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Protein Kinases as Therapeutic Targets in Neurodegenerative Diseases

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Abstract

Background: *Age-related neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), are characterized by progressive neuronal degeneration, synaptic dysfunction, and accumulation of misfolded protein aggregates. These disorders pose serious health risks by causing progressive cognitive impairment, motor dysfunction, disability, and increased mortality among affected individuals. Increasing evidence implicates dysregulated protein kinase signaling in the pathogenesis of these disorders through mechanisms involving aberrant phosphorylation, mitochondrial dysfunction, neuroinflammation, impaired proteostasis, and neuronal death. Consequently, protein kinases have emerged as promising therapeutic targets for disease modification.*

Methods: *This narrative review critically synthesizes current evidence from preclinical and clinical studies investigating protein kinases implicated in major neurodegenerative disorders. Relevant literature focusing on kinase-mediated pathogenic pathways, selective kinase modulation, translational progress, and therapeutic relevance was evaluated and integrated. Key kinases examined include Casein Kinase 1 delta (CSNK1D), Colony Stimulating Factor 1 Receptor (CSF1R), Dual Leucine Zipper Kinase (DLK), Glycogen Synthase Kinase 3β (GSK3B), Leucine Rich Repeat Kinase 2 (LRRK2), Mitogen-Activated Protein Kinase 14 (MAPK14), Receptor-Interacting Serine/Threonine-Protein Kinase 1 (RIPK1), and Rho-Associated Protein Kinase (ROCK).*

Results: *Evidence from experimental and early clinical investigations demonstrates that selective modulation of dysregulated kinase pathways may attenuate neuroinflammation, reduce pathogenic protein aggregation, preserve neuronal integrity, and improve cellular homeostasis. Several kinase-targeted approaches have shown mechanistic and therapeutic promise across AD, PD, HD, and ALS models. However, despite encouraging translational progress, significant limitations persist, including inadequate blood–brain barrier penetration, off-target toxicity, limited long-term safety data, and insufficient clinical efficacy in advanced-stage trials.*

Conclusions: *Protein kinase signaling represents a mechanistically significant and therapeutically promising target in neurodegenerative disease research. Although kinase-targeted interventions demonstrate substantial potential for disease modification, major challenges related to central nervous system delivery, selectivity, safety, and clinical translation remain unresolved. Further mechanistic investigations and the rational development of highly selective kinase inhibitors are essential to advance effective therapeutic strategies for neurodegenerative disorders.*

Keywords: Alzheimer's disease, Kinase inhibitors, Neurodegenerative diseases, Neuroprotection, Parkinson's disease, Protein kinases, Therapeutic targets.
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Introduction

Age-related neurodegenerative diseases pose a growing public health challenge due to increasing human longevity. Disorders such as Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) are characterized by progressive neuronal dysfunction and the accumulation of misfolded protein aggregates. Aging accelerates cognitive decline through disruptions in immune homeostasis, reduced neurogenesis, and altered metabolic signaling. Despite extensive research, most available therapies remain symptomatic rather than curative. Protein kinases play a central role in neuronal survival and communication by regulating intracellular signaling through phosphorylation. Dysregulated kinase activity contributes to pathological protein aggregation, including tau, α-synuclein, and TDP-43, thereby promoting neuronal toxicity. At the mechanistic level, disease-specific kinase signaling networks directly converge on pathogenic protein processing, synaptic failure, and neuronal death. For example, GSK3β and CDK5 drive tau hyper phosphorylation and microtubule destabilization in AD, whereas LRRK2 and PLK2 regulate α-synuclein phosphorylation, vesicle trafficking, and lysosomal dysfunction in PD. In ALS, aberrant activation of CK1 and MAPK pathways promotes TDP-43 phosphorylation, cytoplasmic mislocalization, and stress-granule persistence, linking kinase dysregulation to selective neuronal vulnerability. The spatiotemporal precision of kinase action, especially protein kinase A (PKA) and associated enzymes, is essential for dendritic branching, synaptic signaling, mitochondrial dynamics, and neurite elongation[1]. The breakdown of these

regulatory circuits leads to the anomalies in synapses and morphology that are characteristic of neurodegenerative diseases. Therapeutic regulation of aberrant kinase-mediated phosphorylation represents a rational disease-modifying hypothesis; however, its clinical feasibility remains constrained by pathway complexity, safety concerns, and translational challenges. One of the post-translational changes linked to neurodegeneration that has been researched the most is protein phosphorylation. Kinases catalyze this change, and a dynamic equilibrium is maintained by phosphatases, which counteract it by eliminating phosphate groups[2]. Phosphorylation can change a substrate's functioning and set off a series of downstream pathogenic processes. For instance, abnormal phosphorylation of tau within its microtubule-binding and proline-rich domains facilitates the production of neurofibrillary tangles in AD[3,4]. Sustained synaptic activity, efficient mitochondrial trafficking, robust mitochondrial quality-control mechanisms, and enough neurotrophic signaling are all necessary for optimal neuronal function. When taken as a whole, these actions protect the dendritic arbors' complex structure and axonal integrity. Dopamine synthesis, L-type Ca2+ channel regulation, dendritic elongation, dendritic spine remodeling, and axonal rebuilding are among the elements of neuritic physiology that are impacted by distinct PKA isoforms[5,6]. Basal PKA activity promotes the development of neurons, whereas hyperactivation causes the simplification of dendritic structures and disturbs pre- and postsynaptic compartments. Reduced cyclic AMP concentrations in spiral ganglion neurons promote dendritic extension, whereas increased levels jeopardize dendritic stability and cause cell death without the need for external damage[7]. To address translational challenges, it is important to note that kinase-targeted strategies face significant preclinical and clinical hurdles. These include limited brain penetrance of inhibitors, off-target effects due to kinase homology, compensatory signalling pathways, and toxicity arising from chronic kinase suppression. Moreover, discrepancies between animal models and human disease, lack of predictive biomarkers, and difficulties in patient stratification have constrained clinical success. Overcoming these barriers will require improved disease models, isoform-specific inhibitors, and robust translational biomarkers. This review provides an integrated, clinically informed synthesis of protein kinase dysregulation across major neurodegenerative diseases, emphasizing convergent molecular pathways underlying shared clinical features. Beyond summarizing key kinase targets, it critically evaluates translational progress and limitations, including blood–brain barrier constraints, off-target effects, compensatory signaling, and gaps between preclinical models and human disease, offering a realistic framework for future therapeutic development.

Materials and Methods

Objectives and methodological approach: The primary objective of this review is to critically examine the role of dysregulated protein kinase signaling in the pathogenesis of major neurodegenerative disorders, including AD, PD, HD, and ALS. Specifically, the review aims to (i) elucidate disease-relevant kinase-mediated mechanisms underlying protein aggregation, synaptic dysfunction, mitochondrial impairment, and neuroinflammation; (ii) evaluate key kinases as potential therapeutic targets; and (iii) assess the translational progress and limitations of kinase-targeted interventions. This review adopts a narrative and integrative methodological approach. Relevant literature was identified through comprehensive searches of major biomedical databases, including PubMed, Scopus, and Web of Science, complemented by manual screening of reference lists. Studies were selected based on mechanistic relevance, experimental rigor, and translational significance rather than predefined inclusion criteria. By synthesizing evidence from preclinical and clinical studies, this approach enables critical interpretation of complex kinase signaling networks and emerging therapeutic strategies beyond the scope of systematic review frameworks.

Literature search strategy: This narrative review is based on a comprehensive survey of the published literature. Relevant articles were identified through systematic searches of major electronic databases, including PubMed, Scopus, and Web of Science. The search strategy employed combinations of keywords and Medical Subject Headings (MeSH) terms related to protein kinases and neurodegenerative diseases, such as “protein kinases,” “kinase signaling,” “Alzheimer’s disease,” “Parkinson’s disease,” “Huntington’s disease,” “amyotrophic lateral sclerosis,” and “neurodegeneration.” Additional studies were identified by manual screening of reference lists from key articles. Selection of literature was guided by relevance to kinase-mediated mechanisms, experimental evidence, and translational significance rather than by predefined inclusion or exclusion criteria, consistent with the narrative review methodology.

Inclusion and exclusion criteria: The literature search was conducted using combinations of relevant keywords and controlled vocabulary terms, including “protein kinases,” “kinase signaling,” “kinase inhibitors,” “neurodegenerative diseases,” “Alzheimer’s disease,” “Parkinson’s disease,” “Huntington’s disease,” “amyotrophic lateral sclerosis,” “tau phosphorylation,” “α-synuclein,” “TDP-43,” “mitochondrial dysfunction,” and “neuroinflammation.” Studies were selected based on their relevance to kinase-mediated molecular mechanisms, disease pathogenesis, and therapeutic or translational significance. The review incorporated original experimental research, preclinical studies, clinical trials, and authoritative review articles to provide both mechanistic depth and clinical context. Priority was given to peer-reviewed studies presenting robust experimental evidence or clinically meaningful insights. Articles were excluded if they lacked mechanistic relevance, focused on non-neurological conditions, or did not address kinase-related signaling pathways. This selective approach ensured a coherent and focused synthesis of the literature while maintaining breadth across major neurodegenerative disorders, in keeping with the narrative review methodology.

Search scope and time frame: The literature incorporated in this narrative review encompasses peer-reviewed studies published between 2009 and 2025, thereby capturing both seminal mechanistic investigations and contemporary advances in protein kinase signaling relevant to neurodegenerative diseases. This temporal range was selected to ensure comprehensive coverage of foundational discoveries while emphasizing recent experimental, translational, and therapeutic developments. Earlier landmark studies were selectively included where essential to contextualize kinase biology, disease pathogenesis, or signaling paradigms. Collectively, this

defined search scope enables a balanced synthesis of historical and current evidence, allowing readers to assess the currency, depth, and scientific evolution of kinase-targeted research in AD, PD, HD, and ALS.

Results

Alzheimer's disease (AD): An increasing amount of scientific data suggests that the formation and progression of a number of neurodegenerative diseases, the most well-studied of which is AD, are significantly influenced by the abnormal regulation of the PKA cascade. PKA, a serine/threonine kinase controlled by intracellular cyclic adenosine monophosphate (cAMP), is the primary orchestrator of neuronal survival, synaptic flexibility, and long-term memory consolidation[9]. PKA phosphorylates several downstream effectors, including the cAMP response element-binding protein (CREB), under normal physiological equilibrium. This subsequently initiates transcriptional sequences that are necessary for synaptic stabilization, neuronal differentiation, and neuronal development. Dysregulated PKA signaling disrupts these transcriptional and post-translational regulatory mechanisms, making neurons more vulnerable to synaptic instability and degeneration. Reported studies have demonstrated that subtoxic levels of amyloid-β Aβ(1-42) severely disrupt intracellular systems that maintain synaptic plasticity, even if cortical neurons are not immediately cytotoxically damaged by Aβ[10]. The activation of prosurvival kinases, such as extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3-kinase (PI3K)/Akt signaling cascades, is disrupted by exposure to such nonlethal Aβ levels[11]. This interference requires brain-derived neurotrophic factor (BDNF). The resulting suppression reduces the expression of genes necessary for brain endurance and recovery by lowering the phosphorylation of CREB and other significant transcriptional regulators[12]. Reduced dendritic spine shape, BDNF signaling suppression, and increased synaptic attrition all impair long-term potentiation (LTP), the electrophysiological underpinning of learning and memory retention[13]. In AD, the alteration of PKA activity by Aβ peptides is especially detrimental, accelerating cognitive decline through intricate biochemical anomalies. Tau phosphorylation and related cytoskeletal components are decreased by the Aβ-induced reduction in PKA catalytic activity, which in turn encourages the development of neurofibrillary tangles and interferes with axonal transport. Moreover, mitochondrial alterations brought on by exposure to Aβ (1-42) are characterized by elevated reactive oxygen species (ROS), decreased ATP synthesis, and compromised oxidative phosphorylation[14]. Localized energy shortage brought on by these mitochondrial anomalies disrupts synaptic transmission and hinders organelle trafficking along hippocampal neurites. All of these findings showed that PKA is a crucial defense for the structure of neurons and highlight its disruption, particularly in the presence of Aβ-induced stress, sets off a complex series of molecular abnormalities that eventually result in synaptic collapse, bioenergetic exhaustion, and neurodegeneration - all of which are indicators of AD. From a clinical perspective, kinase-mediated abnormalities in AD extend beyond molecular pathology and directly influence disease progression and symptom severity. Hyperactivation of kinases such as GSK3β and CDK5 not only promotes tau hyperphosphorylation and neurofibrillary tangle formation but also correlates with synaptic loss and cognitive impairment observed in patients. Concurrent dysregulation of MAPK and PKA signaling pathways exacerbates neuroinflammatory responses and disrupts CREB-dependent transcription of neurotrophic factors, including BDNF, thereby accelerating memory decline and hippocampal dysfunction. These observations support a mechanistic continuum linking kinase dysregulation to both neuropathological hallmarks and clinically measurable cognitive deterioration in AD.

Parkinson's disease (PD): The PKA signalling pathway has a major impact on maintaining synaptic function and neuronal health. This route has been thoroughly studied in the setting of PD using a range of in vitro and in vivo models as well as post-mortem analyses of human brain tissue. There is consistent evidence of significantly lower levels of BDNF mRNA in neurons in the substantia nigra, a crucial dopaminergic area impacted in PD. This molecular deficiency often appears before the clinical manifestation of cognitive and motor deficits, suggesting that disturbed neurotrophic signaling contributes to the early phases of PD. Two of the most noticeable pathological characteristics of PD are morphological fragmentation and mitochondrial dysfunction[15]. Since then, anomalies in mitochondrial-associated PKA signalling have gained recognition as being crucial to the disease's development. PKA-dependent cellular models of PD exhibit markedly decreased phosphorylation of dynamin-related protein 1 (Drp1), a crucial modulator of mitochondrial fission and network architecture. Similarly, phosphorylation of Drp1 by PKA is reduced in genetic PD models that use RNA interference to inhibit PTEN-induced kinase 1 (PINK1)[16]. These molecular disruptions are also linked to the enhanced activation of Drp1 by calcineurin (protein phosphatase 2B, PP2B), which results in excessive mitochondrial fragmentation and energy instability. These results all suggest a biological connection between PD-related neuronal loss, dysregulated PKA signalling, and mitochondrial failure. Therapeutic strategies aimed at preserving signaling integrity have demonstrated neuroprotective effects in experimental models; however, whether these benefits translate to sustained clinical efficacy in PD remains unresolved. Treatment options for PD may involve targeting the dysregulated PKA signalling pathway and restoring proper mitochondrial function. By addressing these molecular disruptions, it may be possible to prevent excessive mitochondrial fragmentation and energy instability, ultimately reducing neuronal loss associated with the disease. Developing therapies that focus on maintaining signalling integrity and promoting mitochondrial homeostasis could theoretically confer neuroprotective effects, although long-term clinical benefit has yet to be established. In PD, alterations in kinase signaling exhibit a direct relationship with characteristic motor and non-motor symptoms. LRRK2- and MAPK-driven abnormalities disrupt vesicular trafficking, lysosomal degradation, and mitochondrial quality control, thereby contributing to dopaminergic neuronal vulnerability within the substantia nigra. Clinically, these molecular disruptions manifest as progressive motor impairment, bradykinesia, rigidity, and postural instability, while also contributing to non-motor features such as cognitive decline and autonomic dysfunction. Importantly, the convergence of kinase dysregulation on mitochondrial fragmentation and α-synuclein pathology highlights shared molecular mechanisms

that underlie both neuronal degeneration and symptom progression in PD.

Hutchinson disease (HD): One of the main causes of the molecular chain reaction that initiates and progresses HD is mitochondrial malfunction. The scientific literature is still disjointed and unclear despite the increased attention being paid to this research, particularly regarding the anomalies in PKA signalling pathways that have been observed in several HD experimental setups. It has been demonstrated that naïve R6/1 transgenic mouse model, which express mutant huntingtin protein, exhibit considerably higher enzymatic activity of hippocampal PKA than their wild-type counterparts[17]. After Rp-cAMPS, a selective and reversible inhibitor of PKA, is administered to the hippocampus, studies on R6/2 mouse strains have shown that the improvement of PKA activation is directly related to the restoration of long-term memory function[18]. This result aligns with the previously published findings. Significant cognitive impairments have also been linked to aberrant hippocampus PKA signalling, according to complementary observations from R6 rat models. Furthermore, it has been demonstrated that by preventing the formation of mutant huntingtin aggregates and facilitating the phosphorylation of Rpt6, a crucial regulatory element of the proteasome complex, Pharmacological modulation of the PKA pathway has been shown to enhance proteasomal function and improve cognitive performance in experimental models, though its relevance to human disease progression remains uncertain. The concept that dysregulated PKA signalling is a crucial biochemical link between mitochondrial impairment and synaptic maladaptation in HD is supported by the growing body of research. Therefore, it may be possible to improve both the abnormalities in proteostasis and cognitive decline that are characteristic of this debilitating neurodegenerative disease by precisely modulating this signaling axis.

In addition to PKA dysregulation, multiple kinase pathways contribute to HD pathogenesis. Aberrant activation of CDK5 and stress-associated MAPKs (JNK and p38) promotes mutant huntingtin toxicity, synaptic instability, mitochondrial dysfunction, and neuronal apoptosis. Impaired BDNF–CREB signaling further exacerbates transcriptional repression of survival genes. Collectively, these findings indicate that HD is a network-driven signaling disorder, warranting carefully timed and context-specific kinase modulation to avoid adverse effects. In HD, dysregulated kinase signaling links mutant huntingtin toxicity to clinical manifestations through interconnected pathways involving mitochondrial dysfunction, impaired proteostasis, and transcriptional dysregulation. Aberrant PKA, CDK5, and MAPK activity disrupts CREB-mediated neurotrophic support and synaptic plasticity, leading to progressive cognitive impairment and motor dysfunction characteristic of the disease. These kinase-driven signaling failures contribute to early synaptic abnormalities that precede overt neuronal loss, thereby providing a molecular explanation for the temporal dissociation between early clinical symptoms and later widespread neurodegeneration observed in HD patients.

Amyotrophic Lateral Sclerosis (ALS): Despite being relatively uncommon, ALS is a neurological disease where the persistent degeneration and consequent attrition of both upper and lower motor neurons are its defining characteristics. Epidemiological and mechanistic evidence suggests that environmental insults, such as ionizing radiation, exposure to heavy metals, and various neurotoxic pollutants, are linked to the pathogenesis of ALS by causing oxidative stress and upsetting mitochondrial structural and functional homeostasis[19]. Genetic changes in the TARDBP locus, which codes for the TDP-43, are linked to about 4% of familial ALS (fALS) symptoms[20]. A hallmark of ALS pathology is the aggregation and cytoplasmic mislocalization of TDP-43, which is normally nuclear. Similarly, autosomal dominant FUS mutations cause cytoplasmic FUS inclusions. FUS is a multifunctional DNA- and RNA-binding protein essential for RNA metabolism, DNA repair, and gene regulation, interacting with over 5,500 neuronal pre-mRNA transcripts[21]. FUS's neuropathogenicity in ALS results from two mechanisms: the loss of its normal nuclear activities and the harmful development of aberrant cytoplasmic function. Convergent experimental results consistently showed substantial abnormalities in mitochondrial shape, bioenergetic efficiency, and dynamic turnover in both ALS patients and the related experimental models. Specifically, pathogenic hexanucleotide repeat expansions in C9orf72 cause mitochondrial complex I failure, mostly through pathways of haploinsufficiency or total loss of function[22]. Stabilizing complex I and controlling vital intracellular functions like autophagic flux and RNA metabolism depend on the C9orf72 protein, which is found in the inner mitochondrial membrane. Cellular stress is made worse by the buildup of abnormal protein aggregates, including TDP-43 and FUS inclusions, which interfere with autophagy initiation, vesicular trafficking, and C9orf72 function. Furthermore, the identification of harmful variations in genes encoding protein kinases, such as TBK1 and NEK1, has confirmed the critical involvement of kinase-mediated signaling cascades in the development of ALS. Together, these findings highlight the critical role that kinase networks play in coordinating the pathobiological continuum and molecular genesis of ALS.

Beyond TDP-43 and FUS proteinopathies, kinase-mediated signaling abnormalities play a central role in ALS progression. TANK-binding kinase 1 (TBK1) is a critical regulator of selective autophagy and mitophagy through phosphorylation of optineurin and p62. Loss-of-function mutations in TBK1 impair clearance of damaged mitochondria and protein aggregates, thereby accelerating motor neuron degeneration. Similarly, NEK1 participates in DNA damage repair and mitochondrial integrity, and its disruption sensitizes neurons to oxidative stress and apoptotic signalling. Stress-activated kinases, including JNK and p38 MAPK, are persistently activated in ALS models and patient tissues, contributing to neuroinflammation, microglial activation, and cytokine-mediated toxicity. Casein kinase 1 (CK1) further promotes pathological phosphorylation of TDP-43, enhancing its cytoplasmic aggregation and persistence within stress granules. These converging kinase pathways link defective RNA metabolism, impaired autophagic flux, and mitochondrial dysfunction into a unified pathogenic cascade. Collectively, this evidence underscores that ALS is driven by coordinated signaling network failure rather than isolated molecular events, supporting kinase pathways as rational but complex therapeutic targets in motor neuron disease.

Kinase network dysfunction in ALS contributes to selective motor neuron vulnerability and rapid disease progression. Aberrant activation of stress kinases and impaired TBK1-mediated autophagy promote TDP-43 pathology, mitochondrial dysfunction, neuroinflammation, and clinically progressive weakness, denervation, respiratory failure, and disease severity.

Discussion

Critical protein kinase targets: Numerous signalling cascades, including receptor endocytosis, DNA repair, autophagy, cytoskeletal remodeling, cellular survival, proliferation, and motility, are coordinated by the central modulator ABL1. Increased oxidative stress, mitochondrial dysfunction, and the intracellular buildup of misfolded proteins are common features of neurodegenerative disorders. Dysregulated ABL1 activity in forebrain neuronal populations has been linked to the onset and advancement of both neurodegenerative and neuroinflammatory processes. ABL1 activity is elevated in both preclinical models and people with PD. The phosphorylation of important genetic risk factors, such as α-synuclein and the E3 ubiquitin ligase Parkin, is at tyrosine 39[23]. In experimental settings, genetic deletion of ABL1 protects against MPTP-mediated neurotoxicity while also reducing α-synuclein aggregation, neuropathological characteristics, and behavioral deficits. Targeted pharmacological inhibition of ABL1 in PD murine models has produced neuroprotective effects, despite the known promiscuity of current inhibitors and their possibly limited CNS penetrance[24]. However, such results must be interpreted cautiously. Recurrent mutations within the ABL1 kinase domain have led to the synthesis of a number of ATP-competitive inhibitors, including nilotinib, dasatinib, bosutinib, and ponatinib. These drugs do, however, have significant off-target interactions that affect kinases such as c-KIT, CSF1R, and PDGFRA/B[25]. Bosutinib has been the subject of clinical trials aimed at treating degenerative dementias, despite the current lack of comprehensive CNS and plasma pharmacokinetic profiles (NCT02921477). Bafetinib (INNO-406), which is now being assessed clinically in PD patients following validation in preclinical mouse studies (NCT02970019), is a promising candidate to elucidate the function of c-Abl in PD pathogenesis due to its potential for increased CNS permeability[26]. Together, the current ABL1 inhibitors' low CNS bioavailability and poor selectivity restrict their therapeutic potential, thereby endangering both clinical efficacy and tolerability.

Integrated network of critical protein kinase targets: Rather than functioning as isolated molecular entities, protein kinases implicated in neurodegenerative diseases form an interconnected signaling network that collectively regulates neuroinflammation, protein aggregation, mitochondrial integrity, and neuronal survival. CSNK1D, GSK3β, and MAPK14 converge on pathological phosphorylation events that drive tau, α-synuclein, and TDP-43 aggregation, thereby linking abnormal proteostasis to synaptic dysfunction across AD, PD, and ALS. These phosphorylation-driven pathologies are further amplified by stress-responsive kinases such as DLK and MAPK14, which activate JNK and p38 pathways in response to axonal injury and cellular stress, promoting neuronal degeneration when chronically activated. Neuroinflammatory signaling represents another major point of convergence. CSF1R-mediated microglial activation interacts functionally with RIPK1-dependent necroptotic and inflammatory cascades, creating feed-forward loops that sustain cytokine release, axonal damage, and neuronal loss. ROCK signaling further integrates inflammatory and cytoskeletal pathways by regulating microglial polarization, actin dynamics, and mitophagy, thereby influencing both immune responses and neuronal resilience. In PD, LRRK2 acts as a central hub connecting vesicular trafficking, autophagy, cytoskeletal remodeling, and inflammatory signaling, with downstream interactions involving MAPK and ROCK pathways that exacerbate dopaminergic neuron vulnerability.

Importantly, these kinase pathways exhibit substantial cross-talk and compensatory signaling, explaining why inhibition of a single kinase often yields limited or transient therapeutic benefit. Collectively, this integrated perspective highlights that neurodegeneration arises from coordinated kinase network dysfunction rather than single-pathway abnormalities. Therefore, effective therapeutic strategies will likely require context-specific and network-aware kinase modulation; however, implementing such approaches poses substantial pharmacological and clinical challenges.

Casein Kinase 1 delta (CSNK1D): The essential family of serine/threonine kinases known as CK1 phosphorylates around 140 substrates. This activity is essential for several cellular processes, including vesicular trafficking, microtubule dynamics, cell cycle regulation, apoptosis, and intracellular transport. One of its isoforms, CSNK1D, has become a key modulator of circadian rhythm, and its dysregulation has been closely associated with the sleep-wake abnormalities frequently observed in AD[27]. Abnormal CSNK1D activity has been linked to the pathogenesis of numerous neurodegenerative illnesses, indicating a wider role in neuronal homeostasis than only circadian rhythm. Pharmacological targeting of CSNK1D has shown promising effects in selected preclinical models; however, these findings are largely limited to short-term experimental systems, and the relevance of CSNK1D inhibition to long-term disease progression in patients remains uncertain. This illustrates its ability to regulate neuroinflammation, protein aggregation, and neuronal survival. Strong mechanistic validation using disease-representative animal models is still essential in spite of these advancements, particularly in TDP-43-associated disorders that continue to attract a lot of research interest. Recent developments by Pfizer have produced powerful, highly selective, and central nervous system-permeable CSNK1D inhibitors. In preclinical and early clinical trials, these inhibitors have demonstrated favorable pharmacological profiles in early-stage studies, although comprehensive clinical safety and efficacy data are still lacking. All of these findings highlight the highlight CSNK1D inhibition as an investigational strategy with potential relevance to disease-associated proteinopathies, pending validation in long-term and disease-representative models[28]. Ongoing research into the molecular contributions and pharmacological manipulation of CSNK1D is set to inform the development of next-generation therapeutics for a range of crippling neurodegenerative illnesses.

Colony Stimulating Factor 1 Receptor (CSF1R): The main modulators of neuroinflammatory processes linked to neurodegenerative diseases are microglial cells. The tyrosine

kinase colony stimulating factor 1 receptor (CSF1R) controls the growth of microglia[29]. Microglia play a crucial role, as evidenced by the complete absence of microglia in rodents and rats lacking CSF1R. Several preclinical neurodegenerative models and human post-mortem brain tissues have been shown to exhibit increased CSF1R expression. Interleukin-34 (IL-34), which is mostly found in neurons, and colony-stimulating factor 1 (CSF1), which is also produced by microglia, are the two main ligands that control CSF1R activity[30]. Axonal spheroids and pigmented glia (ALSP), a sign of adult-onset leukoencephalopathy, have been conclusively associated with mutations in the CSF1R gene. However, a major limitation in targeting CSF1R is the lack of selectivity among its inhibitors. Members of the class III receptor tyrosine kinase (RTK) family include CSF1R, c-KIT, FLT3, and PDGFRs[31]. Consequently, several additional kinases are likewise affected by most CSF1R inhibitors. Examples of broad-spectrum RTK inhibitors that also block CSF1R function are sunitinib and mastitinib. Masitinib, a class III RTK inhibitor undergoing Phase III clinical trials for ALS (NCT02588677; NCT03127267), exemplifies this difficulty[32]. Current CSF1R inhibitors' limited clinical tolerability and uneven preclinical results may be reflected in their poor selectivity and low CNS penetration.

Dual Leucine Zipper Kinase (DLK): A mitogen-activated protein kinase called dual leucine zipper kinase (DLK) triggers the neuronal stress signaling pathway that is dependent on c-Jun N-terminal kinase (JNK)[33]. It controls context-specific axonal regeneration and degeneration, acting as a molecular sensor of injury. Importantly, DLK signaling exhibits a dual role, contributing not only to injury-induced degeneration but also to adaptive axonal repair processes depending on temporal and cellular context. The data suggest that prolonged DLK activation may hasten neuronal death; its presence or absence can affect axonal regrowth following neuronal injury. DLK is an evolutionarily conserved regulator of neuronal degeneration after many types of brain injury, according to research, especially that done by Genentech. Genentech-engineered compounds have demonstrated effectiveness in reducing synaptic degradation, neuronal attrition, and functional decline in experimental models of AD, PD, ALS, and acute brain injury through genetic alteration or pharmacological inhibition of DLK[34]. However, these neuroprotective effects are largely derived from acute or short-term experimental models, and sustained DLK inhibition may carry risks by interfering with endogenous regenerative responses. Through high-throughput screening, small-molecule DLK inhibitors that decrease c-Jun phosphorylation in animal models were first identified. Shape-based scaffold hopping was then used to improve the process. Furthermore, even though the pharmacokinetic characteristics and selectivity of medications like sunitinib and tozasertib are not ideal for CNS penetration, retinal ganglion cell studies have shown how effective these drugs are at inhibiting DLK. These findings suggest that targeting DLK could be a biologically compelling therapeutic rationale for neurodegenerative diseases and acute brain injury. Consistent with this complexity, early translational efforts highlight the need for precise temporal control of DLK modulation rather than continuous inhibition in chronic neurodegenerative settings. The development of more potent and selective DLK inhibitors with improved pharmacokinetic properties could advance mechanistic understanding and inform future therapeutic development, provided that safety, timing, and context-dependent effects are carefully addressed. Further research is needed to fully understand the potential benefits and limitations of targeting DLK in the central nervous system (CNS) Figure 1.

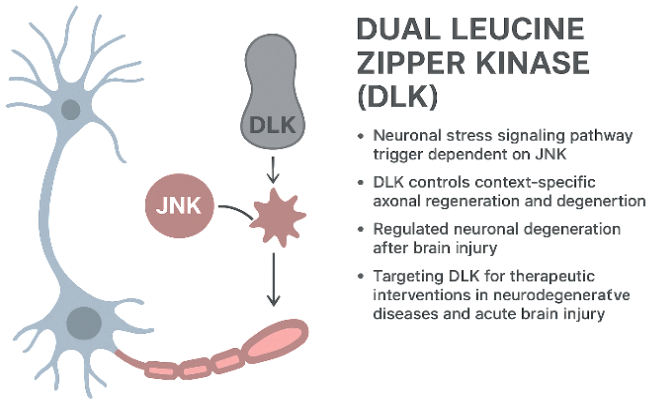

Figure 1. DLK-mediated neuronal stress signalling and its therapeutic targeting

Glycogen Synthase Kinase 3 Beta (GSK3B): Glycogen Synthase Kinase 3 Beta (GSK3B) encodes a serine/threonine kinase with two variations. Both forms can phosphorylate more than forty different substrates and are always active. Numerous biological processes, including microtubule organization, cell formation, mitotic regulation, inflammation (especially in the innate immune system), insulin and Wnt signaling, and glycogen degradation, are mediated by these substrates. GSK3β's location within the cell, interactions with other proteins, and site-specific phosphorylation are some of the variables that closely govern its function. Its ability to bind to substrates can be either increased (by Y216 phosphorylation in the activation loop) or decreased (by S9 phosphorylation)[35]. Although GSK3β inhibitors have been shown to work as drugs

in a variety of experimental settings, their possible side effects have prevented them from being used in humans. As a tau kinase in the context of AD, GSK3β directly stimulates the synthesis of amyloid-β (Aβ), which in turn leads to neurodegeneration[36]. Its function in the hierarchical regulation of phosphorylation has been highlighted by structural investigations of the Y216-monophosphorylated GSK3β linked to peptide substrates as well as the unphosphorylated apo-enzyme, which have shown a preference for pre-phosphorylated targets[37]. Crystallographic studies of chemically diverse inhibitor complexes have clarified the structural elements that affect binding affinity and selectivity, which have given crucial information for structure-based drug design. Two small-molecule inhibitors for neurological conditions that have advanced to human clinical trials are tideglusib and AZD1080. Clinical trials NCT00948259, NCT01049399, and NCT01350362 assessed them. Although a radiolabeled analogue of tideglusib has been created, clinical pharmacokinetic information is not yet available.

Leucine Rich Repeat Kinase 2 (LRRK2): Both familial and sporadic forms of PD are genetically linked to the large multidomain enzyme leucine-rich repeat kinase 2 (LRRK2)[38]. It has both kinase and GTPase activities. LRRK2 may act as a dimeric GTPase, according to the structural analysis of its ROC (Ras of complex proteins) domain in relation to GDP and Mg^{2+}. As shown by objective protein–protein interaction assays and other experimental techniques, LRRK2 is involved in several important cellular functions, including the control of autophagy, lysosomal maturation, and vesicular trafficking. Genetic knockout mice show that the lack of LRRK2 impairs autophagic clearance, resulting in the buildup of α-synuclein even when there is no discernible neurodegeneration[39]. Many drugs have been reported to block LRRK2's kinase function since the G2019S mutation is the most common and causes elevated kinase activity and neurotoxicity. Both wild-type and mutant LRRK2 are inhibited in the low micromolar range by the anthracene and phenanthrene derivatives LDN-73794 and LDN-22684, although in different ways[40]. A different drug, the oral indazole derivative MLi-2, is much more potent against the G2019S mutant form and has better pharmacokinetic characteristics and greater brain penetration. Structural studies have demonstrated a crucial link between the 14-3-3 protein and LRRK2, highlighting its regulatory importance. Given the genetic link between PD vulnerability and LRRK2 and its role in defective protein activity, the hunt for LRRK2 inhibitors as possible treatments is well-founded. Currently, a wide variety of selective, neuropenetrative, and potent inhibitors are available. Reports of on-target toxicity in non-human primates have hampered the advancement of several candidates to clinical trials, highlighting the ongoing safety and dosage concerns in long-term therapeutic uses.

Mitogen-Activated Protein Kinase (MAPK14): The serine/threonine kinase p38α, which is widely expressed in many cell types, is an essential member of the mitogen-activated protein kinase (MAPK) family. Upstream MAP2Ks precisely control its activation in response to a variety of cellular stressors, such as endoplasmic reticulum-derived, oxidative, metabolic, inflammatory, and environmental insults. This stress signalling cascade, regulated by MAPK, is now a key player in the pathophysiology of neurodegenerative disorders[41]. Throughout the prodromal stages of PD, AD, and ALS, dysregulation of p38α activity is frequently seen, indicating that it plays a crucial role in the molecular mechanisms causing neuronal dysfunction and degeneration[42] (Figure 2). While p38α inhibition has demonstrated neuroprotective effects in selected preclinical AD models, although these findings have not yet translated into consistent clinical benefit, clinical translation has been constrained by pathway redundancy, systemic toxicity, and insufficient CNS selectivity. These results demonstrate the critical role of the MAPK signalling axis in the neuropathophysiology of degenerative disorders. The inherent redundancy and complexity of MAPK networks, the strict requirement for penetration of the CNS, and the need for high target specificity to minimize off-target interactions and systemic toxicity are some of the obstacles that hinder the use of p38α-targeted strategies in clinical practice, despite these encouraging results. Consequently, the rational advancement of p38α-regulating drugs necessitates the development of sophisticated methods that offer precise molecular engagement in brain situations. Such approaches may improve the translational feasibility of MAPK-targeted therapies, though substantial challenges related to specificity and toxicity remain.

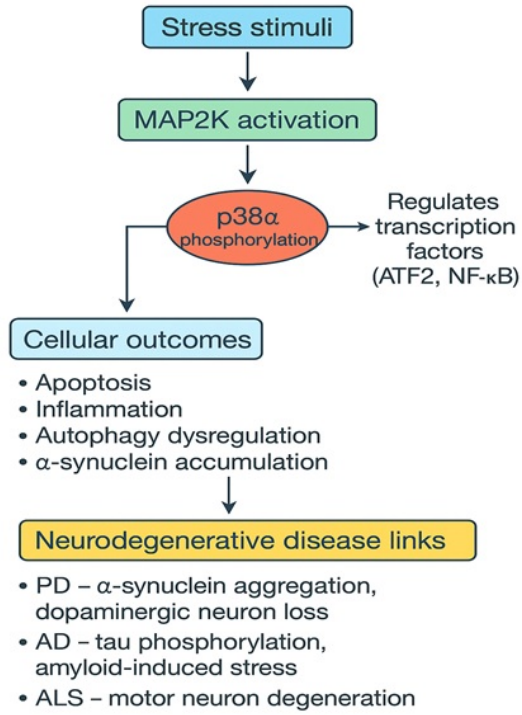

Figure 2. MAPK14 pathway in neurodegenerative disease

Receptor-Interacting Serine/Threonine-Protein Kinase 1 (RIPK1): Necroptosis depends on RIPK1's kinase activity[43]. It is an essential part of the protein complex known as the "necrosome," which starts things like MLKL activation, phosphorylation, and oligomerization, which reduce RIPK1 kinase activity in order to reduce axonal degeneration and the axon-myelin abnormalities that have been seen in experimental mouse models. Studies indicate that in the R6/2 transgenic model of HD, necrostatin-1s (Nec-1s), a particular RIPK1 inhibitor, provides neuroprotection against ischemic injury[44]. A variety of small-molecule inhibitors can inhibit RIPK1. These inhibitors bind to the protein in a number of ways. ATP-competitive substances like GSK2982772 and allosteric inhibitors like Nec-1s. Sorafenib, ponatinib, tozasertib (VX-680), and the PERK inhibitors GSK2606414 and GSK2656157 are other kinase inhibitors that act against RIPK1. Clinical trials examining DNL747, a powerful, orally accessible, brain-penetrant RIPK1 inhibitor, in populations with AD (NCT03757325) and ALS (NCT03757351) have concluded enrolment[45]. Although there is a mechanistic justification for blocking RIPK1 in necroptotic pathways, the pathway causes neurodegeneration.

Rho-Associated Kinases (ROCKs): Signalling pathways belonging to the Rho GTPase family control the actin cytoskeleton. In neurodegenerative illnesses like AD, ALS, HD, and PD, rho-associated kinases (ROCKs) also interfere with these pathways[46]. In addition to controlling the cytoskeleton, ROCK1 and ROCK2 share substrates that are involved in autophagy and vesicular trafficking. Blocking ROCK activates the Parkin-mediated mitophagy pathway, protecting neurons[47]. In ALS models, especially those that show a genetic connection to familial ALS, pharmacological and genetic therapies that use ROCK inhibitors like Y-27632 and fasudil be helpful. ROCK activity also affects microglial morphologies; proinflammatory ("M1") microglia require ROCK signalling to remain active, whereas ROCK suppression can produce anti-inflammatory ("M2") phenotypes[48]. In the last few decades, a large number of ATP-competitive type I ROCK inhibitors have been designed. Some of them, such as fasudil, ripasudil (K-115), and Y-27632, are chemically different. Since ROCK2 is mostly found in the CNS while ROCK1 is more strongly linked to vascular responses and cell death, selective ROCK2 inhibitors, like KD025 (SLx-2119) and LYC-30937, represent investigational therapeutic targets with potential relevance to neurodegenerative pathology[49]. Currently, atherosclerosis, glaucoma, hypertension, cerebral vasospasm, and aortic stiffness are among the disorders for which ripasudil and fasudil are being studied or used in clinical settings. Their poor safety margins, variable blood pressure, and low oral absorption, however, make them unsuitable for long-term use. Phase II clinical trials of fasudil in ALS patients have been carried out in spite of these obstacles (NCT01935518, NCT03792490), although the outcomes have not yet been made public.

Integrated kinase networks and pathway cross-talk in neurodegeneration: Rather than functioning as isolated entities, CSNK1D, CSF1R, DLK, GSK3β, LRRK2, MAPK14, RIPK1, and ROCK form an interconnected kinase network that collectively drives neurodegeneration through convergent mechanisms involving protein aggregation, neuroinflammation,

mitochondrial dysfunction, and neuronal death. CSNK1D and GSK3β directly regulate pathological phosphorylation of disease-defining proteins such as tau, α-synuclein, and TDP-43, thereby linking aberrant proteostasis to cytoskeletal instability and synaptic failure. These phosphorylation events sensitize neurons to stress-activated pathways mediated by DLK and MAPK14, which amplify axonal injury responses, oxidative stress signaling, and pro-apoptotic transcriptional programs. Neuroinflammatory signaling represents a key point of convergence within this kinase network. CSF1R-dependent microglial activation interfaces with MAPK14 and RIPK1 signaling to sustain chronic inflammation, cytokine release, and necroptotic cell death. RIPK1 further links inflammatory cues to neuronal loss by integrating TNF-α signaling with programmed necrosis, a mechanism increasingly implicated across AD, PD, and ALS. In parallel, LRRK2 and ROCK regulate cytoskeletal dynamics, vesicular trafficking, and mitochondrial quality control, thereby connecting inflammatory stress to defects in axonal transport, autophagy, and mitophagy. LRRK2-mediated kinase hyperactivity also potentiates MAPK and ROCK signaling, creating feed-forward loops that exacerbate dopaminergic vulnerability in PD. Importantly, these kinases influence one another through compensatory and antagonistic interactions, explaining why single-target inhibition often yields limited clinical benefit. For example, inhibition of GSK3β or LRRK2 can unintentionally enhance MAPK or RIPK1 activity, while ROCK inhibition modulates both inflammatory and mitochondrial pathways. Collectively, this network-based perspective highlights those effective therapeutic strategies must account for kinase cross-talk and pathway hierarchy rather than treating each kinase as an independent target.

Cross-talk and network interactions between kinase pathways in neurodegeneration: Protein kinase signaling in neurodegenerative diseases functions as an interconnected and highly dynamic network rather than as isolated linear pathways. Extensive cross-talk exists between major kinase cascades, enabling synergistic amplification or antagonistic modulation of pathogenic processes. In AD, GSK3β and CDK5 cooperatively drive tau hyperphosphorylation, cytoskeletal destabilization, and synaptic failure, while reciprocal regulation between the PI3K/Akt and GSK3β pathways determines neuronal survival versus apoptotic vulnerability. MAPK pathways, including ERK, JNK, and p38, integrate upstream oxidative and inflammatory stress signals with downstream transcriptional and inflammatory responses, thereby amplifying neurodegenerative cascades. In PD, LRRK2 signaling converges with MAPK and ROCK pathways to co-ordinately regulate vesicular trafficking, cytoskeletal dynamics, mitochondrial quality control, and neuroinflammation. Aberrant LRRK2 activity enhances MAPK-driven inflammatory signaling and ROCK-mediated cytoskeletal rigidity, creating a synergistic network that exacerbates dopaminergic neuron stress and α-synuclein pathology. In HD, dysregulated PKA signaling interacts with MAPK and CDK5 pathways to link mitochondrial dysfunction, impaired CREB-mediated transcription, and synaptic maladaptation. PKA normally exerts antagonistic control over pro-apoptotic kinases such as JNK and p38; disruption of this protective axis allows stress-activated pathways to dominate, accelerating neuronal injury and cognitive decline. In ALS, TBK1-mediated autophagy pathways intersect with MAPK and CK1 signaling, integrating mitochondrial damage, defective RNA metabolism, and inflammatory activation. NEK1 further interfaces with these networks through regulation of DNA damage responses and mitochondrial integrity. These synergistic interactions promote persistence of TDP-43 and FUS aggregates, impaired mitophagy, and progressive motor neuron loss. Antagonistic interactions are equally critical in shaping disease trajectories. Pro-survival kinases such as PKA and Akt counterbalance stress-activated kinases including JNK, p38, and RIPK1. Loss of this regulatory equilibrium shifts signaling dominance toward neurotoxic cascades, creating feed-forward loops of inflammation, oxidative stress, and cell death. Collectively, these observations underscore that neurodegeneration is driven by coordinated signaling network failure rather than single-pathway dysfunction. Therefore, therapeutic strategies must consider kinase network interactions and pathway hierarchy, as selective modulation of one kinase can have cascading effects across multiple disease-relevant signaling axes.

Translational Challenges: Limitations of Animal Models: Despite their indispensable contribution to deciphering kinase-driven mechanisms in neurodegeneration, currently available animal models exhibit limited predictive validity for human therapeutic outcomes. Transgenic and toxin-based rodent models typically recapitulate isolated pathological hallmarks—such as protein aggregation, neuroinflammation, or motor impairment—yet seldom reproduce the full temporal progression, selective neuronal vulnerability, and clinical heterogeneity characteristic of human AD, PD, HD, and ALS. Fundamental interspecies differences in brain cytoarchitecture, kinase isoform distribution, signaling network topology, and compensatory feedback regulation further constrain the extrapolation of pharmacokinetic, pharmacodynamic, and safety profiles from animals to patients. Consequently, numerous kinase inhibitors that demonstrate robust target engagement and neuroprotection in preclinical models fail to achieve clinical efficacy due to inadequate blood–brain barrier penetration, unanticipated off-target liabilities, or disruption of essential physiological signaling in the human CNS. Moreover, the paucity of validated translational biomarkers and the limited representation of age-dependent, sporadic disease mechanisms in experimental models impede rational patient stratification and dose optimization. Collectively, these limitations underscore the necessity for integrating human-relevant platforms, including induced pluripotent stem cell–derived neuronal systems, three-dimensional brain organoids, and longitudinal molecular biomarker strategies, to enhance translational fidelity and bridge the persistent gap between preclinical kinase biology and successful clinical intervention in neurodegenerative disorders.

Conclusion: Protein kinases play a central role in coordinating the molecular networks underlying neurodegenerative diseases by regulating pathological protein phosphorylation, mitochondrial dysfunction, impaired proteostasis, neuroinflammation, synaptic failure, and neuronal survival. Across AD, PD, HD, and ALS, dysregulated kinase signaling converges on shared pathogenic pathways, providing a mechanistic basis for overlapping clinical manifestations such as cognitive decline, motor impairment, and progressive functional disability. Importantly, the pathological relevance of individual kinases varies across diseases and disease stages,

underscoring the need to interpret kinase alterations within their specific biological and clinical contexts rather than as universal drivers of neurodegeneration. Although several kinases have emerged as potential therapeutic targets, the translation of molecular insights into clinically effective interventions remains challenging. While kinases such as GSK3β, LRRK2, RIPK1, MAPKs, and TBK1 exhibit mechanistic links to key disease processes, their therapeutic modulation is limited by pathway redundancy, compensatory signaling mechanisms, off-target effects due to kinase homology, and the risk of disrupting essential physiological functions. In addition, limitations of preclinical models, restricted blood–brain barrier penetration, interspecies differences, and the absence of robust predictive biomarkers have contributed to the modest or inconsistent outcomes observed in clinical trials. These factors highlight that mechanistic relevance alone is insufficient to ensure therapeutic viability. Future research should therefore prioritize kinases with clearly defined causal roles in disease progression, demonstrable impact on clinically meaningful endpoints, and feasible therapeutic windows. Emphasis should be placed on isoform- and context-specific modulation, biomarker-guided patient stratification, and the use of human-relevant experimental models to improve translational predictability. Rather than viewing kinase inhibition as a broadly applicable strategy, kinase-based interventions should be developed as precision tools tailored to disease stage, dominant pathogenic pathways, and patient heterogeneity. Such an approach is essential to enhance the scientific rigor, clinical relevance, and translational realism of kinase-targeted therapies in neurodegenerative disorders.

Ethical Considerations

Not applicable.

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Conflict of Interest

The authors declare that they have no competing interests.

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