Etiological and Mechanistic Analysis of Autolysosomal Acidification Failure in Neuronal Autophagy

1. Introduction: The Thermodynamic Imperative of Lysosomal pH in Neuronal Homeostasis

The survival of post-mitotic neurons is predicated on the efficient clearance of intracellular waste, a task largely delegated to the autophagy-lysosomal pathway (ALP). Unlike proliferative cells, which can dilute aggregated proteins and damaged organelles through cell division, neurons must actively degrade these substrates to prevent cytotoxicity over a lifespan that can span decades. The fulcrum of this degradative capacity is the lysosomal proton gradient. The maintenance of a highly acidic luminal pH (typically 4.5–5.0) is not merely a passive environmental requirement for hydrolase activity; it is an electrochemical potential energy source that drives solute transport, calcium buffering, and the fusion of autophagosomes with lysosomes.[1]

The failure to acidify the autolysosome constitutes a catastrophic event in neuronal physiology. When the proton gradient dissipates, proteolytic enzymes such as cathepsins become catalytically inert. This results in the accumulation of undigested autophagic substrates—including amyloid-beta (Aβ), alpha-synuclein, and defective mitochondria—within the lumen of "giant" autolysosomes.[3] This pathological state, termed "lysosomal storage," is a convergent feature of major neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS).[3]

This report provides an exhaustive analysis of the multifactorial etiologies underlying autolysosomal acidification failure in neurons. We dissect the biophysical collapse of the V-ATPase proton pump, the disruption of ion counter-transport systems, the dysregulation of kinase signaling networks, the failure of fusion machinery, and the impact of environmental toxins and glial dysfunction.

2. The V-ATPase Complex: Structural Integrity, Assembly, and Chaperone Defects

The primary engine of lysosomal acidification is the Vacuolar-type H+-ATPase (V-ATPase), a rotary nanomotor that couples ATP hydrolysis to proton translocation. The complex is composed of two domains: the cytosolic V1 domain (subunits A–H), responsible for ATP hydrolysis, and the membrane-embedded V0 domain (subunits a, c, c'', d, e), which functions as the proton pore.[6] In neurons, the integrity of this complex is paramount, and its dysfunction is the most direct cause of acidification failure.

2.1 Structural Vulnerability and Ischemic Dissociation

The V-ATPase is a dynamic complex. The V1 and V0 domains can reversibly dissociate, a regulatory mechanism used to conserve ATP during starvation or glucose deprivation. However, in pathological states such as ischemic stroke, this dissociation becomes irreversible. Studies indicate that the A subunit of the V1 sector and the V0a1 subunit are susceptible to rapid degradation or dissociation following cerebral artery occlusion, halting proton pumping immediately.[7] Furthermore, the V-ATPase serves as a signaling hub, interacting with the Ragulator complex to sense amino acids and regulate mTORC1. Dysfunction in the pump therefore creates a dual deficit: a failure of degradation (pH elevation) and a failure of metabolic signaling (mTORC1 dysregulation).[2]

2.2 The Critical Role of V-ATPase Assembly Factors

Efficient proton pumping requires the precise assembly of the V-ATPase in the endoplasmic reticulum (ER) prior to its trafficking to the lysosome. This process is orchestrated by a suite of dedicated assembly factors, the failure of which leads to a paucity of functional pumps.

2.2.1 VMA21: The Master Chaperone

VMA21 is an essential ER-resident chaperone that orchestrates the assembly of the V0 proton-translocating pore. It binds to the hydrophobic subunits (c, c'', d) and prevents their premature degradation. Crucially, VMA21 possesses an ER-retrieval motif. It escorts the nascent V0 domain to the Golgi to allow V1 binding but is then retrieved back to the ER to catalyze further assembly cycles.8
Pathogenic mutations that reduce VMA21 expression or impair its retrieval function lead to X-linked Myopathy with Excessive Autophagy (XMEA). In this condition, the assembly of the V0 domain is stalled; fewer pumps reach the lysosome, resulting in a chronic elevation of lysosomal pH. This de-acidification blocks the final step of autophagy, causing the accumulation of massive, non-degradative autophagic vacuoles that eventually consume the cytoplasm.9

2.2.2 The TLDc Protein Family and Oxidative Protection

Recent genomic screens have identified the TLDc domain-containing proteins—specifically NCOA7, OXR1, and TBC1D24—as critical regulators of V-ATPase function. These proteins associate with the V-ATPase and appear to stabilize the complex, particularly under conditions of oxidative stress.[11] Mutations in *TBC1D24* are linked to epilepsy and neurodegeneration, suggesting that the failure to stabilize the proton pump against the high oxidative load of the neuronal environment contributes to acidification defects. Similarly, DMXL2 is required for the V0/V1 interaction, and its deficiency leads to Ohtahara syndrome, a severe epileptic encephalopathy.[11]

2.3 Presenilin-1: A Non-Canonical V-ATPase Chaperone

One of the most significant breakthroughs in understanding Alzheimer's pathology is the identification of Presenilin-1 (PS1) as a specific chaperone for the V0a1 subunit of the V-ATPase, a function independent of its role in the γ-secretase complex.

- **Mechanism of Chaperoning:** The PS1 holoprotein aids in the N-glycosylation of the V0a1 subunit within the ER. Glycosylation is a critical quality control step; without it, V0a1 is misfolded and targeted for ER-associated degradation (ERAD) rather than being trafficked to the lysosome.[12]
- **FAD Mutations:** Familial Alzheimer's Disease (FAD) mutations in *PSEN1* disrupt this chaperone function. Consequently, neurons from FAD patients exhibit a drastic reduction in lysosomal V0a1 levels, leading to a pH elevation from ~4.5 to >6.0.[13]

- **Calcium Dysregulation:** The failure of acidification in PS1 mutants triggers secondary calcium defects. The lysosomal calcium channel TRPML1 is pH-sensitive; abnormal alkalization leads to dysregulated calcium efflux, which further impairs the fusion of autophagosomes with lysosomes, creating a feed-forward loop of proteostatic failure.[13]

3. The Amyloidogenic Blockade: Metabolite-Driven Inhibition

In addition to chaperone failure, the accumulation of specific protein aggregates can directly inhibit the catalytic activity of the V-ATPase. This phenomenon is central to the "inside-out" hypothesis of amyloid toxicity in Alzheimer's Disease.

3.1 The APP-βCTF Inhibitory Axis

While extracellular amyloid-beta (Aβ) plaques are the hallmark of AD, intracellular accumulation of the β-C-terminal fragment of APP (APP-βCTF) appears to be the primary driver of acidification failure.[3]

- **Steric Inhibition:** APP-βCTF accumulates in the endolysosomal membranes of AD neurons and binds directly to the V-ATPase complex. This binding event allosterically inhibits the pump or destabilizes the V0-V1 coupling, effectively "jamming" the motor.[16]
- **The YENPTY Phosphorylation Switch:** The toxicity of APP-βCTF is regulated by phosphorylation at the tyrosine-682 residue within its YENPTY internalization motif. Kinases such as Fyn, which are upregulated in AD brains, phosphorylate this site. Phosphorylated APP-βCTF exhibits a significantly higher affinity for the V-ATPase, exacerbating the acidification defect.[16]
- **Down Syndrome:** This mechanism is prevalent in Down Syndrome (Trisomy 21), where the extra copy of the *APP* gene drives the overproduction of APP-βCTF. This leads to "endosomal-lysosomal meltdown"—the formation of giant, neutral autolysosomes that fail to degrade Aβ, leading to early-onset AD pathology.[15]

3.2 PICALM and Sorting Defects

The phosphatidylinositol binding clathrin assembly protein (PICALM), a top genetic risk factor for AD, regulates the sorting of SNAREs (like VAMP8) and autophagic precursors. Reduced PICALM levels, often observed in AD brains, impair the delivery of V-ATPase subunits and fusion machinery to the autophagosome. This trafficking defect acts synergistically with APP-βCTF inhibition to compromise lysosomal acidity.[19]

4. Ion Homeostasis: The Counter-Ion Imperative

Proton pumping is electrogenic; the accumulation of H+ ions generates a transmembrane voltage (positive inside) that opposes further pumping. To sustain acidification, this electrical potential must be dissipated by a "shunt" current—either the influx of anions (Cl-) or the efflux of cations (K+, Na+).

4.1 Chloride Transport: The ClC-7/OSTM1 Complex

ClC-7 is a 2Cl-/1H+ antiporter that localizes to lysosomes and is critical for providing the chloride counter-ion flux.

- **Mechanism:** By transporting two Cl- ions into the lumen for every proton exported, ClC-7 neutralizes the membrane potential, allowing the V-ATPase to pump against the concentration gradient.
- **OSTM1 Interaction:** ClC-7 is obligatorily associated with OSTM1 (Osteopetrosis Associated Transmembrane Protein 1), a heavily glycosylated beta-subunit that shields ClC-7 from lysosomal proteases.[20]
- **Neuronal Phenotypes:** Loss of either ClC-7 or OSTM1 leads to osteopetrosis and severe neurodegeneration (neuronal ceroid lipofuscinosis). While some studies debated the pH effect in non-neuronal cells, functional assays in neurons confirm that ClC-7 is essential for deep acidification. Furthermore, luminal chloride may directly activate cathepsin C and other hydrolases, meaning ClC-7 loss creates a "double hit": pH elevation and ionic imbalance.[21]

4.2 Potassium Channels: TMEM175 and Membrane Potential

TMEM175 is a non-canonical K+ channel identified as a major genetic risk factor for Parkinson's Disease.[24]

- **pH Plasticity:** Unlike ClC-7, which facilitates deep acidification, TMEM175 appears to act as a "leak" channel or potential regulator. It is crucial for lysosomal *pH plasticity*—the ability of the organelle to adjust its pH in response to metabolic demand. Dysfunction of TMEM175 leads to a unstable pH (either hyper-acidic or alkaline depending on the context), which impairs the degradation of alpha-synuclein.[18]
- **Mechanistic Link:** By conducting K+, TMEM175 sets the resting membrane potential of the lysosome. Defects in this channel hyperpolarize the membrane, altering the electrochemical driving force for the V-ATPase.

4.3 Calcium Channelopathies: TRPML1 and TPC2

Lysosomal calcium release is essential for fusion and fission events. Disruption of these channels affects pH indirectly by blocking the delivery of pumps or regulating membrane dynamics.

Channel	Function	Role in Acidification Failure	Disease Link
TRPML1	Ca2+ Release (PI(3,5)P2 activated)	Required for autophagosome-lysosome fusion. Loss prevents the "hybrid" organelle from acquiring somatic V-ATPases. pH-dependent gating creates a feedback loop.	Mucolipidosis IV, AD, PD [25]
TPC2	Na+/Ca2+ Release (NAADP activated)	**Agonist-Dependent:** NAADP activation can	AD, LSDs [27]

		cause alkalinization (acting as a proton leak). PI(3,5)P2 activation supports acidification/fusion. Hyperactivity in AD leads to alkalinization.	

4.4 Zinc Dyshomeostasis: ATP13A2 (PARK9)

ATP13A2 is a P5-type ATPase that transports polyamines and heavy metals (Zn2+, Mn2+) across the lysosomal membrane.

- **Zinc Toxicity:** Loss of ATP13A2 leads to the accumulation of Zinc in the mitochondria and lysosomes. Excess lysosomal Zinc inhibits V-ATPase function and hydrolase activity, leading to pH elevation.[29]
- **Mitochondrial Coupling:** The resulting mitochondrial dysfunction (ROS production) further oxidizes lysosomal membrane proteins, exacerbating the acidification defect.[30]

5. Kinase Signaling and Trafficking Networks in Parkinson's Disease

In Parkinson's Disease, acidification failure is often a downstream consequence of dysregulated kinase signaling that mislocalizes lysosomes to cellular regions where acidification is inefficient.

5.1 LRRK2 Hyperactivity and the Rab Phosphorylation Cascade

Mutations in *LRRK2* (e.g., G2019S) increase its kinase activity, leading to the hyperphosphorylation of a subset of Rab GTPases, including Rab8, Rab10, and Rab29.[32]

5.1.1 The "LYTL" Pathway and Centrosomal Trapping

Lysosomes typically undergo retrograde transport to the perinuclear region (soma) to mature and acidify. This positioning is controlled by the interplay between kinesin (anterograde) and dynein (retrograde) motors.

- **Mechanism:** LRRK2 phosphorylates Rab10 on the lysosomal surface. Phospho-Rab10 recruits the effector RILPL1. The Rab10-RILPL1 complex interacts with the p150Glued subunit of dynactin, but rather than promoting transport, it anchors lysosomes to the centrosome or interferes with motor coordination.[34]
- **Consequence:** This "Lysosomal Tubulation/sorting driven by LRRK2" (LYTL) pathway disrupts normal trafficking dynamics. Lysosomes become trapped in peripheral or centrosomal clusters, preventing their maturation. Peripheral lysosomes are notoriously less acidic than their somatic counterparts.[36]
- **PPM1H Regulation:** The phosphatase PPM1H normally dephosphorylates Rab10, counteracting LRRK2. Loss of PPM1H mimics LRRK2 hyperactivity, locking lysosomes in this pathological, poorly acidified state.[38]

5.2 Transcriptional Repression of the CLEAR Network

Beyond trafficking, LRRK2 negatively regulates the MiT/TFE family of transcription factors (TFEB, TFE3, MITF), which control the Coordinated Lysosomal Expression and Regulation (CLEAR) gene network.

- **Nuclear Exclusion:** LRRK2 signaling promotes the phosphorylation and cytoplasmic sequestration of TFEB/TFE3. This reduces the transcription of *V-ATPase subunits* and *cathepsins*. Thus, the neuron is starved of the very components needed to maintain low pH.[39]

5.3 Rab29 and TGN-Lysosome Trafficking

Rab29 (PARK16) recruits LRRK2 to the Trans-Golgi Network (TGN) and lysosomes. Overexpression of Rab29 induces TGN fragmentation and lysosomal clustering. This structural collapse disrupts the sorting of nascent V-ATPase complexes from the Golgi to the lysosome,

preventing the replenishment of the proton pump pool.[40]

5.4 Glucocerebrosidase (GBA1) and Lipid-Induced Leak

Mutations in *GBA1* reduce the activity of beta-glucocerebrosidase (GCase), leading to the accumulation of glucosylceramide (GlcCer) and glucosylsphingosine.

- **Membrane Permeabilization:** These lipids stabilize toxic alpha-synuclein oligomers and alter the biophysical properties of the lysosomal membrane. High levels of sphingolipids induce membrane permeabilization or "proton leak," making it thermodynamically impossible for the V-ATPase to maintain a gradient.[24]
- **Feedback Loop:** GCase itself requires acidic pH to function. The lipid-induced alkalinization inhibits the remaining enzyme, creating a catastrophic feed-forward loop.[43]

6. The Fusion Machinery: SNAREs and Tethers

Acidification of the autophagosome occurs largely *after* fusion with a competent lysosome. Therefore, fusion failure is functionally equivalent to acidification failure.

6.1 The Neuronal SNARE Switch: SNAP29 vs. SNAP47

Recent evidence delineates two distinct SNARE complexes for autophagy, a distinction critical for neuronal survival.

- **Starvation Autophagy:** Utilizes STX17-**SNAP29**-VAMP8.
- **Basal/Selective Autophagy:** Utilizes STX17-**SNAP47**-VAMP8.[44]
- **The "Default" Complex:** Neurons are rarely starved; they rely on constitutive (basal) autophagy to clear aggregates. Therefore, they depend heavily on **SNAP47**. SNAP47 is recruited to autophagosomes via binding to PI(4,5)P2 and ATG8s. Disruptions in phosphoinositide signaling prevents SNAP47 recruitment, blocking fusion.[44]
- **Metabolic Regulation:** In nutrient-rich conditions (typical for most neurons), SNAP29 is **O-GlcNAcylated**, which inhibits its participation in fusion complexes. This enforces reliance on SNAP47. Metabolic disorders (diabetes) that alter O-GlcNAcylation levels can

therefore dysregulate this switch, stalling neuronal autophagy.[44]

6.2 The HOPS Complex and VPS41

The HOPS complex (Homotypic Fusion and Protein Sorting) tethers the autophagosome to the lysosome.

- **VPS41:** This subunit is specific for HOPS function in fusion (as opposed to the CORVET complex in endosomes). VPS41 mutations or deficiency lead to the accumulation of undegraded autophagosomes. VPS41 is also required for the neuroprotective clearance of alpha-synuclein.[46]
- **WDR91 Competition:** The protein WDR91 competes with VPS41 for binding to Rab7. Pathological upregulation of WDR91 sequesters Rab7, preventing HOPS assembly and blocking fusion. This results in "HOPS bodies"—enlarged, neutral endolysosomal compartments.[46]

6.3 EPG5 and Specificity

EPG5 is a tether that confers specificity to the fusion process, ensuring autophagosomes fuse with degradative lysosomes and not other organelles. EPG5 mutations (Vici syndrome) prevent the recruitment of Rab7 and V-ATPases to the fusion site, resulting in a failure to acidify the resulting hybrid organelle.[49]

7. The Axonal Transport Challenge

Neurons face a topological hurdle: autophagosomes form distally in the axon but must travel to the soma to find acidic lysosomes.

7.1 The Acidification Gradient

Lysosomal pH is graded along the axon: distal lysosomes are neutral (pH ~6–7), while somatic lysosomes are acidic (pH ~4.5–5).[50] Maturation and acidification occur during retrograde transport.

- **Dynein/Dynactin Failure:** Mutations in the dynein motor or its regulator dynactin (p150Glued) stall retrograde transport. Autophagosomes remain stranded in the distal axon, unable to access the somatic V-ATPase pool. This leads to axonal swellings filled with neutral, aggregate-laden vacuoles.[51]
- **Snapin:** The adaptor protein Snapin is required to link dynein to late endosomes. Loss of Snapin prevents the retrograde transport of acidification machinery, leading to generalized lysosomal immaturity.[53]

7.2 Local Mitophagy and PINK1/Parkin

While bulk autophagy requires retrograde transport, damaged mitochondria can be degraded locally.

- **Mechanism:** PINK1 accumulates on the outer membrane of depolarized mitochondria and recruits Parkin. This initiates the local formation of autophagosomes.
- **Failure Mode:** In *PINK1* or *Parkin* mutants, this local recognition fails. Furthermore, even if autophagosomes form, the lack of local acidic lysosomes (due to transport defects) prevents degradation. The result is the accumulation of "mitophagic intermediates" that cannot be cleared.[54] *PINK1* deficiency also impairs the phosphorylation of Ubiquitin, a signal required for autophagy receptors (like Optineurin) to bridge the mitochondrion to the autophagosome.[55]

8. Glial-Neuronal Crosstalk: Non-Cell-Autonomous Mechanisms

Neuronal acidification is heavily influenced by the supporting glial cells. Dysfunction in microglia or astrocytes transmits toxicity to neurons.

8.1 Microglia: The PS1 Phosphorylation Switch

In microglia, lysosomal acidification is regulated differently than in neurons.

- **Ser367 Phosphorylation:** While neuronal PS1 acts as a chaperone, microglial PS1 regulates acidification via phosphorylation at Serine 367. Unphosphorylated PS1 in microglia destabilizes V-ATPase V0a1, raising pH. Conversely, phosphorylated PS1 binds Annexin A2, which facilitates the interaction of VAMP8 with Syntaxin 17, enabling fusion.[56]
- **Impact:** Microglial acidification failure prevents the clearance of amyloid plaques and myelin debris, leading to a chronic inflammatory state that is toxic to neighboring neurons.

8.2 Progranulin (GRN) and Myelin Clearance

Progranulin is essential for microglial lysosomal function. *GRN* deficiency (linked to FTD) causes a reduction in Cathepsin D activity and acidification failure. Microglia become engorged with undigested myelin debris, transitioning to a senescent, neurotoxic phenotype that damages neuronal networks.[57]

8.3 Astrocyte Toxicity and Exosomes

- **SUMF1 Deletion:** In Multiple Sulfatase Deficiency (MSD), astrocytes lacking *SUMF1* accumulate lysosomal storage material. These astrocytes fail to provide metabolic support (lactate) to neurons and cannot clear neurotransmitters, causing neuronal death via non-cell-autonomous mechanisms.[58]
- **Toxic Exosomes:** Dysfunctional astrocytes secrete exosomes containing mutant proteins (e.g., SOD1 in ALS) and undigested cargo. Neurons endocytose these exosomes, effectively inheriting the astrocyte's "trash." This overwhelming load saturates the neuronal lysosomal system, leading to secondary acidification failure.[60]

9. Environmental Toxins and Pharmacological Agents

External agents can mimic genetic defects by chemically attacking the V-ATPase or disrupting

membrane integrity.

9.1 Heavy Metals: Lead (Pb) and Cadmium (Cd)

- **Mechanism:** Lead and Cadmium are potent neurotoxins that induce oxidative stress. They can displace essential divalent cations (Zn^{2+}, Mg^{2+}) required for ATPase function. Cadmium increases BBB permeability and accumulates in neurons, where it oxidizes the cysteine residues of the V-ATPase, directly inactivating the pump.[61]
- **Estrogen Mimicry:** Cadmium acts as a metalloestrogen, potentially dysregulating hormonal signaling pathways that control lysosomal biogenesis.[62]

9.2 Pesticides: Rotenone, Paraquat, and Chlorpyrifos

- **Rotenone/Paraquat:** These agents inhibit mitochondrial Complex I. Since V-ATPase acidification is ATP-dependent, the resulting energy crisis leads to immediate alkalization. Rotenone also inhibits the Mitochondrial Calcium Uniporter (MCU), disrupting the Ca^{2+} signaling required for TPC2/TRPML1 function.[63]
- **Chlorpyrifos (CPF):** Exposure to CPF has been linked to dopaminergic loss and increased alpha-synuclein phosphorylation (pS129), correlating with autophagic flux inhibition.[64]

9.3 Pharmacological Agents

- **Chloroquine (CQ):** A lysosomotropic weak base. It diffuses into the lysosome, becomes protonated, and is trapped. This accumulation chemically buffers the pH, neutralizing acidity. It also induces Golgi disorganization, further impairing the delivery of lysosomal enzymes.[65]
- **Proton Pump Inhibitors (PPIs):** Drugs like Lansoprazole, while targeting gastric pumps, have been associated with neuropathy and potentially dementia. The mechanism may involve off-target inhibition of V-ATPases or alterations in lysosomal enzyme processing.[24]

10. Therapeutic Horizons

Understanding the diversity of acidification defects opens new avenues for therapy beyond simple autophagy induction.

Therapeutic Strategy	Target	Mechanism	Status/Reference
Acidic Nanoparticles (PLGA-aNP)	Lysosomal Lumen	Delivery of acidic polymers directly to the lysosome to lower pH mechanically.	Preclinical [18]
Nucleolipids	Lysosomal Membrane	Lipid prodrugs that release organic acids upon lysosomal uptake.	Preclinical [67]
V-ATPase Agonists	V-ATPase	Small molecules (e.g., soluble adenylyl cyclase modulators) that allosterically enhance pumping.	Discovery [68]
Etidronate	V-ATPase/Ataxin-2	Bisphosphonate that modulates V-ATPase and lowers Ataxin-2 levels.	Clinical repurposing [69]
TPC2 Agonists	TPC2 Channel	Compounds like **TPC2-A1-P** that activate TPC2 to promote acidification and exocytosis (distinct	Preclinical [28]

		from NAADP).	
C381	Progranulin/Lysosome	Small molecule that restores lysosomal function and cognition in PD/FTD models.	Preclinical [71]
Clioquinol	Zinc/pH	Chelator that restores pH by reducing lysosomal zinc burden.	Preclinical [72]

11. Conclusion

The failure of autolysosomal acidification in neurons is a complex, convergent phenotype arising from genetic mutations (V-ATPase, PS1, LRRK2), structural failures (assembly chaperones), trafficking defects (axonal transport, SNARE switching), and environmental insults (toxins, drugs). It is the "Achilles' heel" of the post-mitotic neuron. The resulting accumulation of undegraded substrates creates a toxic feedback loop that exacerbates the initial defect. Future therapeutic success will likely depend on precision medicine approaches that identify the specific *cause* of acidification failure—be it a broken pump, a missing chaperone, or a traffic jam—and target it with specific modulators or acidifying agents.

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