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Neuronal Lipophagy in Neurodegenerative Diseases: Mechanisms, Dual Roles, and Emerging Therapeutic Targets

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Abstract:

Neuronal lipophagya specialized form of autophagy targeting lipid droplets for lysosomal degradationhas emerged as a critical regulator of lipid metabolism, redox balance, and mitochondrial function in the central nervous system (CNS). This review comprehensively explores the molecular mechanisms governing neuronal lipophagy and its dual role in the pathogenesis and protection against major neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). Impaired lipophagic flux has been implicated in lipid droplet accumulation, oxidative stress, and mitochondrial dysfunction, while excessive activation may lead to lipid peroxidation and ferroptosis. We examine key regulatory pathwayssuch as TFEB, Rab proteins, LAMP2A, and FOXO transcription factorsand their disease-specific disruptions. Furthermore, we discuss emerging therapeutic strategies including pharmacological agents (resveratrol, metformin, trehalose), gene editing, miRNA modulation, and nanotechnology-based delivery systems. Lifestyle interventions like intermittent fasting, ketogenic diets, and exercise are also evaluated for their capacity to induce neuroprotective lipophagy. Finally, we highlight future directions involving single-cell omics, biomarker discovery, and combinatorial therapies aimed at translating lipophagy modulation into clinical neurotherapeutics. Understanding and harnessing neuronal lipophagy offers a promising frontier for combating the rising burden of neurodegenerative diseases.

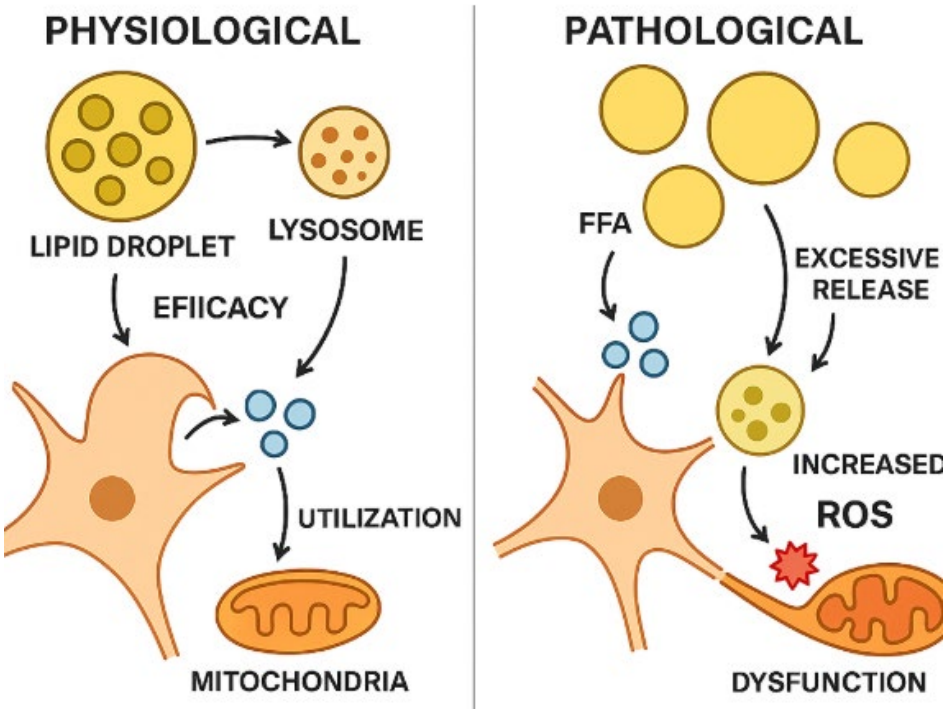
Keywords: Neuronal lipophagy, neurodegenerative diseases, lipid metabolism, autophagy, Alzheimer's disease, Parkinson's disease, TFEB, mitochondrial dysfunction, ferroptosis, nanotherapy, lifestyle interventions, omics, CNS biomarkers.

1. INTRODUCTION

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) constitute a major global health burden, with increasing incidence linked to aging populations. These disorders are characterized by the progressive loss of neuronal function and eventual cell death, often accompanied by protein aggregation, oxidative stress, and metabolic dysregulation. Despite intensive research, effective curative therapies remain elusive, necessitating the identification of novel cellular mechanisms and therapeutic targets.A growing body of evidence implicates lipid metabolism dysregulation as a common pathological feature in NDs.[1-5] Neuronal cells possess a unique

lipid architecture essential for synaptic function, membrane dynamics, and signaling cascades. Lipid droplets (LDs), traditionally viewed as inert lipid stores, have emerged as dynamic organelles involved in buffering toxic lipids, maintaining redox homeostasis, and regulating energy supply. The brain, although comprising only 2% of the body mass, contains approximately 20% of total body cholesterol, underscoring the critical role of lipid management in neuronal physiology.Autophagy is a vital cellular process responsible for the degradation and recycling of cytoplasmic constituents. Among its specialized forms, lipophagy refers to the selective autophagic degradation of lipid droplets via lysosomal pathways. Originally characterized in hepatocytes, lipophagy plays an essential role in lipid mobilization and energy homeostasis. Recent studies have demonstrated its presence and significance in neuronal cells, where tight control of lipid levels is crucial to prevent neurotoxicity.Impairment of neuronal lipophagy has been linked to the pathogenesis of several neurodegenerative conditions. For instance, disrupted lipophagic flux may lead to lipid droplet accumulation, impaired mitochondrial function, and oxidative stress, all of which contribute to neuronal death. Conversely, excessive activation of lipophagy under certain pathological conditions might promote the release of free fatty acids (FFAs) that trigger lipotoxicity.[6-10]

Figure 1: Schematic illustration of the lipophagy process in neurons under physiological vs. pathological conditions, including lysosomal targeting of lipid droplets, FFA release, and interactions with mitochondria and ROS production.



The present review aims to consolidate the current understanding of neuronal lipophagy in the context of neurodegeneration. We will explore the molecular mechanisms regulating lipophagy in neurons, its dual roles in disease progression and protection, and therapeutic strategies targeting this pathway. Furthermore, we highlight future research directions including omics-based profiling, biomarker development, and drug delivery innovations tailored to modulate lipophagy in the central nervous system (CNS). [11-12]

Table 1: Summary of neurodegenerative diseases linked to lipid metabolism dysfunction and associated changes in lipophagy.

Disease	Lipid-Related Features	Lipophagy Status	Pathological Consequence	References
Alzheimer's Disease	Cholesterol dysregulation, phospholipid imbalance	Impaired	Amyloid-β accumulation, synaptic loss	13
Parkinson's Disease	Ceramide buildup, lipid raft alteration	Impaired or dysregulated	α-synuclein aggregation, dopaminergic neuron loss	14
ALS	Mitochondrial lipid peroxidation, altered lipid signaling	Impaired	Motor neuron degeneration, oxidative stress	15

By dissecting the dual nature of neuronal lipophagy, this review seeks to provide insights into its therapeutic potential and the challenges involved in targeting this complex, stage-dependent process in neurodegenerative diseases.

2. Molecular Mechanisms of Neuronal Lipophagy

2.1. Types of Autophagy in Neural Tissue

Neurons, due to their post-mitotic nature and high metabolic demand, rely heavily on autophagic processes to maintain cellular homeostasis. Three primary forms of autophagy operate in the neural milieu:

- **Macroautophagy:** This canonical pathway involves the formation of double-membraned autophagosomes that engulf lipid droplets and deliver them to lysosomes for degradation. Macroautophagy is crucial for clearing large aggregates and organelles and is highly active in long neuronal axons.

- **Microautophagy:** In this process, lysosomal membranes directly invaginate to engulf small portions of cytoplasmic content, including lipid droplets. Although less well-characterized in neurons, microautophagy may contribute to lipid turnover under stress conditions.
- **Chaperone-Mediated Autophagy (CMA):** CMA selectively targets proteins bearing KFERQ-like motifs, directing them to lysosomes via LAMP2A. In neurons, CMA has also been shown to regulate lipid metabolism indirectly by modulating lipid droplet-associated proteins.

Compared to hepatic lipophagy, neuronal lipophagy is less studied but displays unique regulatory features due to the brain's high lipid content and compartmentalization. While hepatocytes use lipophagy for energy production during fasting, neurons may use it for membrane remodeling and to prevent lipid-induced toxicity rather than energy extraction.[16-20]

2.2. Regulators in Neurons

Lipophagy in neurons is governed by a complex network of regulators, some of which overlap with those in hepatic tissue but exhibit brain-specific dynamics:

- **LAMP2A:** A critical receptor for CMA, LAMP2A is highly expressed in neurons. Its abundance regulates the lysosomal uptake of lipid-associated proteins and is often reduced in aged or diseased brains.
- **ATGL (Adipose Triglyceride Lipase):** While predominantly studied in peripheral tissues, ATGL also contributes to neuronal lipid catabolism by hydrolyzing triglycerides and facilitating lipophagy initiation.
- **PNPLA8 (Patatin-like Phospholipase Domain-containing Protein 8):** This mitochondrial lipase is implicated in neuronal lipid remodeling and the formation of autophagic vesicles around lipid droplets.
- **Rab Proteins (Rab7, Rab10):** These small GTPases regulate vesicle trafficking, essential for the maturation of autolysosomes. Rab7, in particular, is crucial for the lysosomal degradation of lipid droplets in neurons.
- **TFEB (Transcription Factor EB):** A master regulator of lysosomal biogenesis and autophagy, TFEB modulates the transcription of genes involved in lipid metabolism. Its activation enhances lipophagy and is considered neuroprotective.
- **FOXO Transcription Factors:** These stress-responsive factors modulate the expression of autophagy and lipid metabolism genes. FOXO3, for example, activates pathways that lead to enhanced lipid clearance under oxidative stress.

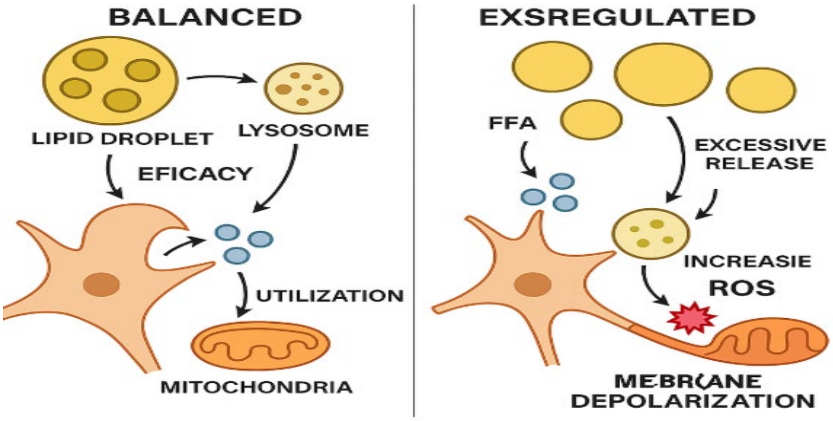
Neuronal lipid droplets are smaller and more dynamic compared to those in peripheral tissues. They are enriched in polyunsaturated fatty acids (PUFAs), making them more susceptible to

peroxidation, and are strategically positioned near mitochondria and synaptic terminals, highlighting their functional importance in rapid lipid turnover and signaling.

2.3. Interplay with Mitochondrial Dynamics and Oxidative Stress

Lipophagy is intricately connected to mitochondrial health in neurons. Lipid droplets serve as a buffer against excess FFAs, which, if unregulated, can induce mitochondrial dysfunction via oxidative stress and lipid peroxidation. During neuronal stress, lipophagy is activated to prevent FFA accumulation and ROS generation.Conversely, mitochondrial impairment can feedback into lipophagy regulation. For example, mitochondrial fission and reduced ATP production impair autophagosome formation. Dysregulated lipophagy, in turn, exacerbates mitochondrial oxidative damage, creating a vicious cycle.[21-25]

Figure 2: Interaction between lipophagy, lipid droplets, and mitochondria in neurons. The diagram illustrates how balanced lipophagy supports mitochondrial function, while dysregulation leads to ROS production, membrane depolarization, and neuronal injury.



Understanding this crosstalk is essential, as interventions aimed at restoring lipophagy may also rejuvenate mitochondrial function, offering a two-pronged strategy for neurodegenerative disease management.[26-27]

3. Lipophagy in Specific Neurodegenerative Disorders

3.1. Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, marked by extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau. Both pathological proteins disrupt autophagy-lysosome pathways, with downstream consequences on lipid metabolism.Aβ accumulation has been shown to

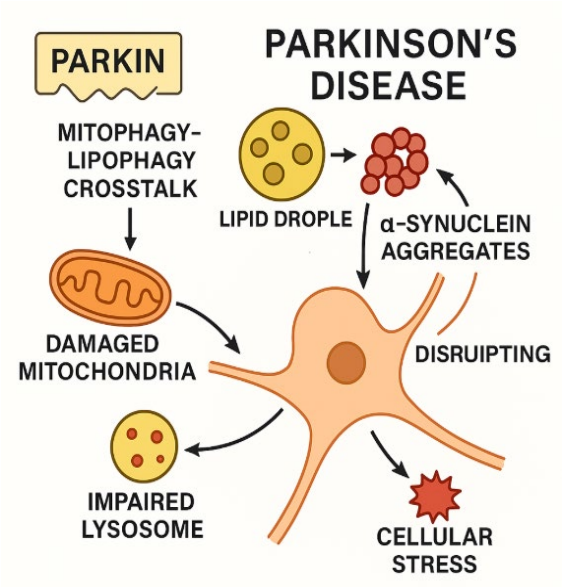
impair autophagosome-lysosome fusion, leading to defective clearance of lipid droplets (LDs) and other cellular debris. Additionally, hyperphosphorylated tau impairs axonal transport of autophagosomes, further exacerbating lipophagic dysfunction. Postmortem AD brains exhibit increased lipid droplet accumulation in neurons, indicating impaired lipophagic clearance.This lipid dysregulation contributes to membrane rigidity, endoplasmic reticulum (ER) stress, and mitochondrial dysfunction. Furthermore, reduced expression of lipophagy-regulating proteins like LAMP2A and TFEB has been documented in AD models, linking impaired lipophagy to neuronal stress and synaptic loss.

3.2. Parkinson's Disease

Parkinson's disease (PD) is characterized by dopaminergic neuronal loss in the substantia nigra and the presence of Lewy bodies composed of α-synuclein. Emerging data reveal that α-synuclein interacts with lipid droplets and impairs their turnover via lipophagy.

Parkin, an E3 ubiquitin ligase mutated in familial PD, is not only critical for mitophagy but also implicated in lipid homeostasis. Loss of Parkin impairs the degradation of damaged mitochondria and associated lipid droplets, highlighting the mitophagy-lipophagy crosstalk in PD pathology.Rab7 dysfunction has been observed in PD, leading to impaired autophagosome maturation and lipid droplet accumulation. The dysregulation of TFEB in dopaminergic neurons further contributes to impaired lysosomal degradation of lipid stores, promoting cellular stress and neurodegeneration.[28-33]

Figure 3: Schematic of α-synuclein and Parkin-mediated disruption of mitophagy-lipophagy crosstalk in dopaminergic neurons in Parkinson's disease.



3.3. Amyotrophic Lateral Sclerosis (ALS)

ALS is a fatal neurodegenerative disease affecting upper and lower motor neurons. Accumulation of lipid droplets has been reported in spinal cord motor neurons of ALS patients and transgenic models, indicating impaired lipid turnover.TDP-43, a key pathological protein in ALS, disrupts RNA processing and has been shown to interfere with autophagic flux, including lipophagy. This interference results in defective lipid clearance, exacerbated oxidative stress, and compromised mitochondrial function.Additionally, mutations in autophagy-related genes such as SQSTM1 (p62) and UBQLN2, commonly found in ALS, further highlight the relevance of impaired autophagy-lipid interactions in disease progression.[34-37]

3.4. Huntington's Disease and Other Tauopathies

Huntington's disease (HD) and related tauopathies (e.g., frontotemporal dementia) exhibit altered lipid profiles and impaired lipid degradation pathways. In HD, mutant huntingtin protein interferes with TFEB nuclear translocation, suppressing lysosomal biogenesis and lipid clearance.Similarly, tauopathies lead to hyperphosphorylated tau-mediated blockade of axonal transport and lysosomal trafficking, culminating in lipid droplet accumulation. These accumulated lipids become prone to peroxidation, generating reactive lipid species that damage cellular membranes and organelles.[38-40]

Table 2: Summary of lipophagic impairments in major neurodegenerative disorders.

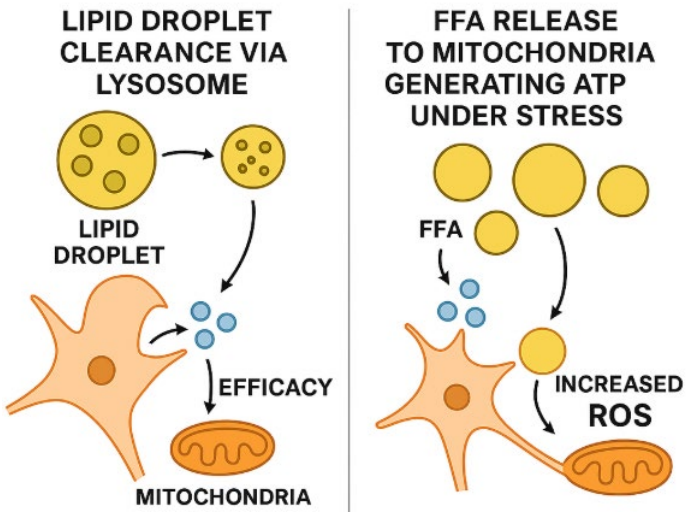
Disease	Pathological Protein	Lipophagic Disruption	Key Consequences	References
Alzheimer's	Aβ, Tau	Impaired LD clearance, reduced LAMP2A/TFEB	Synaptic loss, ER stress	41
Parkinson's	α-synuclein, Parkin	Mitophagy-lipophagy decoupling	Mitochondrial damage, LD accumulation	42
ALS	TDP-43, p62	Autophagic flux block, LD buildup	Motor neuron death, oxidative stress	43
Huntington's	mHtt, Tau	TFEB inhibition, lysosomal dysfunction	Lipid peroxidation, neurotoxicity	44

4. Dual Role of Lipophagy in Neurodegeneration

4.1. Neuroprotection via Lipid Clearance and Mitochondrial Support

Under physiological conditions, lipophagy serves as a vital neuroprotective mechanism. Neurons rely on tightly regulated lipid turnover to avoid accumulation of toxic lipids and to supply energy substrates during metabolic stress. Through selective autophagic degradation of lipid droplets (LDs), lipophagy facilitates the clearance of excess free fatty acids (FFAs) and oxidized lipids, preventing their integration into neuronal membranes where they could exert cytotoxic effects.Lipophagy also supports mitochondrial function by providing fatty acid substrates for beta-oxidation, enhancing ATP production under conditions such as fasting, hypoxia, or neuronal injury. This lipid-to-energy conversion enables neurons to maintain synaptic transmission and ionic gradients in energy-deprived states. Additionally, removal of peroxidized lipids through lipophagy mitigates oxidative damage, preserving mitochondrial integrity and reducing reactive oxygen species (ROS) generation.[45-50]

Figure 4: Dual role of lipophagy: beneficial lipid clearance and FFA supply to mitochondria for ATP generation under stress.



4.2. Neurotoxicity via Excessive Lipid Mobilization

While basal lipophagy is essential for neuronal homeostasis, excessive or dysregulated lipophagy can contribute to neurotoxicity. Overactivation of lipophagy may result in the uncontrolled release of FFAs into the cytoplasm, overwhelming the mitochondrial oxidation capacity and leading to lipid peroxidation. This peroxidative damage to cellular membranes,

including those of mitochondria and synapses, triggers apoptotic pathways and neuroinflammation.

One of the key outcomes of this process is ferroptosis, a form of regulated cell death driven by iron-dependent lipid peroxidation. Neurons are particularly susceptible to ferroptosis due to their high PUFA content and oxidative environment. Furthermore, hyperactivation of lipophagy may deplete membrane-stabilizing lipid species, impairing vesicular trafficking and synaptic plasticity.Thus, lipophagy operates within a narrow optimal range in neurons, and its imbalance whether hypo- or hyper-active can lead to detrimental effects.[51-55]

Table 3: Protective vs. toxic effects of lipophagy in neurons.

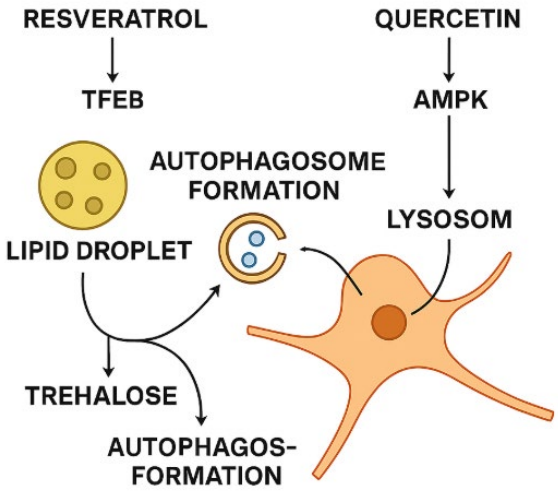
Lipophagy Status	Functional Role	Beneficial Effects	Pathological Outcomes	References
Balanced/Moderate	Lipid clearance, FFA supply	Mitochondrial support, reduced ROS	Neuroprotection, energy balance	56
Excessive/Uncontrolled	FFA overflow, lipid peroxidation	Mitochondrial overload	Ferroptosis, synaptic damage	57
Deficient	Lipid droplet accumulation	ER stress, oxidative damage	Neuronal death, neurodegeneration	58

5. Lipophagy as a Therapeutic Target

5.1. Pharmacological Activators and Inhibitors

Several small-molecule compounds have been identified to modulate lipophagy, offering therapeutic promise in neurodegenerative conditions. Among these, natural polyphenols such as resveratrol and quercetin have been shown to enhance autophagic flux and activate TFEB, thereby promoting lipophagic degradation of lipid droplets. Metformin**, a** well-established AMPK activator, stimulates autophagy and has demonstrated neuroprotective effects in models of Alzheimer's and Parkinson's diseases. **Trehalose**, a disaccharide autophagy enhancer, facilitates lipophagy by promoting autophagosome formation and lysosomal fusion.However, a critical challenge in translating these compounds into effective therapies lies in their limited permeability across the blood-brain barrier (BBB). CNS drug delivery remains a major hurdle, with issues related to drug bioavailability, metabolic stability, and off-target effects. Efforts are underway to design brain-penetrant analogs and utilize novel drug carriers to overcome these barriers.59-62

Figure 5: pharmacological modulators of lipophagy and their mechanisms of action in neuronal cells.



5.2. Genetic and Epigenetic Modulators

Genetic modulation of lipophagy offers another avenue for therapeutic intervention. Transcriptional regulators such as TFEB can be overexpressed to enhance lysosomal biogenesis and lipid catabolism. Preclinical studies show that TFEB activation restores lipid clearance and mitigates neurotoxicity in AD and HD models.Epigenetic mechanisms, including microRNAs (miRNAs), have also emerged as critical modulators. miR-155 and miR-214-3p, for example, negatively regulate autophagy-related genes and impair lipophagy under pathological conditions. Inhibiting these miRNAs may rescue autophagic function and promote neuroprotection.Advanced genome editing techniques like CRISPR/Cas9 can be employed to upregulate or silence genes implicated in lipophagy pathways. These approaches offer high specificity and the potential for long-term correction of lipophagic defects, though concerns about off-target effects and delivery remain.[63-66]

5.3. Nanotechnology-Based Delivery Systems for Brain-Targeted Lipophagy Modulation

Nanotechnology holds significant potential for delivering lipophagy-modulating agents across the BBB with enhanced precision and efficacy. Lipid-based nanoparticles, polymeric micelles, and dendrimers have been engineered to encapsulate drugs such as resveratrol or TFEB activators, protecting them from degradation and enabling targeted delivery to neuronal tissue.Functionalization of nanocarriers with ligands that bind to BBB transporters (e.g., transferrin, lactoferrin) or incorporation of stimuli-responsive elements (e.g., pH-sensitive or redox-responsive coatings) further enhances specificity and controlled release. These nanosystems can be tailored to co-deliver gene editing tools or RNAi molecules alongside pharmacological agents, offering a combinatorial approach to restore lipophagy.[67-70]

Table 4: Emerging strategies for lipophagy-targeted therapeutics in neurodegeneration.

Strategy	Target	Mode of Action	Advantages	Challenges	References
Small Molecules	AMPK, TFEB	Activate autophagy/lipophagy	Easy administration	Poor BBB penetration	71
miRNA Inhibition	miR-155, miR-214-3p	Restore autophagy gene expression	High specificity	Delivery, stability	72
TFEB Overexpression	Lysosomal biogenesis	Enhances lipid clearance	Broad lysosomal effect	Potential for overactivation	73
Nanocarriers	CNS-targeted delivery	Enhanced BBB penetration	Targeted, sustained release	Complexity, scalability	74

6. Lifestyle, Diet, and Neuroprotection via Lipophagy

Lifestyle interventions such as dietary modifications and physical activity have emerged as potent modulators of autophagy, including lipophagy, offering non-pharmacological avenues for neuroprotection. Among these**,** intermittent fasting**,** ketogenic diets**,** and regular exercise have demonstrated consistent ability to induce autophagy in neuronal tissues.[75-76]

Fasting and Caloric Restriction

Intermittent fasting (IF) and caloric restriction (CR) are powerful inducers of autophagic flux. These metabolic stressors activate AMPK and inhibit mTOR, thereby upregulating lipophagy. Animal studies show that fasting enhances neuronal lipid droplet degradation, improves mitochondrial function, and reduces oxidative damage effects linked to improved cognitive performance and delayed neurodegeneration.[77]

Ketogenic Diets

Ketogenic diets, characterized by high fat and low carbohydrate intake, shift metabolism toward lipid utilization and ketone body production. This metabolic switch upregulates lipophagy to meet the brain's altered energy demands. In preclinical models of Alzheimer's and Parkinson's diseases, ketogenic interventions have been associated with reduced lipid peroxidation, improved autophagic flux, and preservation of synaptic integrity.

Physical Exercise

Exercise acts as a systemic autophagy inducer. In neurons, exercise-triggered signals such as elevated BDNF (brain-derived neurotrophic factor) and increased mitochondrial biogenesis correlate with enhanced lipophagy. Both aerobic and resistance training have shown to reduce lipid droplet accumulation and improve energy homeostasis in aged or disease-affected brain regions.[78-80]

Clinical Evidence and Gaps

Despite promising preclinical data, clinical studies assessing lipophagy modulation by lifestyle interventions are sparse. Human trials have reported improvements in cognitive function, metabolic parameters, and brain imaging biomarkers following fasting or ketogenic diets, but direct evidence of enhanced lipophagy in human neurons remains lacking. Biomarkers for lipophagic activity and standardized protocols for lifestyle interventions need to be established for translational applications.[80-85]

Figure 6: Lifestyle-based regulation of lipophagy in the brain: fasting, ketogenic metabolism, and exercise signaling pathways leading to autophagy induction.

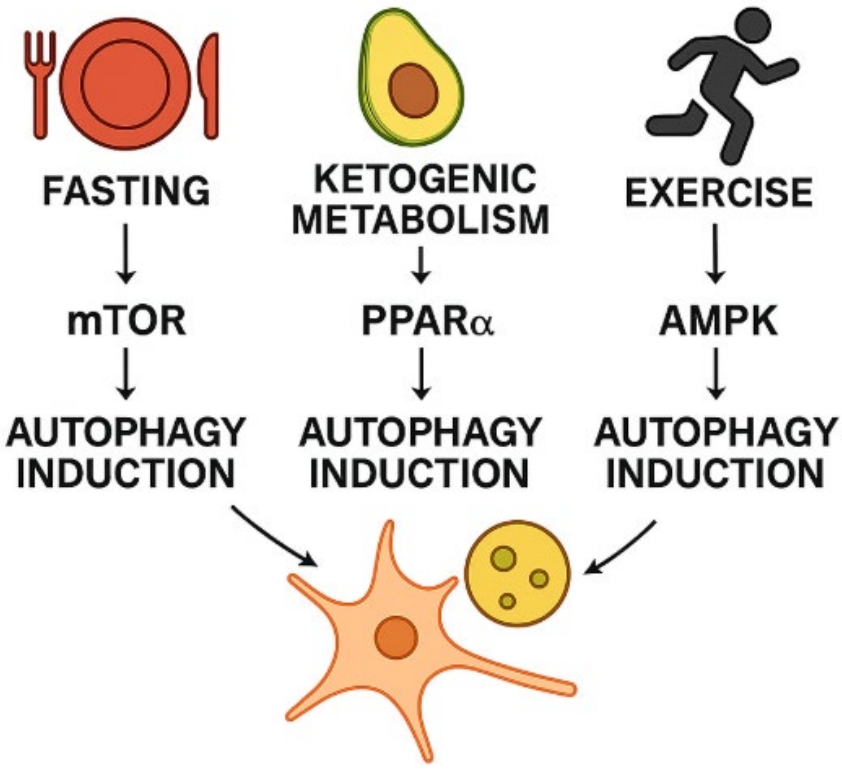


Table 5: Summary of lifestyle interventions and their proposed effects on neuronal lipophagy.

Intervention	Mechanism	Lipophagy Pathways	Neuroprotective Outcomes	References
Fasting	AMPK activation, mTOR inhibition	↑ Autophagy, ↑ TFEB	Reduced ROS, improved cognition	86
Ketogenic Diet	Ketone metabolism, lipid shift	↑ Lipid mobilization, ↑ LD clearance	Reduced lipid peroxidation	87
Exercise	BDNF, mitochondrial biogenesis	↑ Mitophagy, ↑ lipophagy	Enhanced synaptic plasticity	88

7. Future Perspectives

Advancing the therapeutic and diagnostic potential of lipophagy in neurodegenerative diseases requires a multi-dimensional research strategy. Several innovative directions are currently being explored and hold great promise for clinical translation

Single-Cell Omics to Map Neuronal Lipophagy States

Emerging technologies in single-cell transcriptomics and proteomics enable high-resolution profiling of individual neurons, allowing the identification of cell-type-specific lipophagic activity. These approaches can map spatial and temporal dynamics of lipophagy across different brain regions and disease stages. Integrating single-cell data with lipidomics and spatial transcriptomics could uncover unique lipophagy-related signatures in vulnerable neuronal populations.

Lipophagy Biomarkers for Early Diagnosis

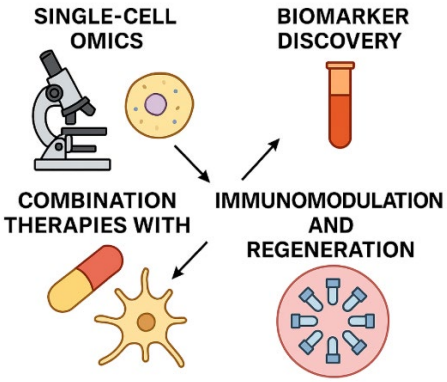
There is an urgent need to develop reliable biomarkers that reflect lipophagic activity in the human brain. Potential candidates include circulating lipophagy-related miRNAs, lysosomal enzyme levels, or lipid droplet-associated proteins detectable in cerebrospinal fluid (CSF) or

blood. Early diagnostic tools based on lipophagy biomarkers could facilitate pre-symptomatic intervention and monitoring of therapeutic responses.

Combining Lipophagy Modulation with Immunotherapy and Neuroregeneration

Given the multifactorial nature of neurodegenerative disorders, integrating lipophagy-targeted strategies with other therapeutic modalities may enhance efficacy. For instance, lipophagy activation can complement immunotherapies by reducing lipid-induced neuroinflammation. Likewise, improved lipid turnover supports mitochondrial health, which is essential for successful neuroregenerative interventions such as stem cell therapies and neurotrophic factor delivery. 89-95

Figure 7: Future roadmap for lipophagy research: from single-cell omics and biomarker discovery to combination therapies with immunomodulation and regeneration.



8. Discussion

The intricate role of neuronal lipophagy in maintaining central nervous system (CNS) homeostasis has emerged as a critical axis in the pathophysiology of neurodegenerative diseases. As this review illustrates, lipophagy acts as both a defender and a potential disruptor within the neuronal milieu, its function contingent upon a finely balanced interplay between lipid turnover, mitochondrial health, and autophagic capacity. The dualistic nature of lipophagy protective under physiological or moderately stressed conditions, yet destructive when dysregulated highlights its complex regulatory architecture and therapeutic promise.[95-120]

In Alzheimer's disease (AD), the dysfunction of key lipophagy regulators such as TFEB and LAMP2A correlates with the accumulation of lipid droplets (LDs), impaired autophagosome maturation, and oxidative damage. These molecular events synergize with hallmark pathologies like amyloid-beta and tau aggregation, exacerbating synaptic loss and cognitive decline. Similarly, in Parkinson's disease (PD), the convergence of mitophagy-lipophagy

disruption due to Parkin mutations and α-synuclein toxicity exemplifies how impaired lipid clearance amplifies dopaminergic neuronal stress. The pathogenic framework extends to ALS and Huntington's disease (HD), where autophagy gene mutations and TFEB inhibition respectively contribute to lipid peroxidation, neuroinflammation, and neuronal apoptosis.

A pivotal observation across these disorders is that lipid droplets in neurons are not inert stores but dynamic entities involved in redox regulation, mitochondrial interaction, and synaptic plasticity. Their accumulation or excessive mobilization creates a metabolic bottleneck, tipping the neuronal fate toward degeneration. The emerging understanding that lipophagy failure contributes to ferroptosis a form of lipid-peroxidation-driven cell death further solidifies its central role in neurodegeneration.Therapeutically, modulating lipophagy presents a compelling strategy. [121-150] Pharmacological agents like resveratrol, metformin, and trehalose have shown efficacy in restoring autophagic flux, yet their translation is hindered by challenges such as blood-brain barrier permeability and target specificity. Novel approaches leveraging nanotechnology-based delivery systems offer promising solutions, enabling the encapsulation and targeted release of lipophagy modulators to neuronal populations. Concurrently, gene therapy tools, including TFEB overexpression and miRNA inhibition, hold potential for long-term correction of lipophagic defects.Lifestyle interventions such as intermittent fasting, ketogenic diets, and exercise represent attractive, non-invasive methods to enhance neuronal lipophagy. These interventions stimulate AMPK and inhibit mTOR, activating lipid degradation pathways and improving mitochondrial resilience. However, while preclinical models provide compelling evidence, human trials remain sparse, and the field lacks reliable biomarkers to monitor lipophagic flux in vivo.[151-170]

Looking forward, integrating single-cell omics with spatial lipidomics may unravel cell-type-specific lipophagy networks, unveiling vulnerable neuronal subpopulations and facilitating precision interventions. Moreover, combining lipophagy enhancement with immunotherapeutics and regenerative strategies may address the multifactorial etiology of neurodegenerative diseases more effectively than monotherapies.In conclusion, neuronal lipophagy stands at the crossroads of lipid metabolism, autophagy, and neurodegeneration. Unraveling its mechanistic intricacies and therapeutic modulators offers a novel path for halting or even reversing the trajectory of debilitating neurodegenerative conditions. The future of lipophagy research lies in translational convergence bridging molecular insights with clinical innovation. [170-191]

9. Conclusion

Neuronal lipophagy has emerged as a critical cellular mechanism in maintaining lipid homeostasis, mitochondrial integrity, and redox balance in the central nervous system. As neurodegenerative diseases such as Alzheimer's, Parkinson's, ALS, and Huntington's disease

continue to impose an escalating burden on global health, understanding the mechanistic nuances of lipophagy is increasingly essential. This review has elucidated the dualistic nature of lipophagyits role in promoting neuronal survival through controlled lipid degradation and its potential to cause neurotoxicity when dysregulated or overactivated.Evidence across multiple neurodegenerative models highlights that impaired lipophagic flux contributes to lipid droplet accumulation, mitochondrial dysfunction, oxidative stress, and ultimately neuronal death. Conversely, therapeutic strategies that restore or fine-tune lipophagyranging from small molecules, gene editing, and miRNA modulation to nanotechnology-based delivery systems and lifestyle interventionshold significant promise for disease mitigation.Nonetheless, clinical translation remains hindered by challenges such as blood-brain barrier penetration, lack of specific biomarkers, and limited human data. Future research must focus on integrating omics technologies, developing non-invasive diagnostics, and pursuing combinatorial therapies that align lipophagy modulation with immunoregulation and neuroregeneration.

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