respiratory efficiency increased the formation of reactive species; these, in turn, oxidized proteins of the electron transport chain, mitochondrial DNA, and membrane lipids, worsening energetic failure. In neurons, which have a high metabolic demand and a prolonged axonal extension, the inability to maintain functional mitochondria in synaptic compartments may compromise neurotransmission before cell death.

The consistency of the PINK1–Parkin axis represented one of the most robust mechanistic lines of evidence from the review. Different studies showed that loss of mitochondrial membrane potential stabilized PINK1, promoted Parkin recruitment, and targeted the damaged organelle to mitophagy[4–6]. Loss of PINK1 produced structural and functional changes that were partially reduced by Parkin expression[7,8]. This sequence showed coherence across cellular, genetic, and animal models, strengthening the causal

relationship.

Despite this consistency, extrapolation to sporadic human diseases requires caution. Most experiments used intense pharmacological depolarization, protein overexpression, or genetic deletions. In age-related neurodegeneration, impaired mitophagy likely develops gradually and interacts with reduced mitochondrial biogenesis, lysosomal alterations, protein aggregation, and chronic inflammation. Thus, PINK1–Parkin axis dysfunction should be understood as part of a quality-control network rather than an exclusive explanation for all forms of dopaminergic degeneration.

The interaction between oxidative stress and innate immunity was supported through different pathways. Reactive species generated by mitochondria and NADPH oxidase acted not only as injurious agents, but also as regulatory signals for NF-κB and NLRP3. NADPH oxidase activation in astrocytes and microglia preceded glutathione reduction and neuronal death in different models[2,24]. The combination of rotenone with LPS showed that mitochondrial dysfunction and inflammation produced synergistic dopaminergic toxicity[25]. This finding was especially relevant for multifactorial models, in which genetic predisposition, environmental exposures, and systemic inflammation may converge on the same intracellular pathways.

The NLRP3 inflammasome occupied a prominent position in this circuit. The phagocytosis of fibrillar beta-amyloid caused lysosomal rupture and NLRP3 activation in microglia[13]. The absence of NLRP3 or caspase-1 reduced amyloid pathology and cognitive impairment in experimental models[10]. These results indicated that inflammasome activation did not occur only as an nonspecific response to damaged tissue, but functionally contributed to disease progression.

The relationship between NLRP3 and proteinopathy was bidirectional. Aggregated proteins activated the inflammasome, whereas ASC particles released by microglial cells accelerated beta-amyloid aggregation[12]. NLRP3 activation also intensified tau-related changes [11]. In experimental Parkinson's disease, inhibition of this pathway reduced α-synuclein aggregation and neuronal loss [28]. Thus, the inflammasome represented

a convergence point among different pathological proteins, although the magnitude of its contribution may vary depending on the disease and its stage of progression.

The therapeutic relevance of NLRP3 remained predominantly preclinical. Its prolonged inhibition may reduce pathological inflammation, but it can also interfere with defense against infections, tissue repair, and the clearance of cellular material. In addition, the benefits observed in animal models depended on the phase of the intervention. Early blockade of an inflammatory response that may be protective can yield results different from those obtained during chronic inflammation. Therefore, translation requires defining dose, selectivity, brain/systemic nervous system penetration, and the therapeutic window.

The analysis of glial states confirmed that neuroinflammation should not be interpreted as a uniformly harmful phenomenon. Microglia retained surveillance functions, protein clearance, plaque containment, and support for homeostasis. The identification of disease-

associated populations revealed a progressive transition, with loss of homeostatic genes and acquisition of TREM2-dependent programs[15]. The TREM2−APOE axis took part in this reprogramming[16], while TREM2-mediated recognition of lipids supported survival and microglial responses around the plaques [17].

These results demonstrated the limitations of binary classifications such as ύMl力 and ύM2力. The same pathway may exhibit protective or harmful functions depending on the timing, the brain region, the stimulus intensity, and the cell ′ s metabolic state. Microglia initially recruited to contain plaques and clear debris may, under persistent exposure, lose homeostatic functions and increase the production of oxidizing mediators. Likewise, indiscriminate microglia reduction may decrease neurotoxicity in certain models, but compromise essential functions in other contexts.

The dissociation between amyloid deposition and neuronal loss observed after CSFlR inhibition or microglial depletion reinforced this interpretation [19,20]. The reduction in neurodegeneration without a proportional change in Aβ burden indicated that the presence of plaques did not, on its own, determine the extent of neural damage. The tissue

response to plaques, including glial activation and synaptic alterations, showed comparable or greater importance for functional progression.

APOE4 added a genetic dimension to this interaction. Its expression intensified glial activation (gliosis) and tau-associated neurodegeneration[18]. This finding indicated that genetic risk factors can modify how glial cells respond to aggregated proteins. Rather than acting only on lipid metabolism or the clearance of beta-amyloid, APOE4 influenced the relationship among tau, inflammation, and neuronal loss. This observation supported an integrated interpretation of individual susceptibility, in which genetic variants modulate the response to damage.

Astrocytes also actively participated in the process. Exposure to IL-1α, TNF, and C1q produced by microglia induced astrocytic states associated with the loss of supportive functions and increased toxicity[14]. This result showed that microglial mediators can reprogram other glial populations and expand the injury. However, the original classification of these astrocytes as *ú*A1*"* should not be used as a universal category. Subsequent evidence demonstrated much greater functional diversity, with stimulus-, region-, and disease-phase–dependent states.

Complement-mediated synaptic loss constituted a particularly relevant mechanism at the early stages. The marking of synapses by C1q and C3 promoted their microglial elimination before extensive neuronal death[21]. In tauopathy, C1q blockade reduced synaptic loss[22]. These results provided an explanation for the emergence of functional deficits before advanced structural changes and suggested that physiological synaptic pruning mechanisms were improperly reactivated in the adult brain.

Therapeutic targeting of the complement, however, presents challenges similar to those observed for NLRP3. Inhibition may preserve vulnerable synapses, but it may also interfere with the removal of irreversibly damaged structures, immune defense, and the maintenance of homeostasis. Identifying synapses marked in a pathological manner and defining the phase in which blockade would be beneficial represent fundamental questions for translational research.

In synucleinopathy, TLR2 and TLR4 participated in the recognition of extrace-

llular α-synuclein[26,27]. The results suggested that the release of oligomers by neurons enabled the paracrine propagation of inflammatory signals. TLR2 was associated with the pro-inflammatory activation of microglia, whereas TLR4 showed functions related to both protein activation and clearance. This duality reinforced that innate immunity receptors cannot be classified as exclusively pathogenic.

Ferroptosis expanded the neuronal death model beyond apoptosis. Its characterization established a dependence on iron, depletion of glutathione, and the formation of lipid peroxides as central elements[29]. In dopaminergic neurons, iron chelators and ferroptosis inhibitors reduced cell death[30]. Neuronal deletion of GPX4 caused hippocampal degeneration and cognitive impairment[31], providing causal evidence that loss of defense against lipid peroxides may be sufficient to trigger neurodegeneration.

Nevertheless, identifying ferroptosis in human tissues remains complex. There is no single isolated marker capable of definitively distinguishing it from other forms of oxidative cell death. Changes such as iron accumulation, glutathione reduction, decreased GPX4, and lipid peroxidation are consistent with ferroptosis but may occur in different pathological processes. Assigning this mechanism requires combining morphological, biochemical, and functional alterations, ideally accompanied by rescue with specific inhibitors. For this reason, the strength of the evidence was greater in experimental models than in human diseases.

NRF2 signaling was presented as a counterpoint to oxidative and inflammatory mechanisms. Deficiency of NRF2 worsened dopaminergic injury, glial activation, and the expression of inflammatory mediators[32]. In Alzheimer's models, its absence increased Aβ, tau phosphorylation, oxidative stress, and cognitive impairment[33]. Pharmacological activation of NRF2 and stimulation of the microglial α7–NRF2–HO-1 axis produced neuroprotective effects[34,35].

These results indicated that NRF2 did not act only as a regulator of antioxidant enzymes. The pathway influenced glutathione metabolism, detoxification, mitochondrial function, and the inflammatory state of glial cells. Thus, it

showed potential to simultaneously interrupt different components of the neurotoxic circuit. However, chronic and systemic activation of NRF2 may produce different effects depending on the cell type, the disease stage, and the presence of comorbidities. Most interventions were also administered before or shortly after the experimental injury, a condition distinct from the treatment of established human diseases.

Integrated synthesis allowed proposing a model in which genetic alterations, aggregated proteins, toxins, and metabolic disturbances converged on mitochondrial function. The increase in reactive species activated inflammatory pathways, while the glial response intensified redox imbalance. The complement promoted synaptic loss, and the combination of iron, lipid peroxidation, and reduced antioxidant defenses favored ferroptosis. Neuronal death released new damage-associated signals, restarting and amplifying the circuit.

From a translational standpoint, the results suggested that interventions targeting a single mediator may show limited efficacy in diseases characterized by redundant and interdependent networks. Isolated inhibition of a cytokine, for example, may not correct mitochondrial dysfunction or ferroptosis. Combined strategies or interventions directed at convergence points, such as NRF2, NLRP3, mitochondrial quality control, and lipid metabolism, showed a stronger biological rationale. Still, excessive modulation of these pathways may compromise physiological defense, repair, and adaptation mechanisms.

The review presented limitations. The first was the predominance of preclinical studies, which reduced the ability to infer therapeutic efficacy in humans. The second was heterogeneity across species, cell types, aggregated proteins, toxins, genetic manipulations, and measurement methods. The third corresponded to incomplete reporting of randomization, blinding, and sample size calculation in part of the animal studies. In cellular experiments, high concentrations and acute exposures may have produced more intense responses than those observed in human diseases.

The inclusion of models of cerebral ischemia broadened the understanding of the general mechanisms of neural injury, especially the NRF2 pathway, but it also

increased clinical heterogeneity. Acute ischemia has a temporal dynamics profile different from that observed in Alzheimer's and Parkinson's diseases. Their results were interpreted as mechanistic evidence on oxidative stress and neuroprotection, rather than as direct replication of chronic neurodegenerative diseases.

Another limitation was the inability to combine quantitatively the results. The diversity of models, markers, and effect measures prevented a methodologically appropriate meta-analysis. The qualitative synthesis made it possible to identify convergences, but it did not estimate the relative magnitude of each mechanism. In addition, the literature may present publication bias in favor of experiments with positive results.

Despite these limitations, convergence among genetic manipulations, pharmacological interventions, animal models, and observations in human tissues provided plausibility to the integrated model. The most consistent findings involved mitochondrial dysfunction, PINK 1–Parkin mitophagy, NLRP3 activation, glial reprogramming, complement-mediated synaptic loss, GPX4-associated ferroptosis, and NRF2-mediated antioxidant response.

Subsequent studies should prioritize human-relevant models with higher physiological validity, such as neurons and glial cells derived from human pluripotent stem cells, organoids, multicellular co-cultures, and spatial or single-cell studies in human tissues. Longitudinal studies are also needed to determine the sequence linking oxidative stress, glial activation, and neuronal loss. The identification of biomarkers that simultaneously reflect the redox state, inflammasome activity, mitochondrial function, and lipid peroxidation could support patient stratification and the definition of therapeutic windows.

In summary, the discussion of the studies showed that neural degeneration emerged from the progressive failure of cellular maintenance systems and the transformation of initially adaptive responses into chronic injury processes. Integration of mitochondrial metabolism, redox signaling, innate immunity, and regulated cell death provided a more comprehensive framework for understanding neurotoxicity and indicated that neural preservation depends on restoring

the balance between damage generation, antioxidant defense, cellular clearance, and resolution of inflammation.

CONCLUSION

This systematic review showed that oxidative stress, neuroinflammation, and neural degeneration constitute molecularly interdependent processes. The convergence of evidence indicated that genetic alterations, aggregated proteins, toxins, and metabolic disorders impair mitochondrial function, increase the formation of reactive species, and activate innate immunity mechanisms. The persistence of these alterations promotes synaptic dysfunction, loss of glial homeostasis, and progressive neuronal death.

Mitochondrial dysfunction and defective PINKl–Parkin–mediated mitophagy showed consistent experimental evidence, especially in models of dopaminergic degeneration. The accumulation of damaged mitochondria intensified redox imbalance, impaired energy production, and increased vulnerability to calcium overload and activation of cell death pathways.

Neuroinflammation did not exhibit an exclusively harmful nature. Microglia and astrocytes performed surveillance, debris clearance, and damage containment functions, but persistent activation altered their homeostatic programs and increased the production of cytokines, reactive species, and complement components. In this context, NLRP3 served as a convergence point between beta-amyloid, tau, α-synuclein, and the inflammatory response, while complement activation contributed to the pathological elimination of synapses.

Ferroptosis emerged as a relevant mechanism of neuronal death, associated with iron accumulation, glutathione depletion, GPX4 deficiency, and lipid peroxidation. However, direct evidence in humans remained limited, requiring more specific marker combinations to distinguish it from other forms of oxidative cell death. In contrast, NRF2 showed an integrative role in maintaining antioxidant defenses, regulating glutathione, and modulating the glial response.

Although mechanistic consistency was high in experimental models, the predominance of cellular and animal studies limited direct extrapolation to

clinical practice. Differences between species, acute exposures, extensive genetic manipulations, and heterogeneity of outcomes constrained estimates of the relative contribution of each pathway in human diseases.

It has been concluded that neurotoxicity results from a dynamic network in which mitochondrial dysfunction, oxidative stress, neuroinflammation, synaptic loss, and regulated cell death mutually amplify one another. This interdependence suggests that interventions targeting only a single mediator may have limited efficacy. Strategies capable of preserving mitochondrial function, restoring redox homeostasis, selectively modulating the glial response, and preventing lipid peroxidation have greater biological rationale, but they depend on clinical validation and the definition of safe therapeutic windows.

The advancement of this field requires greater integration among human models, longitudinal analyses, single-cell technologies, and biomarkers capable of simultaneously tracking mitochondrial function, redox status, inflammatory activity, and neuronal death. This approach could transform the knowledge mechanistic into into instruments for stratification, prevention, and treatment of diseases associated with neural degeneration.

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