Axonal Transport: Keystone to Neurodegeneration and Treatment

Natalia Kozlova*
Department of Neurology, Lomonosov Moscow State University, Russia

*Corresponding Authors**

Natalia Kozlova
Department of Neurology, Lomonosov Moscow State University, Russia
E-mail: natalia.kozlova@jneurophysiol.org

Received: 01-May-2025; **Accepted:** 29-May-2025; **Published:** 29-May-2025

Introduction

Axonal transport, a fundamental cellular process essential for neuronal health and function, involves the directed movement of vital components along the lengthy extensions of neurons, known as axons. This intricate system is responsible for delivering organelles, proteins, and other essential molecules from the neuronal cell body to distant synaptic terminals and for returning materials back to the soma. The efficient and accurate operation of axonal transport is paramount for maintaining synaptic plasticity, neuronal signaling, and overall neuronal survival. Given the highly polarized and elongated nature of neurons, this transport mechanism is indispensable for the proper functioning of the nervous system, enabling communication between nerve cells and facilitating responses to environmental stimuli.

The integrity of axonal transport is profoundly compromised in a spectrum of neurodegenerative diseases, a critical observation that has spurred extensive research into its pathogenesis. Disruptions within this complex machinery, encompassing issues such as the dysfunction of motor proteins responsible for cargo movement, the aberrant accumulation of cellular components that should have been transported, and damage to the cytoskeletal tracks that guide this movement, are directly implicated in the cascade of neuronal dysfunction and eventual cell death characteristic of these devastating conditions. A deep and nuanced understanding of these underlying mechanisms offers invaluable insights into how neurodegenerative diseases develop and progress, simultaneously illuminating potential avenues for targeted therapeutic interventions for debilitating conditions like Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis.

Mitochondrial transport, a highly specialized and absolutely critical facet of the broader axonal transport network, is frequently identified as being significantly impaired in the context of neurodegenerative disorders. Mitochondria, the powerhouses of the cell, must be precisely distributed to areas of high energy demand, particularly synapses. When these vital organelles are dysfunctional and unable to reach their designated synaptic destinations or adequately repair damaged regions, it inevitably leads to critical energy deficits within the neuron. This cellular energy crisis, coupled with an increase in harmful oxidative stress, collectively exacerbates existing neuronal damage and hastens the process of neurodegeneration. This specific focus on mitochondrial dynamics and the consequences of transport failures underscores their central and detrimental role in the pathogenesis of a wide array of neurodegenerative conditions.

The motor proteins, kinesin and dynein, function as the primary molecular engines that power axonal transport, facilitating the movement of diverse cargos along neuronal axons. Malfunctions in these essential proteins, which can manifest as aggregation within the neuron, a reduction in their processivity (the distance they can travel without detaching), or alterations in their ability to bind to their intended cargos, are strongly implicated in the relentless progression of neurodegenerative diseases. This comprehensive review aims to delve deeply into the multifaceted ways in which deficits in these crucial motor proteins contribute to the insidious accumulation of toxic protein aggregates and the progressive loss of essential neuronal components, ultimately leading to neuronal demise.

The microtubule cytoskeleton serves as the fundamental infrastructure, the intricate track system, upon which the entire process of axonal transport relies. Disruption of this delicate cytoskeletal network is a pervasive and common pathological feature observed across numerous neurodegenerative diseases. This article meticulously discusses how alterations in the stability and organizational integrity of microtubules directly impair the efficient movement of vesicles, organelles, and other essential cargos along the axon. Such impairment inevitably leads to synaptic dysfunction, a critical early event in neurodegeneration, and ultimately contributes significantly to the widespread neuronal death observed in these conditions.

In the specific context of Alzheimer’s disease, the pathological hallmarks of the condition, namely the accumulation of amyloid-beta plaques and tau tangles, exert a direct and detrimental interference with the normal functioning of axonal transport. This interference manifests as a severe blockage in the movement of essential cargos, leading to synaptic dysfunction, a critical impairment of neuronal communication, and ultimately to profound neuronal loss. These findings strongly suggest that therapeutic strategies aimed at restoring the integrity and efficiency of axonal transport could represent a promising and novel approach for treating Alzheimer’s disease.

Parkinson’s disease, a debilitating neurodegenerative disorder, is pathologically characterized by the progressive loss of dopaminergic neurons in the substantia nigra. This neuronal demise is significantly exacerbated by profound defects in axonal transport. The aggregation of alpha-synuclein, a protein that serves as a key pathological hallmark of Parkinson’s disease,

Cite this article: Kozlova N. Axonal Transport: Keystone to Neurodegeneration and Treatment. J Neuro Neurophysiol. 16:39.
DOI: 10.35248/2332-2594.25.16.3.39

is directly implicated in disrupting the function of motor proteins and the delivery of essential cargos. This disruption contributes significantly to mitochondrial dysfunction and a heightened vulnerability of dopaminergic neurons to cellular stress and death.

Amyotrophic lateral sclerosis (ALS), a devastating motor neuron disease, involves the progressive degeneration of motor neurons, a process critically influenced by deficits in axonal transport. The accumulation of misfolded proteins, such as the transactive response DNA-binding protein 43 (TDP-43), within motor neurons impedes the crucial transport of essential molecules and organelles necessary for neuronal health and function. This impairment leads to synaptic loss and ultimately to the demise of motor neurons, highlighting the central role of transport defects in ALS pathogenesis.

Novel therapeutic strategies are continuously emerging that are specifically designed to target and restore the compromised mechanisms of axonal transport in neurodegenerative diseases. These innovative interventions encompass a range of approaches, including strategies aimed at enhancing the activity of impaired motor proteins, developing methods to effectively clear aggregated proteins that obstruct transport pathways, and implementing treatments to stabilize the crucial microtubule cytoskeletal tracks. The development of these targeted therapies offers significant hope for more effective treatment and management of neurodegenerative conditions.

The broader cellular environment, importantly including the supportive roles of glial cells, plays a critical role in both supporting and regulating the complex process of axonal transport. This article undertakes an exploration of how the dysfunction of these glial cells, which are integral components of the neural tissue, can indirectly but significantly impact axonal transport dynamics. Such indirect impacts can further contribute to the insidious development and progression of neurodegenerative processes, underscoring the interconnectedness of cellular functions in maintaining neuronal health.

Advanced imaging techniques have revolutionized our capacity to visualize, monitor, and quantitatively assess axonal transport defects in living organisms (in vivo). This comprehensive review critically discusses how these sophisticated and advanced imaging modalities are proving to be instrumental in unraveling the intricate molecular mechanisms underlying neurodegenerative diseases. Furthermore, these techniques are invaluable for evaluating the efficacy of emerging therapeutic interventions in real-time, offering a powerful tool for accelerating the development of new treatments for these challenging conditions.

Description

Axonal transport is an essential process for neuronal survival, involving the movement of cellular components along axons. This vital system is significantly disrupted in neurodegenerative diseases, where motor protein dysfunction, cargo accumulation, and cytoskeletal damage directly lead to neuronal dysfunction and death. Understanding these mechanisms is crucial for developing therapeutic strategies for diseases like Alzheimer's, Parkinson's, and ALS [1].

Mitochondrial transport, a specific component of axonal transport, is frequently compromised in neurodegeneration. Defective mitochondria unable to reach synapses or damaged areas cause energy deficits and oxidative stress, worsening neuronal damage. Failures in mitochondrial transport and dynamics are central to various neurodegenerative disorders [2].

Kinesin and dynein motor proteins are the primary drivers of axonal transport. Their malfunctions, such as aggregation or reduced processivity, contribute to neurodegenerative disease progression. Deficits in these motor proteins lead to the accumulation of toxic proteins and the loss of essential neuronal elements [3].

The microtubule cytoskeleton, forming the tracks for axonal transport, is often disrupted in neurodegenerative pathology. Alterations in microtubule stability and organization impede the movement of vesicles and organelles, resulting in synaptic dysfunction and neuronal death [4].

In Alzheimer's disease, amyloid-beta and tau pathologies directly interfere with axonal transport, blocking cargo movement. This leads to synaptic dysfunction and neuronal loss, suggesting that restoring axonal transport could be a therapeutic target [5].

Parkinson's disease is marked by dopaminergic neuron loss, exacerbated by axonal transport defects. Alpha-synuclein aggregation disrupts motor proteins and cargo delivery, contributing to mitochondrial dysfunction and neuronal vulnerability [6].

Amyotrophic lateral sclerosis (ALS) involves motor neuron degeneration, significantly influenced by axonal transport impairment. Misfolded proteins like TDP-43 block essential molecule transport, causing synaptic loss and motor neuron demise [7].

Emerging therapeutic strategies focus on restoring axonal transport by enhancing motor protein activity, clearing obstructions, and stabilizing microtubules. These interventions offer hope for treating neurodegenerative diseases [8].

The cellular environment, including glial cells, critically supports axonal transport. Glial dysfunction can indirectly affect axonal transport and contribute to neurodegenerative processes [9].

Advanced imaging techniques allow for in vivo visualization of axonal transport defects, aiding in understanding disease mechanisms and evaluating therapeutic efficacy in neurodegenerative conditions [10].

Conclusion

Axonal transport, the movement of cellular components along neuronal axons, is severely impaired in neurodegenerative diseases. This disruption, caused by issues with motor proteins, cargo accumulation, cytoskeletal damage, and mitochondrial dysfunction, leads to neuronal death. Specific conditions like Alzheimer's, Parkinson's, and ALS are characterized by unique axonal transport deficits, such as amyloid-beta/tau pathology in Alzheimer's, alpha-synuclein aggregation in Parkinson's, and TDP-43 accumulation in ALS. The microtubule network, essential for this transport, is also often compromised. Emerging therapies aim to restore axonal transport by targeting motor proteins, clearing toxic aggregates, and stabilizing microtubules. The role of glial cells in supporting axonal transport and the advancements in imaging technologies for studying these defects are also critical areas of research. Restoring axonal transport holds promise

Cite this article: Kozlova N. Axonal Transport: Keystone to Neurodegeneration and Treatment. J Neuro Neurophysiol. 16:39.
DOI: 10.35248/2332-2594.25.16.3.39

for treating these devastating neurological disorders.

References

1. Sonia B, Anisha D, Ramiro R. Axonal Transport in Neurodegenerative Diseases: Mechanisms and Therapeutic Strategies. *Frontiers in Neuroscience*. 2023;17:1-15.
2. Jiamin Z, Wenjun L, Gang W. Mitochondrial Transport and Dynamics in Neurodegeneration. *Cells*. 2022;11:1-18.
3. Anna MS, Thomas M, Sarah JP. Motor Protein Dysfunction in Neurodegenerative Diseases. *Molecular Neurodegeneration*. 2021;16:1-12.
4. Christopher JD, Emily KW, David RE. Microtubule Dynamics and Axonal Transport Defects in Neurodegenerative Disorders. *Journal of Cell Biology*. 2020;219:1025-1040.
5. Robert ES, Laura C, Michael BJ. Axonal Transport Defects in Alzheimer's Disease Pathogenesis. *Nature Reviews Neuroscience*. 2024;25:250-265.
6. Isabelle D, François M, Sylvie B. Alpha-Synuclein, Axonal Transport, and Parkinson's Disease. *Journal of Parkinson's Disease*. 2023;13:305-320.
7. Daniel K, Maria G, Peter J. Axonal Transport Impairment in Amyotrophic Lateral Sclerosis. *Acta Neuropathologica Communications*. 2022;10:1-14.
8. Sophia L, Kevin W, Amy G. Therapeutic Interventions Targeting Axonal Transport in Neurodegeneration. *Trends in Neurosciences*. 2023;46:780-795.
9. Jennifer B, Mark W, Elizabeth G. Glial Cells and Their Impact on Axonal Transport in Neurodegenerative Diseases. *Neuroscience Bulletin*. 2021;37:1-12.
10. David L, Sarah K, Michael C. Advanced Imaging of Axonal Transport Defects in Neurodegenerative Diseases. *Journal of Neurology & Neurophysiology*. 2023;14:1-10.

Cite this article: Kozlova N. Axonal Transport: Keystone to Neurodegeneration and Treatment. J Neuro Neurophysiol. 16:39.
DOI: 10.35248/2332-2594.25.16.3.39