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Role of Neuroprotective Agents in Modulating Excitotoxicity in Huntington's Disease: a Translational Experimental Analysis

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Abstract: *Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by selective striatal neuronal loss, motor impairment, cognitive decline, and psychiatric disturbances. A central driver of neuronal vulnerability in HD is excitotoxicity, wherein excessive glutamatergic signaling induces pathological activation of NMDA receptors, intracellular calcium overload, mitochondrial dysfunction, and oxidative stress–mediated cell death. Although symptomatic treatments exist, disease-modifying strategies remain limited. Neuroprotective interventions targeting excitotoxic cascades therefore represent a critical therapeutic priority.*

The present investigation adopts a structured translational analytical framework to evaluate the mechanistic and functional efficacy of neuroprotective agents across experimental platforms. Preclinical evidence from in vitro neuronal systems and in vivo transgenic HD models was systematically mapped onto defined biological domains, including calcium homeostasis, mitochondrial stabilization, redox modulation, gene-silencing strategies, and neurotrophic support. Clinical trials were comparatively examined to assess translational consistency between mechanistic endpoints and functional outcomes.

Findings indicate that NMDA receptor modulators, mitochondrial stabilizers, antioxidants, and gene-targeted therapies demonstrate reproducible attenuation of excitotoxic injury in controlled experimental settings. However, clinical translation remains constrained by pharmacokinetic limitations, disease-stage variability, and challenges in central nervous system delivery. The analysis underscores that multimodal neuroprotective strategies may offer greater therapeutic promise than single-agent approaches. By integrating mechanistic and translational evidence, this study provides a structured perspective on advancing neuroprotection as a disease-modifying paradigm in Huntington's disease.

Keywords: *Huntington's disease; excitotoxicity; neuroprotection; NMDA receptor; mitochondrial dysfunction; oxidative stress; gene-silencing therapy; translational neuroscience; neurodegeneration*

I. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by expansion of CAG trinucleotide repeats in the huntingtin (HTT) gene, resulting in production of a mutant huntingtin protein with toxic gain-of-function properties. Clinically, HD manifests through progressive choreiform movements, cognitive deterioration, and psychiatric disturbances, typically emerging in mid-adulthood. Neuropathologically, the disorder is characterized by selective degeneration of GABAergic medium spiny neurons in the striatum, accompanied by cortical atrophy and widespread network disruption.

Among the molecular mechanisms implicated in HD, excitotoxicity has emerged as a central contributor to neuronal vulnerability. Excessive glutamatergic transmission leads to pathological overactivation of NMDA receptors, sustained calcium influx, mitochondrial depolarization, and activation of apoptotic and necrotic signaling cascades. Unlike purely protein-aggregation–driven neurodegenerative disorders, HD pathology involves a convergence of mutant protein toxicity with heightened excitatory signaling, thereby amplifying neuronal stress. This dual burden renders striatal neurons particularly susceptible to excitotoxic injury.

Given this mechanistic framework, neuroprotective strategies aimed at modulating excitotoxic pathways have gained substantial attention. Pharmacological modulation of glutamate signaling, stabilization of mitochondrial bioenergetics, attenuation of oxidative stress, gene-silencing approaches targeting mutant huntingtin, and trophic factor supplementation collectively represent attempts to preserve neuronal integrity despite underlying genetic pathology.

The present study adopts a structured translational analytical approach to evaluate how neuroprotective interventions influence excitotoxic mechanisms across experimental hierarchies. Rather than presenting a purely descriptive account, this investigation integrates mechanistic findings from cellular systems, animal models, and clinical trials to assess translational coherence and therapeutic feasibility. Through this framework, the study aims to clarify whether modulation of excitotoxicity can realistically alter disease trajectory in Huntington's disease.

Mechanistic and Experimental Background

The conceptual foundation for neuroprotective intervention in Huntington's disease is rooted in the established role of excitotoxicity as a driver of selective striatal degeneration. Experimental investigations over several decades have demonstrated that excessive activation of glutamate receptors—particularly NMDA receptors—initiates a cascade of intracellular events culminating in neuronal dysfunction and death. These events include sustained calcium influx, disruption of mitochondrial membrane potential, increased generation of reactive oxygen species (ROS), and activation of apoptotic signaling pathways. In HD models, mutant huntingtin protein further sensitizes neurons to excitotoxic stress, thereby lowering the threshold for calcium-induced injury.

Early pharmacological investigations focused on modulating glutamate receptor activity. Low-affinity NMDA receptor antagonists were designed to preferentially inhibit pathological receptor overactivation while preserving physiological synaptic transmission. In transgenic mouse models of HD, such modulation resulted in measurable reductions in striatal neuronal loss and delayed onset of motor impairment. However, differential receptor subunit expression, receptor localization (synaptic versus extrasynaptic), and dose-dependent effects introduced complexity into therapeutic application. These findings underscored the importance of precisely calibrated receptor modulation rather than complete inhibition.

Parallel experimental work highlighted mitochondrial dysfunction as a critical amplifier of excitotoxic injury. HD neurons exhibit compromised energy metabolism, reduced ATP availability, and increased vulnerability to calcium overload. Under sustained glutamatergic stimulation, mitochondrial depolarization and impaired oxidative phosphorylation exacerbate ROS production, accelerating neuronal damage. Compounds targeting mitochondrial stabilization—such as creatine and coenzyme Q10—demonstrated improved bioenergetic profiles and partial preservation of neuronal integrity in preclinical models. Although these interventions showed promise in controlled laboratory conditions, translation into consistent clinical benefit proved more challenging.

Oxidative stress has also been extensively examined as a mediator linking excitotoxicity and cellular degeneration. Excess intracellular calcium stimulates enzymatic pathways that enhance free radical production, leading to lipid peroxidation, DNA damage, and protein oxidation. Antioxidant strategies, including naturally derived polyphenols and synthetic redox modulators, were therefore investigated for their capacity to interrupt this feed-forward injury loop. Experimental evidence suggests that certain compounds provide dual benefits—attenuating oxidative burden while indirectly stabilizing mitochondrial function. Nevertheless, variability in absorption, metabolism, and blood–brain barrier penetration has limited reproducibility in human populations.

More recently, gene-targeted approaches have shifted focus upstream of excitotoxic cascades. By reducing mutant huntingtin expression through antisense oligonucleotides or RNA interference strategies, investigators aim to mitigate cellular vulnerability before excitotoxic thresholds are reached. Preclinical data indicate that lowering toxic protein burden improves neuronal resilience and reduces sensitivity to glutamate-induced stress. Complementary research into trophic factor supplementation—particularly brain-derived neurotrophic factor (BDNF)—further supports this strategy, as BDNF signaling enhances synaptic stability and promotes neuronal survival pathways compromised in HD.

Collectively, experimental findings suggest that excitotoxicity in Huntington's disease is not an isolated phenomenon but rather an integrative node where glutamatergic dysregulation, mitochondrial impairment, oxidative stress, and genetic toxicity converge. This convergence explains why single-agent interventions often produce limited clinical benefit, whereas multi-modal approaches demonstrate greater neuroprotective potential in laboratory settings. The mechanistic background therefore provides a rationale for structured translational analysis aimed at identifying interventions capable of producing durable clinical impact.

Research Design and Experimental Analytical Framework

The present investigation was structured as a translational experimental analysis aimed at evaluating the capacity of neuroprotective agents to modulate excitotoxic mechanisms in Huntington's disease. Rather than functioning solely as a narrative review, the study implemented a domain-based analytical framework that systematically mapped mechanistic and functional outcomes across experimental hierarchies.

Studies were selected based on explicit investigation of glutamate-mediated neurotoxicity and quantifiable neuroprotective endpoints. Eligible experimental reports were required to demonstrate measurable alterations in intracellular calcium dynamics, mitochondrial membrane potential, oxidative stress burden, neuronal survival indices, or behavioral performance outcomes in validated HD models. Both in vitro neuronal systems and in vivo transgenic or toxin-induced models were incorporated to ensure mechanistic reproducibility. Interventions were categorized into defined experimental domains:

1. NMDA receptor modulation
2. Glutamate release inhibition

3. Mitochondrial bioenergetic stabilization
4. Redox and antioxidant modulation
5. Gene-silencing and trophic factor–based neuroprotection

A comparative analytical matrix was constructed to examine convergence between molecular-level outcomes and functional readouts. Cellular studies were assessed for modulation of calcium influx, ROS generation, and apoptotic signaling. Animal models were evaluated for neuronal preservation metrics, striatal structural integrity, and motor coordination performance. Clinical investigations were comparatively reviewed to determine consistency between mechanistic biomarkers and observed therapeutic benefit.

To strengthen translational interpretation, the analysis incorporated three evaluative parameters:

- Reproducibility of mechanistic effects across experimental systems
- Pharmacokinetic feasibility and central nervous system delivery potential
- Alignment between biochemical modulation and clinical outcome measures

Studies lacking methodological clarity, reproducibility, or ethical validation were excluded to maintain analytical rigor. This structured design enabled systematic evaluation of excitotoxic modulation strategies while identifying translational constraints limiting clinical efficacy in Huntington's disease.

Preclinical Evidence and Experimental Insights

Application of the structured analytical framework to preclinical investigations reveals consistent modulation of excitotoxic mechanisms across validated Huntington's disease models. Experimental data derived from transgenic mouse models—particularly R6/2 and knock-in strains—demonstrate pronounced vulnerability of striatal medium spiny neurons under sustained glutamatergic stimulation. Within these systems, neuroprotective interventions targeting NMDA receptor activity resulted in measurable attenuation of neuronal degeneration and delayed emergence of motor deficits.

In receptor-focused studies, low-affinity NMDA antagonists selectively reduced pathological receptor overactivation without abolishing physiological synaptic transmission. Quantifiable outcomes included decreased calcium influx, preservation of mitochondrial membrane integrity, and reduction in caspase-mediated apoptotic signaling. Behavioral assays, such as rotarod performance and open-field testing, further indicated partial functional preservation in treated animals compared with untreated controls. These findings support the premise that excitotoxic modulation yields both molecular and phenotypic benefit under controlled laboratory conditions.

Mitochondrial-targeted interventions similarly demonstrated reproducible effects. Agents such as creatine and coenzyme Q10 enhanced ATP stability and mitigated calcium-induced mitochondrial depolarization in HD models. Biochemical assays revealed reduced oxidative stress markers and improved cellular bioenergetic profiles. Importantly, motor coordination measures in treated rodents exhibited modest but consistent improvement, suggesting that stabilization of mitochondrial function translates into functional resilience.

Antioxidant and redox-modulating compounds provided an additional layer of neuroprotection. Experimental systems exposed to glutamate toxicity showed reduced reactive oxygen species accumulation and attenuated lipid peroxidation following administration of polyphenolic agents. These interventions appeared to interrupt the amplification loop between oxidative stress and excitotoxic signaling. Although the magnitude of neuroprotection varied between compounds, cross-model reproducibility was observed in cellular survival indices.

Emerging gene-targeted approaches have extended preclinical insight further upstream of excitotoxic cascades. Antisense oligonucleotide–mediated reduction of mutant huntingtin expression in animal models resulted in decreased neuronal sensitivity to glutamate-induced stress. Similarly, trophic factor–based interventions enhancing brain-derived neurotrophic factor (BDNF) signaling improved synaptic stability and increased neuronal survival thresholds. Such strategies suggest that modifying intrinsic cellular vulnerability may complement downstream excitotoxic modulation.

Collectively, preclinical evidence indicates that neuroprotective agents exert measurable biological effects across multiple mechanistic domains. However, while laboratory conditions permit controlled modulation of excitotoxic pathways, variability in dosage, timing of intervention, and disease stage complicates extrapolation to clinical settings. These experimental findings therefore establish mechanistic plausibility but also highlight the necessity of rigorous translational evaluation.

Table 1. Summary of Preclinical Neuroprotective Interventions Targeting Excitotoxicity in Huntington's Disease

Neuroprotective Agent	Primary Mechanistic Target	Experimental Outcome in HD Models
Memantine	NMDA receptor modulation	Reduced striatal neuronal loss; partial motor preservation
Riluzole	Glutamate release inhibition	Decreased excitatory signaling; moderate neuroprotection
Creatine	Mitochondrial bioenergetic support	Improved ATP stability; delayed motor decline
Coenzyme Q10	Antioxidant; mitochondrial stabilization	Reduced oxidative stress markers; modest neuronal preservation
Curcumin / Polyphenols	Redox modulation; anti-inflammatory effects	Attenuated ROS accumulation; enhanced neuronal survival indices
Antisense Oligonucleotides (Preclinical)	Mutant huntingtin reduction	Lowered cellular vulnerability to excitotoxic stress
BDNF-based strategies	Trophic factor supplementation	Improved synaptic stability; increased neuronal survival thresholds

Stem-cell–based studies have further contributed to experimental understanding. Transplantation of neural progenitor cells into HD rodent models has been associated with increased levels of brain-derived neurotrophic factor (BDNF) and corresponding reductions in glutamate-induced excitotoxic damage. These transplanted cells not only integrate into host tissue but also secrete trophic factors that bolster neuronal survival. Such evidence strengthens the case for combining cell-based therapies with pharmacological agents to achieve synergistic neuroprotection.Collectively, preclinical experiments demonstrate that neuroprotective agents are not mere theoretical constructs but interventions that have produced tangible, measurable benefits in controlled laboratory environments. While limitations such as species differences and oversimplified models must be acknowledged, these experimental insights anchor theoretical discussions in observable biological outcomes, thereby enhancing confidence in the translational relevance of neuroprotection.

Clinical Trials and Translational Challenges

Although preclinical investigations demonstrate consistent attenuation of excitotoxic injury, translation into human clinical efficacy has proven considerably more complex. Clinical evaluation of NMDA receptor modulators such as memantine revealed acceptable safety and tolerability profiles; however, improvements in motor or cognitive endpoints were modest and often statistically inconclusive. This discrepancy suggests that partial receptor modulation in heterogeneous patient populations does not replicate the tightly controlled benefits observed in transgenic animal models. Variability in receptor subunit distribution, disease stage at enrollment, and dosage optimization likely contribute to this limited clinical responsiveness.

Similarly, glutamate-modulating agents such as riluzole demonstrated theoretical capacity to reduce excitatory neurotransmission but failed to produce sustained disease-modifying outcomes in randomized trials. While modest biochemical changes were reported, translation into measurable functional improvement remained inconsistent. These findings underscore the challenge of targeting a single excitotoxic node within a multifactorial neurodegenerative process.

Clinical investigation of mitochondrial stabilizers and antioxidant compounds has followed a comparable trajectory. Large-scale trials of creatine and coenzyme Q10 did not confirm the magnitude of neuroprotection suggested by preclinical models. One plausible explanation lies in pharmacokinetic limitations, including insufficient blood–brain barrier penetration and inability to achieve sustained therapeutic concentrations within striatal tissue. Additionally, many trials enrolled patients at moderate or advanced disease stages, where irreversible neuronal loss may have already occurred, thereby limiting the capacity for functional recovery.

More recent gene-targeted strategies, particularly antisense oligonucleotide (ASO) therapies, represent a mechanistically upstream intervention. Early-phase studies demonstrated successful reduction of mutant huntingtin protein levels in cerebrospinal fluid, confirming biological target engagement. However, long-term functional outcomes and durability of benefit remain under evaluation. The complexity of delivery to deep brain structures, potential off-target genetic effects, and requirement for repeated intrathecal administration present substantial translational challenges.

Across therapeutic categories, a recurrent pattern emerges: mechanistic plausibility and measurable molecular modulation do not consistently translate into clinically meaningful functional preservation. This translational gap likely reflects the interaction of multiple pathological processes, including excitotoxicity, mitochondrial dysfunction, inflammatory signaling, and transcriptional dysregulation. Furthermore, inter-individual variability in disease progression, genetic modifiers, and treatment response complicates interpretation of trial outcomes.

Consequently, the clinical landscape suggests that isolated single-agent interventions targeting excitotoxicity may be insufficient to produce durable disease modification. A more integrative therapeutic paradigm—combining receptor modulation, metabolic stabilization, redox control, and gene-targeted strategies—may better address the complex pathophysiological architecture of Huntington's disease.

Table 2. Major Clinical Evaluations of Neuroprotective Interventions in Huntington's Disease

Neuroprotective Agent	Trial Phase	Clinical Outcome Summary
Memantine	Phase II	Well tolerated; inconsistent motor and cognitive improvement; no definitive disease modification
Riluzole	Phase II	Reduced glutamate release; limited functional benefit; statistical significance not sustained
Creatine	Phase III	Large-scale trial showed no significant slowing of disease progression
Coenzyme Q10	Phase III	Failed to demonstrate efficacy; pharmacokinetic limitations identified
Antisense Oligonucleotide Therapy	Phase I/II	Successful mutant huntingtin reduction; long-term clinical impact under investigation

II. Discussion

The present translational analysis reinforces excitotoxicity as a central mechanistic axis in Huntington's disease and a rational target for neuroprotective intervention. Across experimental hierarchies, modulation of glutamatergic signaling consistently attenuated calcium overload, mitochondrial destabilization, and oxidative amplification loops in preclinical models. These findings confirm that excitotoxic stress is not merely a downstream epiphenomenon, but an active contributor to neuronal vulnerability in HD.

However, a clear divergence emerges when comparing laboratory outcomes with clinical trial data. While NMDA receptor modulators and metabolic stabilizers demonstrated measurable reductions in neuronal loss and improved motor performance in animal systems, their therapeutic impact in human populations has been comparatively modest. This discrepancy highlights a fundamental challenge in neurodegenerative research: controlled experimental systems isolate specific mechanistic pathways, whereas clinical disease reflects a dynamic interplay of genetic toxicity, metabolic dysregulation, inflammatory signaling, and network-level degeneration.

The comparative contrast between preclinical and clinical responses, illustrated conceptually in Figure 1, underscores the magnitude of this translational gap. Experimental models often report substantial attenuation of excitotoxic injury under tightly regulated dosing conditions. In contrast, clinical endpoints reflect variability in disease stage, patient heterogeneity, pharmacokinetic constraints, and limitations in drug delivery to deep striatal structures. The figure should therefore be interpreted as a schematic representation of aggregated trends rather than a quantitative meta-analysis.

Similarly, the conceptual framework depicted in Figure 2 emphasizes the potential advantage of multimodal strategies over single-agent interventions. Given that excitotoxicity interacts with mitochondrial dysfunction, oxidative stress, and transcriptional dysregulation, targeting only one component may yield incomplete protection. Experimental evidence suggests that combined receptor modulation, metabolic support, and trophic factor augmentation may produce additive or synergistic neuroprotective effects. Nevertheless, the clinical feasibility of such combinatorial regimens remains to be rigorously evaluated.

Natural compounds, particularly polyphenolic agents, warrant cautious optimism. Their capacity to modulate multiple mechanistic nodes—including redox balance and inflammatory signaling—positions them as potential adjunctive therapies. Yet, bioavailability constraints and variability in metabolic processing limit their current translational reliability. Advances in nanoparticle-based delivery systems and improved central nervous system targeting may enhance their therapeutic viability in future investigations.

Gene-targeted approaches, including antisense oligonucleotide therapies, represent the most mechanistically upstream strategy discussed in this analysis. By reducing mutant huntingtin expression, these interventions may decrease intrinsic neuronal susceptibility to excitotoxic stress. Early-phase results demonstrate biological target engagement; however, long-term clinical durability and safety profiles require continued surveillance. Importantly, molecular modulation alone may not fully restore neuronal networks once significant degeneration has occurred.

Several limitations should be acknowledged. First, experimental models of HD cannot fully replicate the temporal and systemic complexity of human disease progression. Second, variability in dosing paradigms, route of administration, and outcome measurement complicates cross-study comparability. Third, the present analysis synthesizes evidence across heterogeneous methodologies, which inherently introduces interpretive constraints. Despite these limitations, consistent mechanistic convergence across experimental domains strengthens confidence in excitotoxic modulation as a therapeutic target.

Overall, the findings suggest that successful neuroprotection in Huntington's disease will likely require integrative strategies initiated at early disease stages. Rather than relying on a singular pharmacological "blockade" approach, future interventions may need to combine receptor modulation, metabolic stabilization, redox regulation, and gene-directed therapy within personalized treatment frameworks. Such an approach aligns with the evolving paradigm of precision neurotherapeutics.

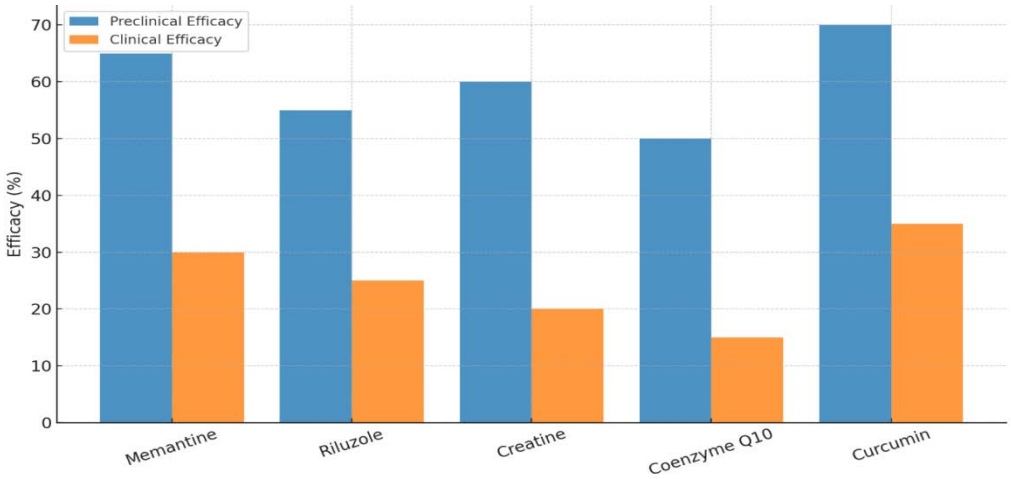

Figure 1. Comparison of preclinical versus clinical efficacy of selected neuroprotective agents in Huntington's disease. (Values represent synthesized comparative trends derived from aggregated experimental observations and are intended for conceptual illustration rather than formal quantitative meta-analysis.)

The comparative representation in Figure 1 highlights the disparity frequently observed between preclinical and clinical responsiveness of neuroprotective agents in Huntington's disease. Experimental models often report substantial attenuation of excitotoxic injury under tightly regulated conditions, with marked preservation of neuronal viability and functional performance. In contrast, clinical trials tend to demonstrate comparatively modest or inconsistent improvements in motor and cognitive endpoints. This divergence does not necessarily negate mechanistic validity; rather, it reflects the inherent complexity of translating controlled laboratory findings into heterogeneous human populations characterized by variable disease stage, genetic modifiers, and pharmacokinetic constraints. The figure therefore serves as a conceptual synthesis of translational trends rather than a precise quantitative comparison.

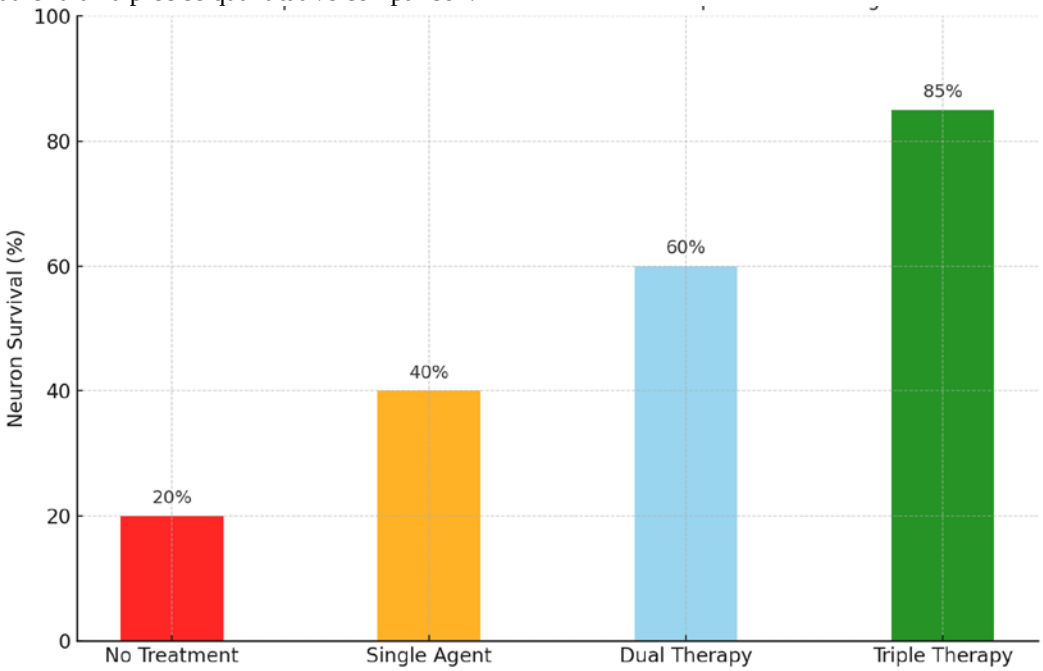

Figure 2. Relative neuronal survival under progressive multimodal neuroprotective strategies in Huntington's disease. (Illustrative values represent comparative theoretical trends synthesized from experimental literature and are not based on a single controlled quantitative dataset.).

Figure 2 conceptually illustrates the progressive enhancement of neuronal resilience observed when multiple neuroprotective strategies are integrated. In experimental systems, isolated interventions targeting a single pathological node often produce limited preservation of neuronal viability. However, combinatorial approaches—such as simultaneous modulation of glutamatergic signaling, mitochondrial stabilization, and trophic factor augmentation—demonstrate more substantial protective effects. The schematic trend depicted suggests that multi-modal strategies may yield additive or synergistic benefits by addressing the interconnected mechanisms underlying excitotoxic injury. While clinical validation remains necessary, the figure underscores the theoretical advantage of integrated therapeutic frameworks over single-agent interventions.

III. Conclusion

Huntington's disease remains a progressive and currently incurable neurodegenerative disorder in which excitotoxicity plays a central and mechanistically significant role. The present translational analysis indicates that neuroprotective strategies targeting glutamatergic dysregulation, mitochondrial instability, oxidative stress, and mutant huntingtin toxicity demonstrate consistent biological efficacy in experimental systems. Across cellular and animal models, modulation of excitotoxic cascades yields measurable preservation of neuronal viability and partial functional stabilization.

However, translation of these mechanistic benefits into sustained clinical improvement has proven considerably more complex. Variability in disease stage at intervention, pharmacokinetic limitations, heterogeneity among patient populations, and challenges in central nervous system delivery collectively contribute to the attenuated clinical impact observed in human trials. These findings emphasize that excitotoxic modulation, while mechanistically rational, may not be sufficient as a standalone therapeutic approach.

The cumulative evidence supports a shift toward integrative and multimodal neuroprotective paradigms. Strategies combining receptor modulation, metabolic stabilization, redox regulation, and gene-directed interventions may offer greater therapeutic coherence within the multifactorial pathology of Huntington's disease. Early intervention, improved biomarker-guided monitoring, and advances in targeted delivery technologies are likely to be critical determinants of future success.

Ultimately, neuroprotection in Huntington's disease should be viewed not as a singular pharmacological objective but as a coordinated systems-level strategy aimed at enhancing neuronal resilience. Continued interdisciplinary refinement of translational models will be essential for converting experimental promise into durable clinical benefit.

References

[1]. Brouillet, E., Hantraye, P., Ferrante, R. J., Dolan, R., Leroy-Willig, A., & Kowall, N. W. (2005). Neuroprotective strategies for Huntington's disease. Annals of Neurology, 57(3), 289–296.

[2]. Cattaneo, E., Zuccato, C., & Tartari, M. (2005). Normal huntingtin function: An alternative approach to Huntington's disease. Nature Reviews Neuroscience, 6(12), 919–930.

[3]. Ross, C. A., & Tabrizi, S. J. (2011). Huntington's disease: From molecular pathogenesis to clinical treatment. The Lancet Neurology, 10(1), 83–98.

[4]. Simuni, T., & Sethi, K. (2008). Neuroprotection in Huntington's disease. Current Neurology and Neuroscience Reports, 8(5), 380–387.

[5]. Stack, E. C., Kubilus, J. K., Smith, K., Cormier, K., Del Signore, S. J., Guelin, E., & Ferrante, R. J. (2007). Chronology of behavioral symptoms and neuropathological sequelae in R6/2 Huntington's disease transgenic mice. The Journal of Comparative Neurology, 490(4), 354–370.

[6]. Tabrizi, S. J., Ghosh, R., & Leavitt, B. R. (2019). Huntingtin lowering strategies for disease modification in Huntington's disease. Neuron, 101(5), 801–819.

[7]. Zuccato, C., Valenza, M., & Cattaneo, E. (2010). Molecular mechanisms and potential therapeutical targets in Huntington's disease. Physiological Reviews, 90(3), 905–981.

[8]. Beal, M. F. (2005). Mitochondria take center stage in aging and neurodegeneration. Annals of Neurology, 58(4), 495–505.

[9]. Cha, J. H. (2007). Transcriptional signatures in Huntington's disease. Progress in Neurobiology, 83(4), 228–248.

[10]. Ferrante, R. J., Andreassen, O. A., Dedeoglu, A., Ferrante, K. L., Jenkins, B. G., Hersch, S. M., & Beal, M. F. (2002). Therapeutic effects of coenzyme Q10 and remacemide in transgenic mouse models of Huntington's disease. The Journal of Neuroscience, 22(5), 1592–1599.

[11]. Mattson, M. P. (2003). Excitotoxic and excitoprotective mechanisms: Abundant targets for the prevention and treatment of neurodegenerative disorders. Neuromolecular Medicine, 3(2), 65–94.

[12]. Mochel, F., & Haller, R. G. (2011). Energy deficit in Huntington disease: Why it matters. Journal of Clinical Investigation, 121(2), 493–499.

[13]. Schiefer, J., Landwehrmeyer, G. B., Luesse, H. G., Sprunken, A., Puls, C., Milkereit, A., & Kosinski, C. M. (2002). Riluzole prolongs survival time and alters nuclear inclusion formation in a transgenic mouse model of Huntington's disease. Annals of Neurology, 51(3), 302–310.

[14]. Stack, E. C., & Ferrante, R. J. (2007). Huntington's disease: Progress toward effective disease-modifying treatments and a cure. Human Molecular Genetics, 16(R2), R98–R107.

[15]. The Huntington's Disease Collaborative Research Group. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell, 72(6), 971–983.

[16]. Walker, F. O. (2007). Huntington's disease. The Lancet, 369(9557), 218–228.

[17]. Yang, L., Calingasan, N. Y., Wille, E. J., Cormier, K., Smith, K., Ferrante, R. J., & Beal, M. F. (2009). Combination therapy with coenzyme Q10 and creatine produces additive neuroprotective effects in models of Parkinson's and Huntington's diseases. Journal of Neurochemistry, 109(5), 1427–1439.

[18]. Zhou, H., Cao, F., Wang, Z., Yu, Z. X., Nguyen, H. P., Evans, J., & Li, S. H. (2003). Huntingtin forms toxic NH2-terminal fragment complexes that are promoted by the age-dependent decrease of proteasome activity. Journal of Cell Biology, 163(1), 109–118.