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Commentary on "Pathophysiology and Therapeutic Perspectives of Oxidative Stress and Neurodegenerative Diseases: A Narrative Review"

Giustino Varrassi[1,2], Y Van Tran[1,3], Phong Van Pham[1,3], Giacomo Farì[1,4], Martina Rekatsina[5], Eleni Moka[6] and Matteo Luigi Giuseppe Leoni[1,7]

[1]VIBRA Group, Fondazione Paolo Procacci, 00193 Rome, Italy
[2]College of Medicine, University of Baghdad, Baghdad, Iraq
[3]Department of Biomedical Engineering, International University, Vietnam National University, 700000 Ho Chi Minh City, Vietnam
[4]Department of Experimental Medicine (Di.Me.S.), University of Salento, Lecce, Italy.
[5]First Department of Anaesthesiology, Aretaieion Hospital, University of Athens School of Medicine, Vassilissis Sofias 76, 11528, Athens, Greece
[6]Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
[7]Department of Medical and Surgical Sciences and Translational Medicine, Sapienza University of Rome, Rome, Italy.

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***Correspondence:**
Giustino Varrassi, VIBRA Group, Fondazione Paolo Procacci, 00193 Rome, Italy; Mobile: +39 348 6068472;
Email: giuvarr@gmail.com

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The review *Pathophysiology and Therapeutic Perspectives of Oxidative Stress and Neurodegenerative Diseases*, offered an ambitious and clinically relevant synthesis of a topic that remains among the most urgent challenges of contemporary medicine.[1] Its central message is clear: neurodegenerative disorders, despite their heterogeneous clinical phenotypes, share convergent biological mechanisms, particularly oxidative stress, mitochondrial dysfunction, neuroinflammation, glial activation and impaired cellular resilience. This concept is important because it shifts attention from disease labels alone toward common pathogenetic pathways that may be therapeutically modifiable.

In this commentary we argue that the review's principal value is conceptual rather than prescriptive. It provides a persuasive map of shared mechanisms, but the gap between biological plausibility and clinical proof is precisely where the field's translational responsibility now lies and where this commentary concentrates its critique.

The demographic premise of the article remains fascinating. Population aging is transforming neurodegenerative diseases from a specialist concern into a major public-health priority. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, prion disorders, spinal muscular atrophy and related conditions differ substantially in clinical expression, genetic architecture and anatomical vulnerability.[2] Yet all involve progressive neuronal or glial dysfunction and functional decline, and current options remain largely symptomatic rather than disease-modifying.

Against this backdrop, the effort to identify convergent inflammatory and oxidative pathways across neurodegenerative disorders is both scientifically compelling and clinically relevant. Among the most notable strengths of the review is its integrative conceptual framework, which portrays oxidative stress and inflammation not as independent pathological phenomena, but as intricately interconnected and self-perpetuating processes. By emphasizing the dynamic bidirectional interplay between redox imbalance and neuroinflammatory signaling, the authors provide a coherent mechanistic perspective that may help

explain the progressive nature of neuronal injury across diverse neurodegenerative conditions. This systems-level approach represents a significant advance over reductionist models and offers a valuable foundation for the development of mechanism-based therapeutic strategies.[1] The review conceptualizes reactive oxygen species generation, mitochondrial dysfunction, lipid peroxidation, impaired endogenous antioxidant defenses, protein misfolding, glial activation, pro-inflammatory cytokine release, blood-brain barrier disruption, and neuronal injury as interconnected components of a highly integrated and self-perpetuating pathogenic network. Within this framework, neurodegeneration is not depicted as the consequence of a linear cascade of molecular events, but rather as the manifestation of a progressive systems-level failure. Mitochondrial dysfunction, oxidative damage, and neuroinflammatory signaling engage in a complex bidirectional interplay, each amplifying the others and driving a vicious cycle of cellular dysfunction. Simultaneously, chronically activated microglia and astrocytes sustain a maladaptive neuroimmune response that progressively compromises neuronal integrity, disrupts synaptic homeostasis, and accelerates the deterioration of neural networks. This perspective offers a compelling mechanistic explanation for the relentless progression and multifactorial nature of neurodegenerative diseases.[3] This convergent, self-amplifying framework is summarized in Figure 1, which illustrates how heterogeneous neurodegenerative phenotypes may share a neuroimmune-redox-mitochondrial axis while emphasizing that therapeutic translation requires biomarker-stratified validation rather than extrapolation from mechanistic plausibility alone.

Equally noteworthy is the review's nuanced and biologically accurate portrayal of microglial function. Rather than depicting microglia as inherently deleterious, the authors appropriately emphasize their indispensable roles in central nervous system homeostasis, including immune surveillance, synaptic remodeling, clearance of cellular debris, and neurotrophic support.[4] The

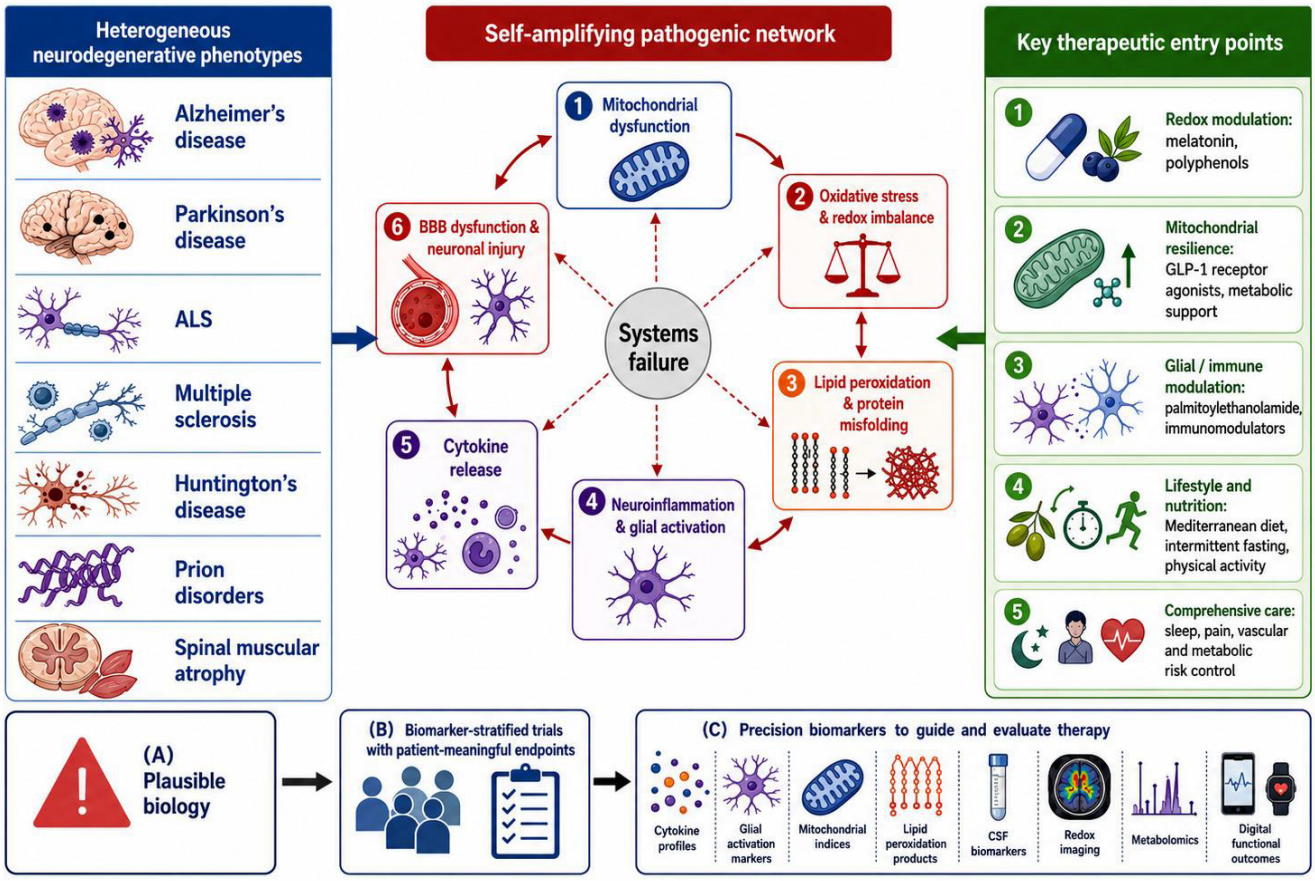

Figure 1 – Convergent neuroimmune-redox-mitochondrial network in neurodegenerative diseases. Clinically heterogeneous neurodegenerative disorders may converge on a self-amplifying pathogenic network involving mitochondrial dysfunction, redox imbalance, lipid peroxidation, protein misfolding, glial activation, neuroinflammation, blood-brain barrier dysfunction, and neuronal injury. Candidate therapeutic strategies may target several of these biological nodes. However, mechanistic plausibility should not be equated with demonstrated clinical efficacy. Translation requires biomarker-stratified trials, biological response assessment, and patient-meaningful endpoints.

pathological transition arises not from microglial activation per se, but from the loss of its physiological regulation and timely resolution. In the aging or diseased brain, persistent, excessive, or maladaptive activation can transform an initially protective response into a potent driver of neurodegeneration, fostering sustained neuroinflammation, synaptic dysfunction, and progressive neuronal loss.[5] This critical distinction between physiological neuroimmune surveillance and chronic, self-sustaining inflammatory activation represents one of the most important conceptual advances in contemporary neurobiology. It also provides a compelling rationale for targeting inflammatory pathways therapeutically, not merely as epiphenomena or biomarkers of tissue injury, but as active contributors to disease initiation and progression.

The importance of mitochondria is equally well grounded. Mitochondria are both sources and targets of oxidative injury, and their central role in energy metabolism and redox signaling makes them especially vulnerable in neurons, which are energy-dependent and difficult to replace.[6] The review correctly notes that mitochondrial DNA is particularly susceptible to oxidative damage and that age-related mitochondrial decline may sensitize the aging nervous system. This perspective strengthens the article's translational value, since many emerging interventions aim to restore mitochondrial resilience rather than merely suppress symptoms.

Another notable strength of the review is the breadth and ambition of its therapeutic perspective. This expansive outlook accurately reflects the current state of the field, where the multifactorial nature of neurodegenerative diseases increasingly argues against single-target approaches. Instead, interventions capable of modulating multiple interconnected pathogenic pathways simultaneously [such as palmitoyl-ethanol-amide (PEA), melatonin, curcumin, omega-3 fatty acids, GLP-1 receptor agonists, and mitochondria-targeted therapeutics] have attracted considerable interest because of their potential to influence oxidative stress, neuroinflammation, mitochondrial dysfunction, and neuroimmune signaling in parallel.[7]

Importantly, the level of evidence supporting these interventions varies considerably. For compounds such as curcumin, melatonin, and several mitochondria-targeted antioxidants, the available evidence remains predominantly preclinical, with encouraging findings derived largely from cellular and animal models. Omega-3 fatty acids have been evaluated in both experimental and early clinical studies, although definitive disease-modifying effects have not been established. PEA has accumulated a growing body of clinical evidence in selected pain and neuroinflammatory conditions, but evidence supporting its use in neurodegenerative diseases remains preliminary. Among the therapeutic candidates discussed, GLP-1 receptor agonists currently possess the most advanced translational profile, with early clinical studies and ongoing trials suggesting potential neuroprotective effects, although their role in routine neurodegenerative disease management remains to be fully defined.

However, the same breadth that makes the review intellectually stimulating also constitutes one of its principal limitations. The therapeutic landscape presented encompasses interventions supported by markedly different levels of evidence, ranging from dietary strategies, nutraceuticals, and in vitro observations to animal-model studies, repurposed pharmacological agents, and emerging biological therapies. While this diversity provides a comprehensive overview of ongoing research efforts, it also raises important concerns regarding the interpretation of translational relevance. Mechanistic efficacy demonstrated in experimental systems, however promising, should not be considered equivalent to evidence derived from rigorously conducted human clinical trials with adequate statistical power and clinically meaningful outcomes. Maintaining this distinction is essential to avoid conflating biological plausibility with therapeutic effectiveness and to ensure that enthusiasm remains grounded in the hierarchy of clinical evidence.

The historical experience with antioxidant therapies provides a particularly instructive illustration of this challenge. Far from being a merely theoretical concern, the translational gap between mechanistic plausibility and clinical efficacy has repeatedly emerged as one of the most persistent obstacles in neurodegenerative research. High-dose vitamin E, despite decades of compelling biological rationale centered on the mitigation of oxidative stress, failed to demonstrate consistent cognitive benefits in patients with Alzheimer's disease;[8,9] while meta-analytic evidence raised concerns regarding increased all-cause mortality at higher dosages.[10] Comparable disappointments have been observed with coenzyme Q10 and creatine in Parkinson's disease, [11,12] as well as with a variety of antioxidant-based interventions investigated in amyotrophic lateral sclerosis.[13] Collectively, these experiences underscore a recurring lesson in translational neuroscience: robust mechanistic foundations, although indispensable for therapeutic innovation, do not guarantee meaningful clinical benefit. In each instance, interventions supported by persuasive experimental evidence ultimately failed to demonstrate efficacy when subjected to the scrutiny of adequately powered clinical trials and clinically relevant outcome measures. These findings serve as a reminder that biological plausibility must be regarded as the starting point, not the endpoint, of therapeutic validation.

The most important message emerging from this review is

therefore one of scientific prudence: biological plausibility should not be mistaken for clinical validation. This distinction is particularly relevant in the field of neurodegeneration, where the translational pathway from mechanistic insight to effective therapy has repeatedly proven far more complex than initially anticipated. Experimental models (including amyloid-based, toxin-induced, transgenic, and inflammation-driven paradigms) have been invaluable for elucidating pathogenic mechanisms and identifying potential therapeutic targets.[14] Nevertheless, these models inevitably reproduce only selected aspects of human disease and cannot fully capture the extraordinary biological complexity of neurodegenerative disorders as they occur in clinical practice. Human neurodegeneration unfolds over decades and is shaped by a dynamic interplay of aging, multimorbidity, polypharmacy, frailty, vascular and metabolic dysfunction, as well as profound genetic, epigenetic, and environmental heterogeneity. Consequently, therapeutic efficacy observed in experimental systems cannot be assumed to translate directly into meaningful clinical benefit. The review should therefore be regarded primarily as a sophisticated and insightful framework for understanding pathogenic mechanisms and prioritizing therapeutic candidates, rather than as evidence that the interventions discussed are ready for implementation in routine clinical care.

Another significant contribution of this review lies in its implicit challenge to the traditional reductionist paradigm that has long dominated neurodegenerative disease research. For decades, investigative efforts have largely centered on disease-defining pathological hallmarks, including amyloid-β and tau accumulation in Alzheimer's disease, α-synuclein aggregation in Parkinson's disease, SOD1 and TDP-43 pathology in amyotrophic lateral sclerosis, demyelinating processes in multiple sclerosis, and mutant huntingtin aggregation in Huntington's disease. While these molecular signatures remain fundamental to understanding disease-specific pathogenesis, the review compellingly argues that oxidative stress, mitochondrial dysfunction, neuroinflammation, and glial dysregulation may constitute convergent downstream pathways shared across otherwise distinct neurodegenerative conditions. This broader perspective carries important therapeutic implications, suggesting that future treatment strategies may need to integrate disease-specific approaches with interventions targeting common mechanisms of cellular resilience, neuroimmune regulation, metabolic homeostasis, and tissue protection.[15]

Within this context, the discussion of PEA is particularly noteworthy. Through its actions on peroxisome proliferator-activated receptor-α (PPAR-α) and related signaling pathways, PEA occupies a unique position at the intersection of neuroinflammation, glial and mast-cell modulation, pain physiology, and neuroprotection.[16] Such pleiotropic activity makes it an intriguing candidate not only for neurodegenerative disorders themselves but also for the chronic pain states, neuroimmune sensitization, sleep disturbances, fatigue, and cognitive symptoms that frequently accompany these conditions. By modulating inflammatory and neuroimmune processes, PEA could theoretically influence overall symptom burden and quality of life in addition to disease-related biological pathways.

Nevertheless, PEA should be evaluated according to the same rigorous standards applied to all emerging therapeutic candidates. Although its mechanistic rationale is compelling and its efficacy in selected chronic pain conditions is increasingly supported by clinical evidence, these observations cannot yet be extrapolated to claims of disease modification in neurodegenerative disorders. At present, PEA should be regarded as a promising and biologically plausible hypothesis-generating intervention whose ultimate clinical value remains to be established through robust, adequately powered translational and clinical studies.

The review's inclusion of lifestyle- and nutrition-based interventions represents another important strength, reflecting an increasingly recognized dimension of neurodegenerative disease prevention and management. Rather than portraying these approaches as curative therapies, the authors appropriately frame interventions such as the Mediterranean diet, extra-virgin olive oil consumption, intermittent fasting, omega-3 fatty acid supplementation, and antioxidant-rich dietary patterns as modulators of the biological processes that underpin oxidative stress, chronic inflammation, metabolic dysfunction, and cellular resilience.[17] This perspective is particularly relevant given the prolonged and often decades-long preclinical evolution of neurodegenerative disorders, during which preventive and disease-delaying strategies may prove as consequential as interventions directed at established pathology. Importantly, the potential value of these lifestyle measures extends beyond their direct effects on neurobiological pathways. Many neurodegenerative diseases coexist with cardiovascular, metabolic, and systemic inflammatory comorbidities, all of which contribute to disease progression and functional decline. In this context, nutritional and lifestyle interventions may offer meaningful benefits through the optimization of vascular health, metabolic regulation, and systemic homeostasis. Although such approaches are unlikely to replace pharmacological therapies, they may represent valuable components of a multidimensional care strategy aimed at reducing risk, preserving function, and improving long-term outcomes, particularly among older adults with multimorbidity and complex clinical needs.

Nevertheless, caution is warranted against overly

simplistic "antioxidant" paradigms. Oxidative stress is not merely the accumulation of harmful reactive species amenable to indiscriminate neutralization; reactive oxygen species also play essential roles in physiological cellular signaling and homeostasis.[18] Consequently, broad suppression of redox pathways may prove ineffective or, under certain circumstances, detrimental. Furthermore, antioxidant compounds differ substantially in their bioavailability, tissue distribution, mitochondrial targeting, pharmacological properties, and clinical effects. The repeated failure of antioxidant-based clinical trials highlights a critical principle: the central question is no longer whether oxidative stress contributes to neurodegeneration, but rather when, where, and in whom redox modulation may translate into meaningful therapeutic benefit.[19]

The narrative nature of the review is well suited to hypothesis generation but inevitably limits the strength of its therapeutic conclusions. A more structured evaluation of methodological quality, translational maturity, and clinical endpoint relevance would have strengthened the interpretative framework. Future reviews should clearly differentiate mechanistic plausibility, preclinical efficacy, preliminary clinical signals, and established therapeutic benefit, thereby enabling readers to appreciate emerging scientific advances without overextending their clinical implications.

From a clinical standpoint, the most valuable contribution of this work is not the endorsement of any individual intervention, but its reconceptualization of neurodegeneration as a dynamic neuroimmune-metabolic disorder. Such a perspective supports a more integrated model of care that combines disease-modifying strategies with optimization of vascular and metabolic health, nutrition, physical activity, sleep quality, pain management, and medication stewardship.[20] Equally important is the development of biomarker-driven approaches capable of identifying those patients in whom oxidative stress and neuroinflammatory processes are active contributors to disease progression and therefore represent meaningful therapeutic targets.

The future of this field will depend on the successful transition from broad biological concepts to precision medicine. Terms such as "neuroinflammation" and "oxidative stress" must be translated into quantifiable and clinically actionable biomarkers, including cytokine profiles, markers of glial activation, indices of mitochondrial dysfunction, lipid peroxidation products, advanced redox imaging modalities, and cerebrospinal fluid signatures.[21,22] Without such biological stratification, clinical trials risk enrolling heterogeneous patient populations, thereby obscuring genuine therapeutic effects. Ultimately, progress will depend on identifying the right intervention for the right biological phenotype at the appropriate stage of disease, transforming mechanistic insight into truly personalized therapeutic strategies.

Several priorities should guide future research in this rapidly evolving field. First, greater emphasis should be placed on the development and validation of robust biomarkers capable of quantifying oxidative stress, neuroinflammation, and mitochondrial dysfunction in vivo. Second, longitudinal studies are needed to clarify the temporal relationship between these biological processes and clinical disease progression. Third, therapeutic investigations should increasingly incorporate biomarker-based patient stratification to identify individuals most likely to benefit from targeted interventions. Finally, greater integration of molecular biomarkers, advanced neuroimaging, retinal imaging, and digital clinical outcomes may facilitate the transition from broadly targeted antioxidant approaches toward precision-medicine strategies capable of addressing the biological heterogeneity that characterizes neurodegenerative disorders.

In conclusion, the review by Rekatsina et al.[1] compellingly highlights a paradigm-shifting concept in modern neuroscience: seemingly distinct neurodegenerative disorders may ultimately converge through common pathways of oxidative stress, neuroinflammation, mitochondrial failure, and glial dysregulation. By integrating these mechanisms into a unified neuroimmune-metabolic framework, the authors challenge the traditional view of neurodegeneration as a collection of isolated proteinopathies and instead propose a dynamic, potentially modifiable biological network. This perspective is both intellectually provocative and clinically relevant. Nevertheless, despite the therapeutic enthusiasm surrounding antioxidant and immunomodulatory strategies, most candidate interventions remain distant from robust clinical validation. The disappointing history of antioxidant trials serves as a critical reminder that mechanistic plausibility alone rarely translates into meaningful patient benefit. Therefore, this review should be interpreted not as a clinical guideline, but as a translational roadmap capable of redefining future research priorities. Its true impact will depend on the development of biomarker-driven, patient-centered clinical trials able to transform experimental promise into tangible therapeutic advances.

Conflict of Interest

The authors declare that they have no competing interests relevant to the content of this article.

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