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Review

Organelles storing Ca^{2+} in the brain cells: New druggable targets in neurodegenerative diseases

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From the Contents

Abstract

Several lines of evidence suggest that targeting dysfunctional calcium (Ca^{2+})-storing organelles and their defective connections may represent a promising therapeutic strategy counteracting neurodegeneration. Dysfunction in these compartments converges to promote oxidative and endoplasmic reticulum stress, energy failure, autophagy blockade or hyperactivation, and progressive neurodegeneration. Within the intracellular scenario, several dysfunctional organelles have been characterized in terms of their capability to hijack Ca^{2+} signaling during neurodegeneration to deadly impact on neuronal tasks in amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, brain ischemia, and neonatal hypoxic injury. This review has focused on the endoplasmic reticulum, mitochondria, and lysosomes, as well as their functional interconnection able to maintain the physiological processes such as lysosomal-dependent autophagy and function, lipid trafficking, and protein quality control. Clinically, looking ahead from the already existing therapies, drugs that enhance mitochondrial Ca^{2+} efflux or modulate mitochondrial Ca^{2+} uniporter regulation at mitochondria-associated membranes-endoplasmic reticulum sites represent innovative opportunities for next-generation strategies aimed at restoring mitochondrial homeostasis and protecting dopaminergic neurons in Parkinson's disease. Furthermore, functional stabilization of the lysosomal channel transient receptor potential mucolipin 1 by the lipid-based formulation of $PI(3,5)P_2$ may extend the lifespan of amyotrophic lateral sclerosis mice by stimulating the nuclear translocation of the master regulator of autophagy activated by lysosomal Ca^{2+} release, namely transcription factor EB. Moreover, dysfunction of lysosomal-dependent autophagy can cause mutant huntingtin accumulation in Huntington's disease through the repression of transcription factor EB and lysophagy induction. Collectively, this growing focus may highlight a shift toward recognizing mitochondria, lysosomes, and endoplasmic reticulum, as well as their ionic machinery and interconnections, as a unifying strategy to maintain neuronal viability and mitigate the neurodegeneration progression in amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, lysosomal storage diseases, brain ischemia, and neonatal hypoxic insult.

Key Words: autophagy; Ca^{2+}-storing organelles; channels; endoplasmic reticulum; endoplasmic reticulum stress; lysosome; mitochondria-associated membranes; mitochondria; neurodegenerative diseases

Introduction

Intracellular organelles including endoplasmic reticulum (ER), mitochondria, lysosomes and nucleus represent the most important calcium (Ca^{2+}) stores within the cells. These various and tiny components are equipped with a proper ionic machinery comprising channels, pumps and transporters handling Ca^{2+}, one of the main regulators of cell proliferation, migration, muscle contraction and relaxation, endocrine regulation of metabolism, learning and memory, neuronal activity and plasticity and, finally, cell death. This machinery is expressed both in excitatory and non-excitatory cells (Tedeschi et al., 2021). It is increasingly evident that those cell functions regulated by Ca^{2+} respond either to the specific origin of this ion or to its concentration. This is to say that cell functions are controlled by the route of Ca^{2+} released and not only by the local level raised. The impact of the original site of Ca^{2+} influx or release is especially known for those processes regulated by the store-operated Ca^{2+} entry (SOCE) mediated by the interaction between the ER Ca^{2+} sensor stromal interaction molecule (STIM) and the plasma membrane channel ORAI culminating in ER Ca^{2+} refilling (Korshunov and Prakriya, 2025). Of interest, modifications of SOCE have been associated with several forms of neurodegeneration, such as Alzheimer's disease (AD), Huntington's disease (HD) and other dysfunction of the nervous system including chronic pain (Popugaeva et al., 2015; Secondo et al., 2018; Wegierski and Kuznicki, 2018; Zhang and Hu, 2020) as well as focal brain ischemia (Secondo et al., 2019; La Russa et al., 2020). Furthermore, lysosomal Ca^{2+} flowing through transient receptor potential mucolipin 1 (TRPML1) lysosomal channel by activating the phosphatase calcineurin may induce the nuclear translocation of the transcription factor EB (TFEB), the master regulator of lysosomal function and autophagy (Sardiello et al., 2009; Settembre et al., 2011; Medina et al., 2015; Di Paola et al., 2018). Of interest, defective autophagy is now considered the causative mechanism of several forms of neurodegeneration (Kyseliov et al., 2007; Settembre et al., 2008a; Nixon and Rubinsztein, 2024; Tedeschi et al., 2025a), thus definitively establishing that aberrant lysosomal Ca^{2+} homeostasis/TFEB signaling may trigger the neurodegenerative process via autophagy dysfunction.

From the functional point of view, organelles respond dynamically to various physiological stimuli in an orchestrated manner, being strictly interconnected (**Figure 1**). Accordingly, these events require a proper crosstalk among organelles through the close interactions termed "organelle contact sites." Such contacts are mediated by "tethering proteins" working as scaffolds to exchange Ca^{2+}, cholesterol, and amino acids, without the occurrence of membrane fusion events (Cohen et al., 2018). For instance, the contact sites between the ER and mitochondria called mitochondria-associated membranes (MAMs) have attracted considerable attention since 1990 for their ability to allow a constant interaction ensuring cell viability (Vance, 1990; Sassano et al., 2022). A tripartite complex formed by the mitochondrial voltage-dependent anion channel 1 (VDAC1), the ER channel inositol trisphosphate receptor (IP_3R), and glucose-regulated protein 75 (GRP75) chaperone was described (Szabadkai et al., 2006). This complex controls lipid trafficking and Ca^{2+} flux in physiology and disease (Vance, 2020; Loncke et al., 2021; Wilson and Metzakopian, 2021; Markovinovic et al., 2022; Sassano et al., 2022; de Ridder et al., 2023; Diokmetzidou and Scorrano, 2025; Liu et al., 2025). Of note, ER-mitochondrial communication is "bidirectional," and, therefore, altered mitochondrial functions, including oxidative phosphorylation, may affect MAMs and, *vice versa*, altered MAMs affect oxidative phosphorylation (Morcillo et al., 2024).

Mitochondria and lysosomes interactions through mitochondria-lysosomes contact sites are also implicated in several key processes such as mitochondrial fission and vesicular transfer via mitochondria-derived vesicles enriched in PINK1 and Parkin (Sugiura et al., 2014; McLelland et al., 2016; Rizzollo and Agostinis, 2025).

A number of studies demonstrated that ER-mitochondria signaling is perturbed during the neurodegenerative process; this event can be considered as a driving mechanism in the onset and progression of most diseases, as occurs in AD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (Blair et al., 2025).

Despite the plasticity of mitochondria/ER contacts sites in response to several stimuli (Hönscher et al., 2014; Sood et al., 2014; Theurey et al., 2016; Boutant et al., 2017; Benador et al., 2018; Young et al., 2018) and in response to Ca^{2+} dynamics (Yi et al., 2004), the interaction among their tethering proteins- such as the ER protein VAPB and

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the outer mitochondrial membrane protein PTPIP51- can be disrupted by the neurodegenerative process (**Figure 2**). Furthermore, neurodegenerative diseases display signs of mitochondrial and lysosomal defects (Wilson and Metzakopian, 2021; Cisneros et al., 2022; Fan and Tan, 2024; Makio and Simmen, 2024; Morcillo et al., 2024; Blair et al., 2025; Rizzollo and Agostinis, 2025). In this context, the impairment in mitochondria-lysosomes contact sites function has been associated not exclusively with neurodegenerative disorders but also with lysosomal storage diseases (LSDs), characterized by lysosomal dysfunction. Of note, most LSDs, including Gaucher disease, display mitochondrial dysfunction (Osellame et al., 2013). Therefore, the mitochondria–lysosomes axis has been considered as a promising target to develop new pharmacological treatments in those pathologies, showing defects in organellar Ca^{2+} homeostasis.

Of course, it is plausible to have some concerns on the putative pharmacological modulation of organellar Ca^{2+} homeostasis. Risks include off-target Ca^{2+} perturbations linked to cardiac and central nervous system (CNS) effects, such as arrhythmias, excitotoxicity, immune effects of lysosomal modulation, and systemic metabolic consequences. Therefore, a comprehensive understanding of how these organelle-specific pathways interact and converge in each neurodegenerative disease is, therefore, crucial, as future strategies may need to target the entire cellular stress network rather than isolated molecular defects to effectively halt or slow neurodegeneration.

Search Strategy

In this study, a validated electronic literature with high transparent key words (e.g., calcium organelles, calcium homeostasis and neurodegeneration) and inclusion criteria (new evidence published on international journals with high impact) have been used. All years were included in the search.

Endoplasmic Reticulum, Mitochondria, and Mitochondria-Associated Membranes

ER, the most efficient Ca^{2+}-storing organelle, is involved in the quality control of proteins and lipids as well as ionic homeostasis modulation. In neuronal cells, ER is divided into somatic and axodendritic compartments, by which it controls several relevant functions. As a Ca^{2+} store ER contains, in its lumen, a high level of Ca^{2+} that can be 5000 times greater than in the cytosol. Physiologically, it is necessary for synaptic signaling, Ca^{2+} waves promoting gene transcription, and correct folding of proteins. Efficient control of ER Ca^{2+} level is due to the coordinated action of a very complex machinery composed of one Ca^{2+}-ATPase named sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump-deputed to continuous refilling of the ion- two types of ER membrane Ca^{2+} channels named IP3R and ryanodine receptors both involved in ER Ca^{2+} release and a transmembrane protein called stromal interaction molecule 1 (STIM1) sensing luminal Ca^{2+} concentrations and, therefore, presiding the occurrence of Ca^{2+} movements inside and outside the organelle. In this respect, STIM1 directly interacts with several ionic proteins located in different compartments: at the plasma membrane, lysosomal, and mitochondrial levels (Tedeschi et al., 2021). For instance, STIM1 plays a pivotal role in SOCE through the physical and functional interaction with the plasma membrane channel ORAI. It is noteworthy that STIM1-rich regions of the ER may preferentially interact with domains of the plasma membrane that are rich in sphingolipids and cholesterol, the so-called lipid rafts (Pani et al., 2008).

Besides SOCE regulating ER Ca^{2+} influx, ER Ca^{2+} fluxes are also due to the Ca^{2+}-induced Ca^{2+} release phenomenon (Verkhratsky and Shmigol, 1996; Majewski and Kuznicki, 2015). Several forms of Ca^{2+}-induced Ca^{2+} release have been described as a consequence of a functional interaction among organelles. Accordingly, Ca^{2+}-induced Ca^{2+} release could be due not only to the functional interplay between mitochondria and ER (Ichas et al., 1997), but also to the interaction between ER and lysosomes (Kinnear et al., 2004).

It is noteworthy that ER stress represents one of the most important detrimental mechanisms shared by several

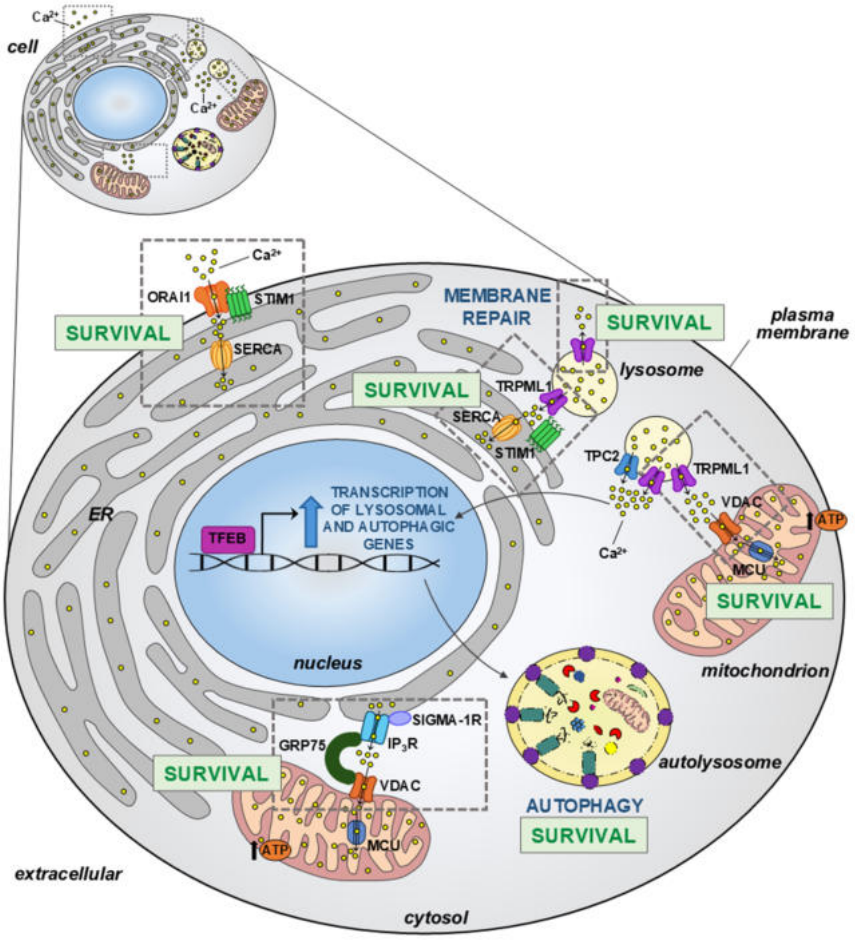

Figure 1 | **Schematic representation of inter-organelle contact sites in neurons and the relative effects on cell fate.**
Schematic representation of different interacting proteins involved in multiple contact sites among organelles in neurons. Effect on cell fate due to a Ca^{2+} transfer process among organelles during neurodegeneration. ER: Endoplasmic reticulum; GRP75: glucose regulatory protein 75; IP_3R: inositol trisphosphate receptor; SIGMAR1: sigma-1 receptor; STIM1: stromal interaction molecule 1; TRPML1: transient receptor potential mucolipin subfamily 1; VDAC: voltage-dependent anion-selective channel.

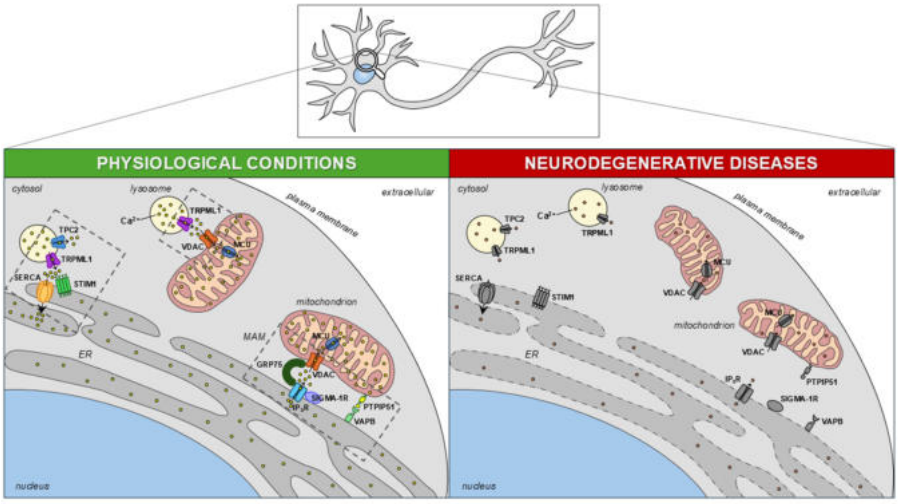

Figure 2 | **Schematic representation of inter-organelle contact sites between ER and mitochondria in neurons under physiological conditions and in neurodegenerative diseases.**
Under physiological conditions, the endoplasmic reticulum (ER), mitochondria, and lysosomes establish multiple contact sites, involving different interacting proteins (i.e., IP_3R/SIGMA1-R/GRP75/VDAC at mitochondria-associated membranes [MAMs]; STIM1/TRPML1 at ER/lysosomes contact sites; VDAC/TRPML1 at mitochondria/lysosomes contact sites). These interactions are aimed at maintaining a proper intracellular Ca^{2+} homeostasis (left). In neurodegenerative diseases, disruption of the interactions among intracellular organelles leads to an impairment in intracellular Ca^{2+} regulation, resulting in a general cell dysfunction (right). ER: Endoplasmic reticulum; GRP75: glucose regulatory protein 75; IP_3R: inositol trisphosphate receptor; SIGMAR1: sigma-1 receptor; STIM1: stromal interaction molecule 1; TRPML1: transient receptor potential mucolipin subfamily 1; VDAC: voltage-dependent anion-selective channel.

neurodegenerative diseases. ER stress is activated when proteostasis is broken with an organellar accumulation of misfolded and unfolded proteins. Afterward, ER stress activates an adaptive unfolded protein response (UPR) to restore proteostasis with epigenetic and transcriptional events that can culminate in a detrimental process

leading to cell death (Chen et al., 2023a). Conversely, mitochondrial dysfunction (e.g., imbalance of energy metabolism, mitochondrial dynamics, or abnormal mitophagy) can lead to several pathological reactions participating in the development of neurodegenerative diseases.

Of note, in virtue of MAMs, ER stress coordinates several other detrimental processes, including oxidative stress and autophagy dysfunction (Han et al., 2013; Rashid et al., 2015; Pereira et al., 2022). In the following paragraphs, the most recent evidence on the involvement of ER, mitochondria, and MAMs in specific neurodegenerative diseases has been summarized, as well as the newest therapeutic approaches. Of note, MAM dysfunction may involve a plethora of altered mechanisms, including IP_3R/VDAC/mitochondrial Ca^{2+} uniporter (MCU) malfunctional gating, dysfunctional $\Delta\psi_m$, and local Ca^{2+} buffering.

Amyotrophic lateral sclerosis

ER dysfunction characterized by Ca^{2+} dysregulation and persistent UPR activation has been recognized as a central event in ALS pathogenesis (Saxena et al., 2009; Walker et al., 2010; Petrozziello et al., 2017).

Very recently, a comprehensive bioinformatic study explored the mechanisms associated with ER stress thus identifying new potential ER-related biomarkers in ALS. Using machine learning algorithms, at least 6 hub genes involved in multiple ER stress-related pathways have been identified. Once again, the prominent role of ER dysfunction has been highlighted as a pathomechanism of the disease, opening new routes for therapeutic intervention (Wang et al., 2025a).

Conversely, modulating mitochondrial Ca^{2+} homeostasis through key channels such as the MCU, VDAC, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (mPTP) may offer a compelling strategy to preserve neuronal viability and counteract the progressive mitochondrial dysfunction in ALS (Israelson et al., 2010; Yi et al., 2011; Yu et al., 2020). In this regard, MCU modulators are under exploration as regulators of mitochondrial Ca^{2+} influx. Although not selective but useful as proof of concept, compounds such as Ruthenium Red derivative Ru265 (Woods et al., 2019; Novorolsky et al., 2020), a cell-permeable MCU inhibitor, and MCU-i11 (Di Marco et al., 2020; Márta et al., 2021), a MICU1-dependent regulator, have been demonstrated to stabilize mitochondria and to provide neuroprotection in cellular and animal models of ALS. Parallel approaches targeting mPTP have also yielded encouraging results. The mPTP and cyclophilin D inhibitors, such as cyclosporine A (Klivenyi et al., 1999; Nguyen et al., 2011) and GNX-4728 (Martin et al., 2014), have shown neuroprotective and survival-prolonging effects in ALS mouse models. Beyond MCU and mPTP regulation, VDAC-targeting approaches have also gained attention due to their crucial role in metabolic regulation, apoptotic Ca^{2+} signaling, and interaction with mutant SOD1 aggregates (Shteinfer-Kuzmine et al., 2022). Recent data reported that structural alterations in VDAC are linked to mitochondrial dysfunction in ALS motor neurons (Pittalà et al., 2022). Additionally, VDAC1 overexpression has been observed to exert protective effects by stabilizing the Complex I–Sirtuin3 axis (Magrì et al., 2024). Although no mitochondrial-specific therapeutics have yet entered clinical trials, mitochondria represent a promising area for drug development.

Moreover, in consideration of the aberrant organellar signaling involving ER-mitochondria connections, an innovative strategy in ALS therapy is directed against MAMs disruption, a crucial mechanism regulating the supply of Ca^{2+} from the ER to mitochondria and deteriorating along with the disease progression (Sakai et al., 2021). For instance, the involvement of intrinsic mitochondrial deficits as well as chronic ER stress in the development of C9ORF72-linked pathology, accounting for over 40% of all known familial and 10% of known sporadic forms of ALS, has been well established (Pilotto et al., 2025). Alleviating ER and mitochondrial defects may rescue ALS motor neurons. Accordingly, the use of the dietary flavanol Kaempferol, lacking evident toxicity, enhances IP_3R-VDAC1 interactions via the ER protein GRP75, thus normalizing also mitochondrial functions in ALS mice carrying *C9ORF72* pathology (Pilotto et al., 2025). In the light of this approach and considering MAM-localized and functioning proteins such as VAPB and sigma-1 receptor (Sig-1R) whose mutations have been involved in familial ALS pathogenesis, stimulation of Sig-1R may reduce aberrant ER Ca^{2+} release to the cytoplasm, thus promoting mitochondrial function (Watanabe et al., 2016; Gaja-Capdevila et al., 2021). This seems to occur through an improvement of mitochondrial/intracellular Ca^{2+} signaling (Tagashira et al., 2023).

Alzheimer's disease

AD is a major age-related form of dementia with signature symptoms (e.g., gradual decline in memory, thinking, reasoning, and behavior) that result from a progressive deterioration of the brain (Wu and Fuh, 2025).

According to the mechanistic framework known as the "calcium hypothesis", the deposition of amyloid-β (Aβ), hyperphosphorylation of tau protein, abnormal synaptic plasticity, and apoptosis can be linked to spatio-temporal disharmonies in the choreography of intracellular Ca^{2+} signals (Wang et al., 2025b). In AD, Ca^{2+} signaling regulation is compromised at both the plasma membrane and intracellular Ca^{2+} stores. In particular, at least three major mechanisms have been characterized in neurons. Toxic Aβ oligomers can insert themselves into the plasma membrane and form Ca^{2+} permeable channels or disrupt membrane integrity (Huang et al., 2022). Aβ and hyperphosphorylated tau can also upregulate or overactivate voltage-gated calcium channels and receptor-operated channels, including N-methyl-D-aspartate receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (Schampel and Kuerten, 2017; Fani et al., 2021; Huang et al., 2022), thereby altering ER morphology and aggravating neuronal vulnerability (Chami and Checler, 2020).

Furthermore, altered Ca^{2+} fluxes across the surface of AD neurons, determined either by the loss of the plasma membrane Ca^{2+}-ATPase or by the reduced activity of the sodium-calcium exchanger (NCX), contribute to cytoplasmic Ca^{2+} overload and/or to defective distribution of Ca^{2+} to intracellular stores (Zaidi et al., 2018; Pannaccione et al., 2020).

Finally, misfolded Aβ and tau induce ER stress, chronically activating the UPR through Protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme-1 (IRE1), and transcription factor-6 (ATF6) pathways (Hetz and Saxena, 2017). This leads to a pro-apoptotic signaling via C/EBP homologous protein (CHOP) and caspase-12 (Cornejo and Hetz, 2013).

Mitochondrial dysfunction is one of the earliest pathological events in AD, detectable even before extracellular Aβ deposition (Wang et al., 2020). Aβ peptides accumulate within mitochondrial membranes, interacting with Aβ-binding alcohol dehydrogenase and cytochrome C oxidase, thereby impairing electron transport chain function and increasing reactive oxygen species (ROS) production (Lustbader et al., 2004; Manczak et al., 2006).

Conversely, tau pathology also contributes to mitochondrial impairment by disrupting axonal transport and altering mitochondrial dynamics, leading to excessive fission and impaired fusion (Manczak and Reddy, 2012; Rai et al., 2020). The ROS overproduction damages lipids, proteins, and nucleic acids, thereby amplifying mitochondrial dysfunction. Moreover, oxidative stress enhances β-secretase/BACE1 expression and tau hyperphosphorylation through the activation of stress kinases such as c-Jun N-terminal kinase and p38 mitogen-activated protein kinase (Leuner et al., 2012; Onyango et al., 2016). These processes establish a self-perpetuating cycle in which mitochondrial dysfunction and oxidative stress mutually exacerbate Aβ and tau pathology, ultimately leading to neuronal loss.

Very recently, it has been proposed that altered ER Ca^{2+} signaling due to the MAM architecture may drive mitochondria-mediated Ca^{2+} dyshomeostasis and cellular pathophysiology. Accordingly, increased ryanodine receptor-dependent Ca^{2+} release may cause mitochondrial dysfunction through mitochondrial Ca^{2+} overload, thus leading to a depolarized mitochondrial membrane potential, increased oxidative stress, caspase-3-mediated apoptosis, and dysfunctional mitophagy in induced pluripotent stem cells (iPSC)-derived human neurons from AD patients as well as in sporadic AD neurons (Mustaly-Kalimi et al., 2025). Of interest, normalizing ryanodine receptor-dependent Ca^{2+} signaling may rescue neurons by restoring mitochondrial activity and delaying AD progression (Mustaly-Kalimi et al., 2025).

In this context, Aβ oligomers also disturb ER-mitochondria contact sites, enhancing Ca^{2+} transfer to mitochondria and triggering permeability transition pore opening and oxidative stress (Area-Gomez et al., 2012; Paillusson et al., 2016). This pathological ER-mitochondria coupling acts as a central hub linking protein misfolding to energy failure and oxidative damage.

Parkinson's disease

PD is a common neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain. A specific pathological hallmark of PD is the intracellular accumulation of misfolded α-synuclein protein, the main component of the Lewy bodies. These pathological alterations underlie not only motor symptoms, including rigidity, bradykinesia, and postural instability, but also non-motor manifestations, such as cognitive impairment and neurofunctional decline (Choong and Mochizuki, 2022). Impaired Ca^{2+} homeostasis has been suggested as one of the main contributing factors to the onset and the progression of the disease (Bastioli et al., 2024). In healthy neurons, Ca^{2+} ion fluxes between the extracellular environment and the intracellular compartments, including ER and mitochondria, are tightly regulated (Dieterich et al., 2008; Mikhaylova et al., 2009; Bastioli et al., 2024). In the context of PD, Ca^{2+} homeostasis can be altered by α-synuclein aggregation and mutations in PD-associated genes (e.g., leucine-rich repeat kinase 2 [LRRK2], DJ-1, Parkin, and PINK1), impairing the crosstalk between mitochondria and ER (Gómez-Suaga et al., 2018; van der Vlag et al., 2020).

Among ER Ca^{2+} machinery components, SERCA pump has emerged as a potential target for the modulation of Ca^{2+} homeostasis. The pharmacological activation of SERCA may offer a safer and potentially more effective strategy to promote cytosolic Ca^{2+} clearance and mitigate Ca^{2+} dysregulation in PD. The relationship between PD pathophysiology and SERCA has been studied in PD models based on DJ-1 deficiency (Solana-Manrique et al., 2021), namely DJ-1β mutants flies and DJ-1-deficient SH-SY5Y neuron-like human cells. DJ mutations have been related to PD though an increased oxidative stress, leading to protein modification and altered Ca^{2+} handling involving the ER, and a reduction of SERCA activity. In these models, the quinoline-amide CDN1163 – acting as an allosteric activator of SERCA through a direct binding to this protein-rescued PD-related phenotypes, suggesting the relevant role exerted by SERCA dysfunction in PD pathophysiology. Conversely, in *C. elegans* models of PD, the inhibition of SERCA pump activity with sca-1 RNA interference can lead to beneficial effects. Although these findings are conflicting, they underscore the importance of the SERCA pump as a target that warrants further investigation (Romero-Sanz et al., 2023). It has been shown that the glucagon-like peptide-1 (GLP-1) analog liraglutide and the dual GLP-1/glucose-dependent insulinotropic polypeptide incretin analog exert a restorative effect in post-mitotic dopaminergic-like neurons where UPR was induced through the irreversible SERCA inhibitor thapsigargin (Panagaki et al., 2023). The mechanisms proposed include the restoration of glycolysis and oxidative phosphorylation processes, induction of mitochondria biogenesis, mitigation of the ectopic GRP78/binding immunoglobulin protein (BiP) and CHOP expression, and restoration of the protein levels of beclin-1, Atg3, Atg7, and microtubule-associated protein 1 light chain 3 (LC3). In this line, recent research has provided encouraging, although not conclusive, evidence supporting the efficacy of drugs targeting the incretin system, particularly GLP-1 receptor agonists and their analogues, in ameliorating motor symptoms of PD (Meissner et al., 2024). Preclinical and clinical investigations have explored the impact of the GLP-1 receptor agonist exenatide on addiction disorders, indicating that this pharmacological agent may enhance synaptic dopamine levels, which could provide symptomatic relief in PD (Klausen et al., 2022; Zhu et al., 2022a). Moreover, mitochondrial dysfunction has emerged as a central feature in the pathophysiology of PD (Park et al., 2018). Recent genetic models, including selective loss of the NDUFS2 subunit of complex I, provide causal evidence linking complex I deficiency to dopaminergic neurodegeneration (Mizuno et al., 1989; Schapira et al., 1990; Keeney et al., 2006; González-Rodríguez et al., 2021). Additionally, mutations in PD-associated genes (e.g., *SNCA*, *LRRK2*, *Parkin*, *PINK1*, *DJ-1*, and *ATP13A2*) converge on mitochondrial failure. In PD, particularly in the presence of PINK1 deficiency or GBA mutations, NCLX dysfunction compromises Ca^{2+}

efflux, precipitating early mitochondrial failure (Kostic et al., 2015; Beccano-Kelly et al., 2023). In parallel, NCX1 and NCX3 activity at the plasma membrane and mitochondrial level may regulate ionic Ca^{2+} balance, attenuating α-synuclein- and rotenone-induced toxicity in striatal brain slices and differentiated SH-SY5Y cells, as well as mitochondrial dysfunction and neuronal death in α-synA53T neurons from midbrain (Sirabella et al., 2018; Bastioli et al., 2019). Moreover, endogenous PINK1 and beclin-1 were both found to relocalize at MAMs, where they promoted the formation of ER-mitochondria contact sites and autophagosome precursors. This event regulates mitochondrial Ca^{2+} and dynamics, exerting neuroprotection (Gelmetti et al., 2017). Recently, the relevance of MAMs dysfunction has been further demonstrated since the distance between ER and mitochondria has been found significantly reduced in human iPSC-derived astrocytes from PD patients, thus decreasing, detrimentally, mitochondrial Ca^{2+} uptake (Dematteis et al., 2024).

Cerebral ischemia

Cerebral ischemia becomes manifest when cerebral blood flow declines below the critical threshold required to sustain neuronal energy metabolism, precipitating in a rapid adenosine triphosphate (ATP) depletion, ionic dyshomeostasis, glutamate-mediated excitotoxicity, mitochondrial dysfunction, and overproduction of ROS, and ultimately engaging regulated cell death pathways such as necrosis, apoptosis, ferroptosis, and autophagy-dependent cell death (Belov Kirdajova et al., 2020). Restoration of the blood flow, while essential for tissue salvage, paradoxically exacerbates cellular injury through ischemia/reperfusion mechanisms involving excessive ROS and reactive nitrogen species, blood–brain barrier disruption, microvascular obstruction, sterile neuroinflammation and excessive autophagy (Liu and Levine, 2015; Liu et al., 2024; Yang et al., 2025).

Ca^{2+} dyshomeostasis is a critical driver of ischemic brain injury. Excessive glutamate release promotes Ca^{2+} influx through NMDA receptors, P2X7 channels, and voltage-gated calcium channels (Zong et al., 2022). At the same time, ATP depletion compromises Ca^{2+} extrusion and sequestration systems such as the plasma membrane Ca^{2+}-ATPase, NCX, and SERCA, further amplifying cytosolic and organellar Ca^{2+} dysfunction (Boscia et al., 2013; Rahi and Kaundal, 2025). In this scenario, Ca^{2+} leak from ER plays an essential role in determining neuron demise in stroke (Sirabella et al., 2009; Sisalli et al., 2014). Accordingly, CDN1163, a SERCA activator, has been shown to have promising effects in preclinical studies restoring ER Ca^{2+} levels (Rahi and Kaundal, 2025). In parallel, dysregulation of SOCE signaling via STIM1 and ORAI1 interaction worsens ischemic neuronal damage, promoting ER Ca^{2+} leak and maladaptive autophagy (Secondo et al., 2019; La Russa et al., 2020; Zhang et al., 2023b). Of course, this imbalance destabilizes not only ER inducing ER stress and ER–mitochondria uncoupling, but also mitochondria determining mPTP opening and ROS generation. As a proof of concept, stating the relevance of ER stress, the pharmacological stimulation of ATF6, the transcription factor initiating protective UPR pathway able to restore ER function, may induce neuroprotection in cardiac arrest–induced ischemia/reperfusion (Yuan et al., 2022). Likewise, selective neuronal ATF6 activation in knock-in mice subjected to permanent middle cerebral artery occlusion yielded long-term neuroprotection, smaller infarcts, and reduced neuroinflammation (Li et al., 2022). Of interest, ischemia/reperfusion studies revealed that microglial activation is tightly controlled by the ER stress–autophagy axis; inhibition of protein tyrosine phosphatase 1B (PTP1B) suppressed PERK-dependent ER stress and maladaptive autophagy in microglia, thereby limiting pro-inflammatory cytokines release and neuronal damage (Zhu et al., 2021). Overall, ER stress pathways represent central modulators in ischemic injury, with STIM1/ORAI1, ATF6, and PERK signaling as promising therapeutic targets.

Mitochondria are central effectors of neuronal death in cerebral ischemia, functioning as both sensors and amplifiers of excitotoxic and oxidative signals. Excessive Ca^{2+} uptake through the MCU triggers ROS overproduction and ferroptosis, whereas pharmacological MCU inhibition using Ru265 may preserve respiration, reduces calpain activation, and attenuates ischemic injury (Marmolejo-Garza et al., 2023; Zong et al., 2024). It is relevant that ischemic stroke compromises mitochondrial membrane integrity and allows mitochondrial components to escape through permeabilization pathways (Bonora et al., 2022). Consequently, realizing dysfunctional mitochondrial fragments by injured neurons may lead to neuroinflammatory cascades via tunneling nanotubes formed between neurons and astrocytes (Gao et al., 2022). With this strategy, astrocytes search to help injured neurons transferring functional mitochondria by extracellular vesicles-mediated passage (Hayakawa et al., 2016; Borcherding and Brestoff, 2023).

Neonatal hypoxic–ischemic brain injury

Neonatal hypoxic-ischemic brain injury (NBHI) is a leading cause of acute brain injury in newborns and is associated with long-term neurological sequelae, including motor deficits, epilepsy, and cognitive impairment (Johnson et al., 2022). The hypoxic–ischemic insult initiates a pathological cascade beginning with primary energy failure, rapid ATP depletion, ionic disequilibrium, lactate accumulation, followed by glutamate-mediated excitotoxicity, oxidative stress, neuroinflammation, and activation of multiple regulated cell death pathways (Wu et al., 2024). Several studies demonstrate that a pivotal role in this process is played by the disruption of Ca^{2+} homeostasis. In fact, in neonatal mice exposed to NBHI, the inhibition of the Ca^{2+}-sensitive kinase Pyk2 attenuates NMDA receptor–dependent signaling and significantly reduces infarct burden (Zhu et al., 2022b). Moreover, the ischemic preconditioning paradigm that fine-tunes early Ca^{2+} signaling has been shown to enhance Ca^{2+}-dependent neurogenesis and increase resilience to subsequent NBHI insults, underscoring the developmental plasticity of Ca^{2+} pathways in the neonatal brain (Brancaccio et al., 2022).

Experimental data from neonatal rat hypoxic-ischemic models demonstrate that the pharmacological attenuation of ER stress with 4-phenylbutyrate reduces neuronal apoptosis and improves neurobehavioral outcomes, highlighting the therapeutic potential of modulating ER function in the immature brain (Mimori et al., 2012). Accordingly, the PERK–CHOP pathway has been shown to mediate neuronal and glial vulnerability following hypoxia and ischemia, linking ER dysfunction to both inflammatory and metabolic injury responses (Shi et al., 2022).

Conversely, mitochondria are central effectors of neuronal injury in neonatal hypoxia–ischemia. Preserving mitochondrial Ca^{2+} buffering capacity and preventing premature mPTP opening significantly contribute to the neuroprotective effects of therapeutic hypothermia during reperfusion (Sosunov et al., 2022). Mechanistically, modulation of MCU reduces Ca^{2+}-induced ROS production and ferroptosis signaling, highlighting mitochondrial Ca^{2+} handling (Marmolejo-Garza et al., 2023).

Despite extensive preclinical research demonstrating the contribution of organelle dysfunction, particularly at mitochondrial and ER level, to neuronal death in neonatal hypoxia and ischemia, clinical translation remains limited. Most ongoing or completed trials continue to focus on therapeutic hypothermia, while organelle-targeted interventions remain largely at the experimental stage. Recent translational efforts have explored mitochondrial protection, such as modulation of complex I activity or use of mitochondrial-targeted peptides, as potential adjuncts to hypothermia, but these approaches have not yet advanced beyond early-phase investigations (NIH Project: "Targeting Mitochondrial Complex I for Neuroprotection in Neonatal Hypoxic-Ischemic Brain Injury," Project ID 11017725). Stem cell-based therapies, although not organelle-specific, have shown indirect effects on mitochondrial integrity and ER stress, offering a broader cytoprotective profile (Ranjan and Gulati, 2023). Overall, there are no registered clinical trials directly targeting organellar channels or pumps (e.g., MCU, SERCA, and plasma membrane Ca^{2+}-ATPase), underscoring a significant translational gap between mechanistic understanding and therapeutic application in NBHI.

Huntington's disease

HD is a genetic neurodegenerative disease characterized by motor, psychiatric, and cognitive symptoms (Gusella et al., 2021). HD is caused by a dominantly inherited CAG trinucleotide repeat expansion in the huntingtin gene on chromosome 4 (McColgan and Tabrizi, 2018). Mutant huntingtin (mHTT) causes defective striatal neuron function, reduction of synaptic contacts, and disruption of immune cell function, culminating in neurodegeneration through several mechanisms (Kim and Fung, 2014; Andre et al., 2016).

For instance, mHTT tends to spontaneously aggregate, forming structures with increasing complexity. The process starts with a conformational change in the N-terminus of mHTT, which misfolds in a structure rich in β-sheets, thus promoting self-aggregation. This abnormal aggregation of mHTT disrupts normal protein-protein interaction and protein-DNA contacts, leading to organelle dysfunction and compromising cellular activities (Tong et al., 2024).

Dysregulation of intracellular neuronal Ca^{2+} signaling by mHTT seems to play an important role in HD progression (Raymond, 2017; Pchitskaya et al., 2018). In fact, mHTT determines a reduction of ER Ca^{2+} levels through the defective modulation of the interaction between IP_3 and IP_3R1. This event, in turn, causes an increase in synaptotoxic SOCE at the level of specific spines of the medium spiny neurons of transgenic HD mice (Tang et al., 2005, 2009; Wu et al., 2016).

In this context, STIM1/2 expression and function become dysfunctional, causing an increase of SOCE in different *in vitro* models of the disease (Vigont et al., 2014; Secondo et al., 2018). Accordingly, in mouse neuroblastoma cells and in primary culture of mouse medium spiny neurons, lentiviral expression of Htt138Q-1exon determines a potentiation of SOCE via STIM1 and ORAI1 modulation (Vigont et al., 2015). Therapeutically, the pharmacological inhibition or the stabilization of SOCE may rescue striatal spine loss in transgenic HD models (Vigont et al., 2015; Wu et al., 2016; Czeredys et al., 2017).

Another mechanism relevant for ER dysregulation during HD progression involves Sig-1R, whose activation by pridopidine may prevent medium spiny neuron spine loss in aging YAC128 co-cultures through the suppression of excessive ER Ca^{2+} release (Ryskamp et al., 2017).

Approximately one-third of all synthesized cellular proteins are produced by ER resident ribosomes and translocate to the ER lumen, where they undergo proper folding and adopt their three-dimensional structures before being packaged and shuttled to the Golgi (Ajoolabady et al., 2022; Wiseman et al., 2022). Improperly folded proteins are destined to the ER-associated degradation pathway for destruction by the proteasome or to the ER-phagy in order to be digested by the lysosome (Wiseman et al., 2022).

In this framework, ER stress is defined as a condition in which the folding capacity of the ER is exceeded, resulting in the accumulation of partially folded, unfolded, or misfolded proteins (Ajoolabady et al., 2022; Wiseman et al., 2022), while UPR promotes the reorganization of the ER quality control pathway to restore ER function (Espina et al., 2023).

GRP78/BiP levels are significantly increased in the hippocampus and, at later stages, in the striatum and cortex of HD mice (Espina et al., 2023). In the same model, the reduction of GRP78/BiP expression prevented the loss of dendritic spines and ameliorated HD hippocampal pathology and memory deficits, likely through the reduction of mHTT accumulation (Espina et al., 2023).

Much like PERK, IRE1α is bound to GRP78/BiP under unstressed conditions, but in the presence of ER stress, GRP78/BiP detaches from IRE1α, allowing its homodimerization or oligomerization and subsequent autophosphorylation (Kim et al., 2022). Indeed, Das et al. (2023) found that the inhibition of IRE1-and therefore the inhibition of the UPR pathway- leads to a lower protein accumulation, especially in conditions of prolonged ER stress, through the activation of the proteasomal machinery and the autophagy program. Moreover, Hassab et al. (2023) proved that dimethyl fumarate, an approved therapy for relapsing multiple sclerosis, blocks both the IRE1α and PERK arms of UPR, which leads to a potent prevention of apoptosis. This, in turn, proved beneficial in restoring dopamine content in the striatum and enhancing locomotor functions in HD.

Ultimately, it appears that the modulation of PERK and IRE1 with the aim of fine tuning the UPR and the complementary degradation machineries might be the winning strategy in HD.

Mitochondrial dysfunction in HD is multifactorial, involving direct and indirect effects of the mHTT on mitochondrial

bioenergetics, Ca^{2+} handling, oxidative stress responses, organelle dynamics, and degradation pathways. These alterations form a pathogenic cascade that exacerbates neuronal degeneration. Indeed, mHTT has been shown to interfere with some mitochondrial functions like impairing electron transport chain efficiency, reducing ATP synthesis, elevating production of ROS, and disrupting Ca^{2+} buffering (Quintanilla and Johnson, 2009). These changes contribute to oxidative damage to nucleic acids, proteins, and lipids, ultimately disrupting mitochondrial dynamics and compromising neuronal viability. Some studies have reported an impairment of complex II, complex III, and complex IV activity that contribute to a dysregulation of Ca^{2+} levels in muscles of HD patients (Browne et al., 1997; Tabrizi et al., 2000; Gizatullina et al., 2006). Moreover, in striatal cells expressing endogenous levels of mHTT, Ca^{2+} overload leads to impaired respiration and subsequently contributes to neuronal death. This impairment is linked to increased mitochondrial membrane permeability, although it occurs independently of substantial cytochrome C release (Milakovic et al., 2006). Elevated levels of nuclear p53 have been detected in HD patient-derived lymphoblasts, and its inhibition has been shown to rescue mitochondrial membrane potential and reduce cytotoxicity (Bae et al., 2005). Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a master regulator of mitochondrial biogenesis and oxidative metabolism, coactivates transcription factors such as nuclear factor erythroid 2-like 1 and nuclear factor erythroid 2-like 2, orchestrating the expression of nuclear-encoded mitochondrial genes (Wu et al., 1999). In HD, PGC-1α expression is markedly repressed, in part due to mHTT-mediated disruption of the TAF4/cyclic adenosine monophosphate (cAMP)-responsive element binding protein (CREB) signaling pathway. Furthermore, decreased cAMP levels and reduced CREB phosphorylation in mHTT-expressing cells further impair PGC-1α activation, contributing to defective mitochondrial gene expression (Cui et al., 2006).

Lysosomes and Lysosome Contact Sites

Lysosomes, intracellular acidic organelles with a luminal pH of approximately 4.5, are involved in a plethora of cellular functions, including macromolecule degradation, lysosomal exocytosis and phagocytosis, plasma membrane repair, autophagy regulation, energy metabolism, maintenance of cellular homeostasis, *etc*. (de Duve, 2005; Medina et al., 2011; Settembre et al., 2013; Samie et al., 2013; Medina et al., 2015; Zhang et al., 2016). In the last decades, these tiny organelles have also emerged as important Ca^{2+}-storing compartments (Patel and Docampo, 2010; Morgan et al., 2011). Indeed, they contain a luminal free Ca^{2+} concentration comparable to that of the ER (approximately 200–600 μM) (Christensen et al., 2002; Lloyd-Evans et al., 2008). Lysosomal Ca^{2+} levels are tightly regulated by the concerted activity of different channels and transporters localized on the lysosomal membrane. Several Ca^{2+}-releasing channels have been identified as mediators of lysosomal Ca^{2+} efflux. Among them, the best characterized are the non-selective Ca^{2+} channels TRPML1 and the two-pore channel 2 (TPC2), which selectively release Ca^{2+} from lysosomes upon stimulation by the lysosomal endogenous second messengers $PI(3,5)P_2$ and NAADP, respectively (Dong et al., 2010; Gerndt et al., 2020; Saito et al., 2023). Additionally, other Ca^{2+} channels, including the ATP-gated cation channel P2X4 (Huang et al., 2014), the Transient receptor potential melastatin 2 (Lange et al., 2009), the P/Q-type voltage-gated Ca^{2+} channels (Tian et al., 2015) and the transient receptor potential ankyrin 1 (Shang et al., 2016), participate in lysosomal Ca^{2+} release into the cytosol. In contrast, at the moment, the mechanism responsible for lysosomal Ca^{2+} uptake is still not fully elucidated. A putative Ca^{2+}/H^+ exchanger was proposed to mediate Ca^{2+} influx within the lysosomal lumen, but its molecular identity remained elusive for years. Very recently, Chen et al. (2025) demonstrated that the transmembrane protein 165 (TMEM165), a putative divalent cation/H^+ exchanger implicated in manganese homeostasis and glycosylation of proteins and lipids in the Golgi network, mediates Ca^{2+} import into the lysosomal lumen and Ca^{2+}-induced proton efflux from these acidic organelles, thereby acting as a lysosomal Ca^{2+}/H^+ exchanger in different cell types.

It is now widely recognized that lysosomal Ca^{2+} release via TRPML1 and TPC2, by promoting the nuclear translocation of TFEB, the master regulator of lysosomal function, induces the activation of autophagy (Medina et al., 2015; Venkatachalam, 2022; Nixon and Rubinsztein, 2024; Tedeschi et al., 2025b; **Figure 3**), an evolutionarily conserved lysosome-dependent process responsible for the clearance of long-lived proteins, protein aggregates and damaged organelles. Physiologically, autophagy is activated by conditions of nutrient deprivation and other stimuli. However, its dysfunctional activation has been associated with pathological processes such as brain ischemia, traumatic brain injury, neurodegenerative diseases, infections, and cancer (Schneider and Cuervo, 2014; **Figure 4**). Specifically, lysosomal homeostasis and autophagy are deficient in several neurodegenerative diseases, including ALS, AD, PD, and HD (Wang et al., 2016; Tedeschi et al., 2019, 2024; Yang and Zhang, 2023; Mançano et al., 2024; Beckers and Van Damme, 2025), while it becomes hyperactivated in ischemic stroke (Zhu et al., 2021; Tedeschi et al., 2023; **Figure 4**). Of note, there are still many questions regarding the use of targeted autophagy and TFEB as a disease treatment strategy. For instance, the hyperactivation of TFEB and/or prolonged inhibition of autophagy may promote tumorigenesis (Caliò et al., 2019). Furthermore, the application of TFEB activators as a therapeutic strategy in neurodegenerative diseases has not been evaluated for long-term application and the safety profile of the putative future drugs. Recently, the Food and Drug Administration approved the first direct TFEB inhibitor, eltrombopag, for the treatment of thrombocytopenia.

Lysosomal dysfunction has also been observed in lysosomal storage diseases, resulting in the progressive accumulation of undigested materials within the lysosomes (Platt et al., 2018), often presenting with CNS neuropathology.

Amyotrophic lateral sclerosis

Impairment in the autophagic flux and lysosomal Ca^{2+} dyshomeostasis play a crucial role in ALS pathogenesis (**Figure 4**). For instance, mutations in p62/SQSTM1, a

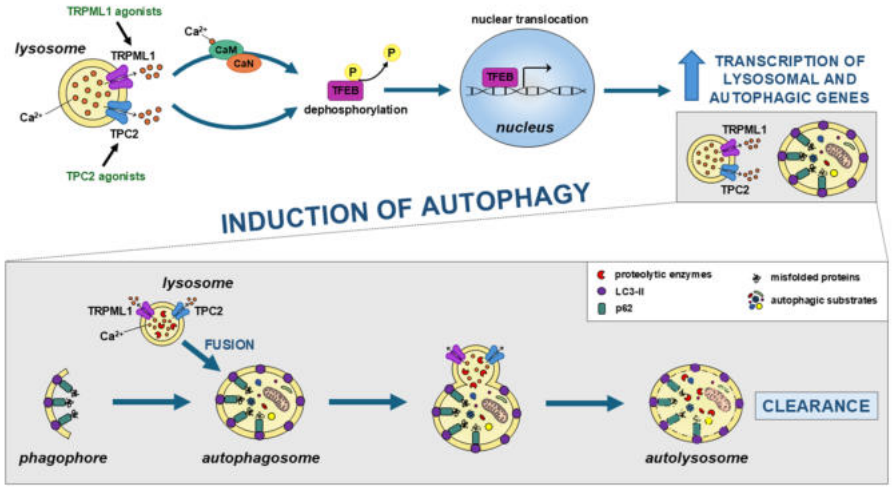

Figure 3 | **Schematic representation of autophagy induction after the stimulation of lysosomal Ca^{2+} channels with specific agonists.**
Stimulation of the lysosomal Ca^{2+} channels TRPML1 and TPC2 with endogenous modulators or specific pharmacological agonists leads to the dephosphorylation and the subsequent nuclear translocation of the master regulator of lysosomal function TFEB. This event, by promoting the transcription of lysosomal and autophagic genes, leads to the activation of autophagy, an evolutionarily conserved process responsible for the clearance of long-lived proteins, aggregated proteins, and damaged organelles. The autophagic process begins with the formation of a membrane structure called a phagophore, which elongates and incorporates cytoplasmic cargoes, forming the autophagosome. The autophagosome then fuses with the lysosome to form the autolysosome, where the enclosed materials are degraded by lysosomal acidic hydrolases.

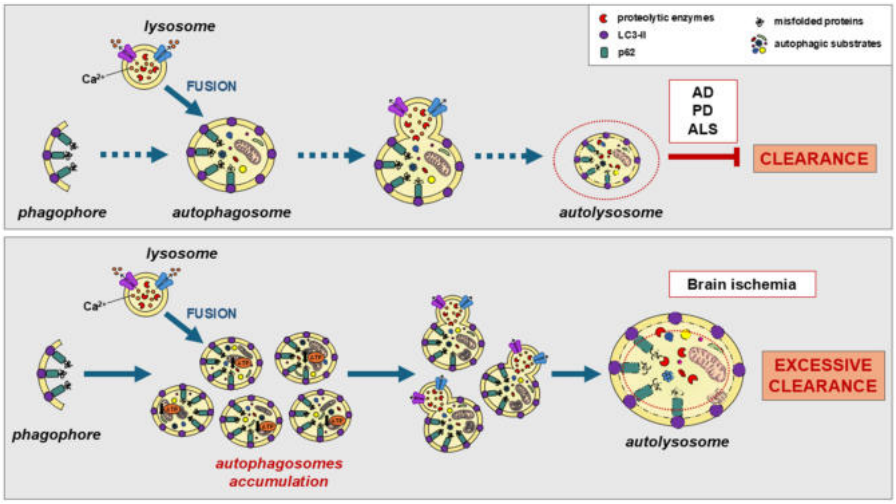

Figure 4 | **Schematic representation of autophagy dysfunction occurring during neurodegenerative diseases.**
Appropriate autophagosome-lysosomal formation is vital for maintenance of neuronal function. During neurodegeneration, autophagy impairment can lead to defective or excessive clearance of autophagosomal cargoes within suffering neurons. In neurodegenerative diseases such as AD, PD, and ALS, the blockade of the autophagic flux leads to a reduction in the clearance of autophagosomal cargoes by autolysosome limitation (top). In acute neurological diseases, such as brain ischemia, the hyperactivation of the autophagy flux leads to hyperfunctional autolysosomes, resulting in an excessive degradative autophagic clearance (bottom). AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; LC3-II: microtubule-associated protein 1 light chain 3 II; PD: Parkinson's disease.

linker protein between the ubiquitin-proteasome system and autophagy, have been found in both familial and sporadic ALS patients (Fecto et al., 2011; Teyssou et al., 2013; Wang et al., 2024). Among them, the L341V substitution in the LIR motif of p62/SQSTM1 significantly reduces its interaction with LC3-II, thereby impairing its ability to deliver ubiquitinated cargoes to forming phagophores (Goode et al., 2016). Additionally, loss-of-function mutations in the autophagy regulator TBK-1, identified in ALS/frontotemporal dementia patients, lead to autophagolysosomal dysfunction in neurons, resulting in the accumulation of damaged lysosomes (Brenner et al., 2024). Moreover, ALS-associated mutations in optineurin (OPTN), a selective autophagy receptor, have been reported to reduce the rate of autophagy and the degradation of damaged mitochondria (Wong and Holzbaur, 2014). Interestingly, in SOD1G93A mice and cell models, *OPTN* gene therapy may induce autophagy and protect mitochondria from damage (Wen et al., 2024).

Mutations in the *FIG4* gene encoding a phosphatase regulating the levels of phosphatidylinositol-3,5-bisphosphate ($PI(3,5)P_2$), originally described in Charcot-Marie-Tooth disease Type 4J, have also been found in a subset of ALS patients (Chow et al., 2009; Osmanovic et al., 2017). In $FIG4^{-/-}$ cells, $PI(3,5)P_2$ deficiency has been shown to suppress lysosomal Ca^{2+} efflux as a result of a reduced stimulation of TRPML1 lysosomal channel, the main target of $PI(3,5)P_2$. Once TRPML1 function is restored in $FIG4^{-/-}$ cells by the stimulation with the synthetic TRPML1 agonist ML-SA1, abnormal lysosomal storage is counteracted (Zou et al., 2015). The same occurs in a neurotoxic model of ALS/Parkinson-dementia complex in which the pharmacological activation of TRPML1 by ML-SA1 counteracts autophagic flux blockade, thus reducing ER stress and preventing motor neuronal death (Tedeschi et al., 2019). Similarly, a recently developed lipid-based formulation of $PI(3,5)P_2$-able to stabilize TRPML1 channel in the active conformation and to stimulate TFEB nuclear translocation- may extend the lifespan of ALS mice, boosting autophagy and preventing motor neuronal loss (Tedeschi et al., 2024). Furthermore, the early pharmacological stimulation of the lysosomal Ca^{2+} channel TPC2 by the antidepressant drug clomipramine and the antipsychotic drug chlorpromazine reverts autophagy dysfunction with the same mechanism (e.g., TFEB nuclear translocation) and prevents mitochondrial damage in a neurotoxic model of ALS/Parkinson-dementia complex (Tedeschi et al., 2025b).

In ALS, autophagy can also be affected by mutations in proteins essential for maintaining the homeostasis of other Ca^{2+}-storing organelles, such as the ER, which functionally cooperate with lysosomes. For instance, the E102Q mutation in the ER chaperone *Sig-1R* gene, reported to cause juvenile ALS, by disrupting Ca^{2+} homeostasis and promoting the accumulation of aggregated proteins leads to the impairment of autophagy, along with the accumulation of stress granules and cytoplasmic aggregation of ALS-linked RNA-binding proteins, such as matrin-3, FUS, and TDP-43 (Dreser et al., 2017). Notably, the pharmacological stimulation of Sig-1R with the selective serotonin reuptake inhibitor fluvoxamine can enhance autophagy by inducing the nuclear translocation of TFEB in C9orf72 ALS cells (Lin et al., 2024).

Alzheimer's disease

Lysosome-dependent autophagy is markedly impaired in neurons of AD patients and in AD preclinical models characterized by significantly enlarged autolysosomes, modified cathepsin activity, and impaired protein degradation (Yang et al., 2011). Since 1997, AD-associated endosomal abnormalities have been described by Cataldo et al. in postmortem AD brain. More recently, additional evidence on the defective "CLEAR Network" has been reported in AD pathogenesis. Mutations or deletions of the presenilin 1 may disrupt v-ATPase assembly and lysosome acidification, which in turn favor defective release of lysosomal Ca^{2+} through TRPML1 (Nixon, 2024). Abnormal cytosolic Ca^{2+} levels also favor the extrusion of H^+ from the lysosomal lumen via the Ca^{2+}/H^+ exchanger. In both cases, the resulting lysosomal alkalization may inactivate the acid-dependent lysosomal enzymes, limit autophagy, and lead to the accumulation of pathogenic proteins (Nixon, 2024).

Several therapeutic strategies have been drawn to stimulate lysosomal activity and autophagic clearance: in this respect, the genetic/pharmacological modulation of lysosomal channels has been taken over. For instance, the overexpression of TRPML1 produces protective effects in AD mice through brain-derived neurotrophic factor restoration (Zhang et al., 2022). In accordance with this evidence, the pharmacological activation of TRPML1 rescues from the AD-like phenotype in iPSC-derived human cortical neurons expressing APOE ε4 (Somogyi et al., 2023).

Notably, loss of function variants in *SORL1*, encoding the sortilin-related receptor protein SORLA that regulates endo-lysosomal trafficking, are causative for AD, and decreased expression of SORLA has been repeatedly observed in human AD brains (Pottier et al., 2012). Very recently, loss of SORLA at the microglial level has revealed the capacity to induce enlarged lysosomes in hiPSC-derived microglia-like cells, thus indicating a new putative therapeutic lysosome-related target in AD (Mishra et al., 2025).

Lysosomal storage diseases

The impairment in lysosomal function is a key feature of LSDs, a heterogeneous group of more than 70 inherited metabolic disorders caused by mutations in genes encoding lysosomal enzymes, transporters, or accessory proteins. These defects lead to the progressive accumulation of undegraded macromolecules within lysosomes, resulting in cellular dysfunction and progressive tissue damage (Platt et al., 2018). In these disorders, the disruption of lysosomal function also affects critical cellular processes such as autophagy, mitochondrial quality control, and ER homeostasis, highlighting the central role of lysosomes as key regulators of cellular homeostasis (Settembre et al., 2013). LSDs commonly affect multiple organs and systems, but the CNS is frequently involved, as occurs in mucolipidosis type IV (MLIV), mucopolysaccharidosis type I (MPS I or Hurler syndrome), mucopolysaccharidosis type IIIA (MPS IIIA or Sanfilippo syndrome type A), Gaucher disease (GD), and Niemann–Pick type C (NPC).

Mucolipidosis type IV

In MLIV, loss-of-function mutations in the *MCOLN1* gene, encoding the lysosomal Ca^{2+}-permeable channel TRPML1 (Bargal et al., 2000; Bassi et al., 2000; Sun et al., 2000), lead to an abnormal accumulation of enlarged vacuolar structures containing phospholipids, sphingolipids, mucopolysaccharides, and gangliosides within the cells (Bach et al., 1975; Bargal et al., 1988). The disease is characterized by defective autophagy, as evidenced by the accumulation of autophagy-related proteins (Curcio-Morelli et al., 2010). Additionally, the impaired fusion of autophagosomes with lysosomes is responsible for the accumulation of autophagosomes and protein aggregates (Vergarajauregui and Puertollano, 2008). Interestingly, targeting lysosomal Ca^{2+} channels or enhancing lysosomal exocytosis could be a useful strategy to ameliorate storage and vacuole accumulation in MLIV. For instance, it has been reported that the pharmacological activation of TRPML1 by ML-SA1 restores lysosomal trafficking and autophagic flux in MLIV (Somogyi et al., 2023). Moreover, AAV-mediated MCOLN1 gene delivery can rescue both neuronal and renal phenotypes in animal models of the disease (Venkatachalam et al., 2015).

MPS I (Hurler syndrome) and MPS IIIA (Sanfilippo syndrome type A)

In MPS I (Hurler syndrome), caused by mutations in the IDUA gene encoding α-L-iduronidase, both the glycosaminoglycans heparan sulfate and dermatan sulfate accumulate, leading to severe somatic and neurological symptoms. Neurodegeneration in Hurler patients is associated with lysosomal enlargement, altered autophagic flux, and accumulation of secondary substrates, including gangliosides and cholesterol (Scott et al., 1995; de la Mata et al., 2016; Ballabio and Bonifacino, 2020). On the other hand, MPS IIIA (Sanfilippo syndrome type A) presents with severe CNS degeneration, caused by sulfamidase deficiency. The disease is characterized by an accumulation of autophagosomes resulting from defective autophagosome-lysosome fusion (Settembre et al., 2008b). This leads to mitochondrial fragmentation, oxidative stress, and early activation of microglia and astrocytes, even before neuronal loss (Pierzynowska et al., 2021; Giaccio et al., 2024). For MPS I treatment, the early hematopoietic stem cell transplantation is the gold standard, whereas the enzyme replacement therapy has a limited efficacy in treating CNS symptoms, since the required supplemental enzyme is too large to cross the blood–brain barrier (Concolino et al., 2018). For MPS IIIA, no approved therapy currently exists, although a number of therapeutic approaches have been proposed, including AAV-based gene therapies (Sorrentino et al., 2019).

Gaucher disease

GD, the most common lysosomal disorder, is caused by mutations in the glucocerebrosidase (*GBA1*) gene, leading to deficient activity of the lysosomal enzyme β-glucocerebrosidase (GCase) and subsequent accumulation of glucosylceramide in lysosomes, especially in macrophages and, in the neuronopathic forms (type 2 or acute neuronopathic, and type 3 or chronic neuronopathic), in the CNS cells (Grabowski, 2012; Aflaki et al., 2016). Impaired GCase activity in this disease leads to a primary lysosomal defect associated with an impairment in the autophagic and proteasomal machinery (Osellame et al., 2013). These organellar dysfunctions, exacerbated by an altered mTORC1-TFEB signaling, converge to amplify neurodegeneration (Palmieri et al., 2017). Enzyme replacement therapy with recombinant GCase is the current standard of care for GD type 1 (non-neuronopathic form) (Grabowski, 2012). However, this strategy offers minimal benefits for neuronopathic forms of GD, due to the limited passage through the blood–brain barrier.

Niemann–Pick type C

NPC is caused by mutations in the NPC1 (95% of cases) or in NPC2 (5% of cases) genes, both encoding proteins essential for intracellular cholesterol trafficking. Ca^{2+} dyshomeostasis is a key feature of NPC pathology. Indeed, mutations in NPC1 disrupt lysosomal Ca^{2+} storage and ER Ca^{2+} signaling, leading to altered SOCE and contributing to synaptic dysfunction and neurodegeneration (Lloyd-Evans, 2008; van Gool et al., 2024). The resulting defect leads to the accumulation of unesterified cholesterol and other lipids within late endosomes and lysosomes, causing widespread cellular dysfunction (Vanier, 2010). Currently, treatment options remain limited and primarily supportive. The only approved disease-specific treatment is the substrate reduction therapy with miglustat, which slows glycosphingolipid synthesis with the aim to reduce lipid accumulation and delay neurological progression (Patterson et al., 2012).

Parkinson's disease

The lysosomal-dependent autophagy plays a vital role in the control of protein quality by disrupting toxic aggregates of α-synuclein associated with PD pathogenesis. Quite a few lysosomal proteins are deregulated in PD (Navarro-Romero et al., 2020), most of which are specific or aspecific cationic channels involved in autophagy control.

Under physiological conditions, transmembrane protein 175 (TMEM175), a highly regulated lysosomal proton channel ubiquitously expressed, regulates lysosomal membrane potential and contributes to lysosomal pH stability. Notably, several GWAS studies point to TMEM175 as a genetic risk factor for PD (Chang et al., 2017; Hu et al., 2022). Accordingly, TMEM175 knockout mice exhibit Parkinson-like motor dysfunctions and a pathological aggregation of α-synuclein in the mouse brain. Furthermore, TMEM175 deficiency leads to a faster fusion of autophagosomes with lysosomes but causes an impairment of lysosomal degradation, leading to a faulty clearance of autophagosomes (Hu et al., 2022; Tang et al., 2023).

GCase is a lysosomal enzyme exhibiting lower activity in PD that leads to a reduced clearance of α-synuclein. In the context of drug repurposing, quetiapine, an atypical antipsychotic commonly utilized for the treatment of bipolar disorder, depression, and schizophrenia, has been shown to be capable of activating wild-type GCase in mice, leading to a reduction in α-synuclein levels in the mouse brain (Burbulla et al., 2021). Additionally, ambroxol, frequently used to facilitate mucociliary clearance, seems to play a neuroprotective role in PD through Ca^{2+} release from lysosome (Fois et al., 2015).

Furthermore, amino acid storage and metabolism are key cellular functions, heavily reliant on lysosomes, mitochondria, and their connections. Indeed, Peng et al. (2023) demonstrated significant changes in various amino acid levels in iPSC–derived dopaminergic neurons, in which mutant parkin may provoke the impairment of mitochondria/lysosomes contact sites compared to isogenic controls. However, the elimination of Rab7 seems to counteract this effect (Peng et al., 2023).

Another element required for a healthy autophagic flux is an organized lysosomal distribution, specifically the clustering of lysosomes around the MicroTubule Organizing Center, since it facilitates the fusion with autophagosomes. Indeed, mutations in genes involved in the shuttle of lysosomes and autophagosomes are implicated in different forms of neurodegeneration. Notably, LRRK2 is considered a putative target in PD therapy. Moreover, the LRRK2 function is essential in regulating the trafficking of lysosomes. Furthermore, the clustering of lysosomes is essential to an efficient degradation of α-synuclein aggregates, as shown by Date et al. (2024), who also demonstrated how albendazole, an approved broad-spectrum anthelmintic, can enhance autophagy through the clustering of lysosomes, thereby promoting the clearance of α-synuclein aggregates.

Moreover, lysosomal ionic dyshomeostasis is involved in PD pathogenesis, guiding all mentioned lysosomal functions. A recent study by Patel's group shows the relevance of TPC2 lysosomal channel defects in PD pathophysiology. In fact, excessive Ca^{2+} entry through voltage-dependent channels in dopaminergic PD neurons, mainly due to Cav1.3 (Caulfield et al., 2023), has been related to a TPC2 dysfunction, thus highlighting a disruptive lysosome–plasma membrane crosstalk in PD. Therefore, pharmacological and molecular strategies able to revert defective lysosomal Ca^{2+} homeostasis caused by pathogenic LRRK2 may be useful to slow the disease progression (Gregori et al., 2025).

Finally, the activation of the other cationic channel TRPML1 through a high-throughput chemical screening has been used to identify new drugs able to promote the autophagosome-lysosome fusion process, autophagic flux, clearance of α-synuclein aggregates, and neuroprotection (Date et al., 2024).

Cerebral ischemia

Lysosome, with the main roles of master regulator of autophagy and important player of intracellular Ca^{2+} dynamics, exerts dual effects in ischemic stroke, being protective or dangerous in neuronal, vascular, or glial cells depending on the level, duration, and intensity. For instance, in neurons, excessive glutamate stimulation activates the lysosomal TPC2 channel and induces the hyperactivation of detrimental autophagy. While basal autophagy is neuroprotective by clearing damaged organelles, uncontrolled autophagic flux may disrupt ionic homeostasis and accelerate cell death (Uchiyama et al., 2008). This is particularly evident in focal ischemia. Accordingly, the inhibition of TPC2 by Ned-19 may preserve Ca^{2+} homeostasis, alleviate ER stress, block maladaptive autophagy, and provide neuroprotection in both *in vitro* hypoxia/reoxygenation models and *in vivo* middle cerebral artery occlusion, reducing infarct volume and neurological deficits (Tedeschi et al., 2023). Moreover, Ischemia/Reperfusion injury induces microglial autophagy that promotes inflammation; inhibition of autophagy may attenuate ER stress via PERK signaling, shifting microglia toward an anti-inflammatory state, thus reducing neuronal injury (Zhu et al., 2021).

Neonatal hypoxic–ischemic brain injury

It has been recently demonstrated that the lysosomal compartment is critically involved in the regulation of autophagy and cell survival during NBHI. Deficiency in cathepsin H, a lysosomal cysteine protease with aminopeptidase activity, may impair TLR3/interferon-β signaling in NBHI, thereby determining a reduction of interferon-β secretion from dendritic cells and, therefore, an exacerbation of the injury (Ni et al., 2021).

In neonatal mice, the loss of the lysosomal channel TMEM175 impairs lysosomal acidification and disrupts the autophagic flux, thereby exacerbating neuronal death after hypoxic–ischemic injury (Zhang et al., 2023a). Very recently, in support of the role of lysosomal ionic homeostasis in NBHI pathophysiology, it has been demonstrated that the inhibition of lysosomal iron accumulation by the competitive inhibitor of succinate dehydrogenase, dimethyl malonate, improves cognitive and motor functions and reduces the infarct volume in neonatal mice subjected to hypoxia and ischemia (Jin et al., 2025).

Huntington's disease

Lysosome density is reduced in HD neuronal dendrites. This event impacts hippocampal synaptic plasticity and spatial learning in HD models. Notably, LTP changes are dependent on the alteration of the defective interplay between ER and lysosomes in exchanging Ca^{2+} in hippocampal spines (Chen et al., 2023b). Moreover, autophagy dysfunction can cause mutant HTT (mHTT) accumulation in HD through the expression of ZKSCAN3, a repressor of the master regulator of autophagy activated by lysosomal Ca^{2+} release, namely TFEB. CRISPR-Cas9-based gene ablation of ZKSCAN3 in HD animal models and iPSC from HD patients leads to improvements in behavioral symptoms (Park et al., 2025). Accordingly, overexpressing TFEB leads to the elimination of HTT aggregates, thereby reducing HD neuropathological signs (Tsunemi et al., 2012). Conversely, mHTT can sequester TFEB, thus reducing its bioavailability and preventing lysophagy, an event contributing to the accumulation of defective lysosomes (Rusmini et al., 2025). Moreover, in respect to the defective autophagy in HD, overexpressing beclin-1 in the early stages of the disease leads to a significant reduction in the number of mHTT aggregates and in the levels of PPP1R1B/DARPP-32 (protein phosphatase 1 regulatory inhibitor subunit 1B), which is involved in dopamine signaling and can define HD progression (Brattås et al., 2021). Mitophagy is also impaired in HD. Although autophagosomes form and fuse with lysosomes efficiently, there is a dysfunction in the sequestration of cellular components that could enhance the levels of damaged protein and organelles in HD cells (Martinez-Vicente et al., 2010). Accordingly, mHTT disrupts the mitophagy process at multiple stages: it interferes with ULK1 and beclin-1, hindering autophagy initiation, and impairs the normal role of HTT in recruiting autophagy receptors (e.g., OPTN, CALCOCO2, and p62/SQSTM1) to damaged mitochondria. Consequently, LC3-II recruitment is diminished, leading to inefficient mitophagy, accumulation of dysfunctional mitochondria, impaired respiration, and increased ROS production in HD (Franco-Iborra et al., 2021).

Therapeutic Opportunities for Intervention against Neurodegeneration

The first "proof of concept" on the clinical relevance and applicability of organelle-targeted drugs has been their proposed use in oncology. Given that ER function is crucial for cell fate by virtue of its peculiar interplay with mitochondria, delivery of specific drugs into the ER has been proposed for cancer therapy. In fact, during the leakage of ER Ca^{2+} flux, this ion accumulates in the mitochondria determining mPTP opening with the consequent release of mitochondrial pro-apoptotic factors triggering cell death. Furthermore, ER plays a key role in most mitochondrial fission events at ER–mitochondria contact sites level.

However, due to the structural complexity of ER, to avoid excessive dilution, therapeutic agents directed to this organelle have been targeted against specific proteins, such as sulfonylurea receptors that are K^+ channels highly expressed on ER membranes.

Accordingly, sulfonamide ligands such as glibenclamide and prodrugs linked to an ER targeting group (toluenesulfonyl) have been developed due to their low toxicity, high efficiency, and selectivity. Once into the ER, these small molecules may trigger ER stress-mediated cell death (Ghosh et al., 2019). Another pharmacological strategy is that of prodrugs activated by high levels of ROS in the ER and lysosomes. Given these strategies, several drugs targeting the ER and lysosome are under clinical investigation in oncology.

However, for the therapy of neurodegeneration, it could be useful to modulate the same above mechanisms, but in the opposite way. To this aim, the development of advanced imaging techniques using traditional confocal and electron microscopy has been used to discriminate the contribution of each organelle in the development of neurodegenerative diseases. Several new druggable targets toward organelles' dysfunction in neurodegeneration have been identified, including Drp1, PINK1, the ER-resident Mfn2, VDAC, and Sig-1R (Zheng et al., 2023).

In this context, several drugs targeting the above proteins have successfully entered into later-phase clinical studies for the treatment of neurodegenerative disorders, depression, and stroke. Among the strategies, pharmacological modulation of Sig-1R has been investigated with particular emphasis. Despite the important role played by Sig-1R in regulating several mitochondrial and ER functions, most of the trials failed, as drugs modulating Sig-1R showed no clinical efficacy.

However, the phase 3, randomized, double-blind, placebo-controlled, parallel arm, multicenter clinical trial on the Sig-1R agonist pridopidine in HD showed a small but clinically relevant group of HD patients in which significant treatment benefit was observed (Reilmann et al., 2025). Of interest, pridopidine was well-tolerated with an excellent safety profile. Therefore, further investigation would be desirable with refined patient selection (Zheng et al., 2023).

Other clinical trials with Sig-1R agonists (blarcamesine, cutamesine, and edonerpic maleate) or antagonist (S1RA) are ongoing in AD, PD, ALS, and stroke patients (Zheng et al., 2023).

Moreover, a large randomized, double-blind, multi-center, parallel group, placebo-controlled clinical trial of ambroxol hydrochloride in patients with PD is now ongoing in phase 3, since ambroxol appeared to slow PD progression in preclinical studies and shows a good safety profile in a small randomized clinical trial (Silveira et al., 2025). Furthermore, although larger sample sizes are needed, a systematic meta-analysis showed that GLP-1 agonists could improve the motor function of PD patients (Messak et al., 2025).

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References

Aflaki E, Moaven N, Borger DK, Lopez G, Westbroek W, Chae JJ, Marugan J, Patnaik S, Maniwang E, Gonzalez AN, Sidransky E (2016) Lysosomal storage and impaired autophagy lead to inflammasome activation in Gaucher macrophages. Aging Cell 15:77-88.
Ajoolabady A, Lindholm D, Ren J, Pratico D (2022) ER stress and UPR in Alzheimer's disease: mechanisms, pathogenesis, treatments. Cell Death Dis 13:706.
Andre R, Carty L, Tabrizi SJ (2016) Disruption of immune cell function by mutant huntingtin in Huntington's disease pathogenesis. Curr Opin Pharmacol 26:33-38.
Area-Gomez E, Del Carmen Lara Castillo M, Tambini MD, Guardia-Laguarta C, de Groof AJ, Madra M, Ikenouchi J, Umeda M, Bird TD, Sturley SL, Schon EA (2012) Upregulated function of mitochondria-associated ER membranes in Alzheimer disease. EMBO J 31:4106-4123.
Bach G, Cohen MM, Kohn G (1975) Abnormal ganglioside accumulation in cultured fibroblasts from patients with mucolipidosis IV. Biochem Biophys Res Commun 66:1483-1490.
Bae BI, Xu H, Igarashi S, Fujimuro M, Agrawal N, Taya Y, Hayward SD, Moran TH, Montell C, Ross CA, Snyder SH, Sawa A (2005) p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. Neuron 47:29-41.
Ballabio A, Bonifacino JS (2020) Lysosomes as dynamic regulators of cell and organismal homeostasis. Nat Rev Mol Cell Biol 21:101-118.
Bargal R, Bach G (1988) Phospholipids accumulation in mucolipidosis IV cultured fibroblasts. J Inherit Metab Dis 11:144-150.
Bargal R, Avidan N, Ben-Asher E, Olender Z, Zeigler M, Frumkin A, Raas-Rothschild A, Glusman G, Lancet D, Bach G (2000) Identification of the gene causing mucolipidosis type IV. Nat Genet 26:118-123.
Bassi MT, Manzoni M, Monti E, Pizzo MT, Ballabio A, Borsani G (2000) Cloning of the gene encoding a novel integral membrane protein, mucolipidin-and identification of the two major founder mutations causing mucolipidosis type IV. Am J Hum Genet 67:1110-1120.
Bastioli G, Piccirillo S, Castaldo P, Magi S, Tozzi A, Amoroso S, Calabresi P (2019) Selective inhibition of mitochondrial sodium-calcium exchanger protects striatal neurons from α-synuclein plus rotenone induced toxicity. Cell Death Dis 10:80.
Bastioli G, Piccirillo S, Graciotti L, Carone M, Sprega G, Taoussi O, Preziuso A, Castaldo P (2024) Calcium deregulation in neurodegeneration and neuroinflammation in Parkinson's disease: role of calcium-storing organelles and sodium-calcium exchanger. Cells 13:1301.
Beccano-Kelly DA, Cherubini M, Mousba Y, Cramb KML, Giussani S, Caiazza MC, Rai P, Vingill S, Bengoa-Vergniory N, Ng B, Corda G, Banerjee A, Vowles J, Cowley S, Wade-Martins R (2023) Calcium dysregulation combined with mitochondrial failure and electrophysiological maturity converge in Parkinson's iPSC-dopamine neurons. iScience 26:107044.

Beckers J, Van Damme P (2025) The role of autophagy in the pathogenesis and treatment of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Autophagy Rep 4:2474796.
Belov Kirdajova D, Kriska J, Tureckova J, Anderova M (2020) Ischemia-triggered glutamate excitotoxicity from the perspective of glial cells. Front Cell Neurosci 14:51.
Benador IY, Veliova M, Mahdaviani K, Petcherski A, Wikstrom JD, Assali EA, Acín-Pérez R, Shum M, Oliveira MF, Cinti S, Sztalryd C, Barshop WD, Wohlschlegel JA, Corkey BE, Liesa M, Shirihai OS (2018) Mitochondria bound to lipid droplets have unique bioenergetics, composition, and dynamics that support lipid droplet expansion. Cell Metab 27:869-885.
Blair K, Martinez-Serra R, Gosset P, Martín-Guerrero SM, Mórotz GM, Atherton J, Mitchell JC, Markovinovic A, Miller CCJ (2025) Structural and functional studies of the VAPB-PTPIP51 ER-mitochondria tethering proteins in neurodegenerative diseases. Acta Neuropathol Commun 13:49.
Bonora M, Giorgi C, Pinton P (2022) Molecular mechanisms and consequences of mitochondrial permeability transition. Nat Rev Mol Cell Biol 23:266-285.
Borcherding N, Brestoff JR (2023) The power and potential of mitochondria transfer. Nature 623:283-291.
Boscia F, D'Avanzo C, Pannaccione A, Secondo A, Casamassa A, Formisano L, Guida N, Scorziello A, Di Renzo G, Annunziato L (2013) New roles of NCX in glial cells: activation of microglia in ischemia and differentiation of oligodendrocytes. Adv Exp Med Biol 961:307-316.
Boutant M, Kulkarni SS, Joffraud M, Ratajczak J, Valera-Alberni M, Combe R, Zorzano A, Cantó C (2017) Mfn2 is critical for brown adipose tissue thermogenic function. EMBO J 36:1543-1558.
Brancaccio P, Anzilotti S, Cuomo O, Vinciguerra A, Campanile M, Herchuelz A, Amoroso S, Annunziato L, Pignataro G (2022) Preconditioning in hypoxic-ischemic neonate mice triggers Na+-Ca2+ exchanger-dependent neurogenesis. Cell Death Discov 8:318.
Brattås PL, Hersbach BA, Madsen S, Petri R, Jakobsson J, Pircs K (2021) Impact of differential and time-dependent autophagy activation on therapeutic efficacy in a model of Huntington disease. Autophagy 17:1316-1329.
Brenner D, et al. (2024) A TBK1 variant causes autophagolysosomal and motoneuron pathology without neuroinflammation in mice. J Exp Med 221:e20221190.
Browne SE, Bowling AC, MacGarvey U, Baik MJ, Berger SC, Muqit MM, Bird ED, Beal MF (1997) Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. Ann Neurol 41:646-653.
Burbulla LF, Zheng J, Song P, Jiang W, Johnson ME, Brundin P, Krainc D (2021) Direct targeting of wild-type glucocerebrosidase by antipsychotic quetiapine improves pathogenic phenotypes in Parkinson's disease models. JCI Insight 6:e148649.
Caliò A, Segala D, Munari E, Brunelli M, Martignoni G (2019) MiT family translocation renal cell carcinoma: from the early descriptions to the current knowledge. Cancers 11:1110.
Cataldo AM, Barnett JL, Pieroni C, Nixon RA (1997) Increased neuronal endocytosis and protease delivery to early endosomes in sporadic Alzheimer's disease: neuropathologic evidence for a mechanism of increased beta-amyloidogenesis. J Neurosci 17:6142-6151.
Caulfield ME, Manfredsson FP, Steece-Collier K (2023) The role of striatal Cav1.3 calcium channels in therapeutics for Parkinson's disease. Handb Exp Pharmacol 279:107-137.
Chami M, Checler F (2020) Alterations of the endoplasmic reticulum (ER) calcium signaling molecular components in Alzheimer's disease. Cells 9:2577.
Chang D, Nalls MA, Hallgrímsdóttir IB, Hunkapiller J, van der Brug M, Cai F; International Parkinson's Disease Genomics Consortium; 23andMe Research Team; Kerchner GA, Ayalon G, Bingol B, Sheng M, Hinds D, Behrens TW, Singleton AB, Bhangale TR, Graham RR (2017) A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. Nat Genet 49:1511-1516.
Chen JH, Xu N, Qi L, Yan HH, Wan FY, Gao F, Fu C, Cang C, Lu B, Bi GQ, Tang AH (2023b) Reduced lysosomal density in neuronal dendrites mediates deficits in synaptic plasticity in Huntington's disease. Cell Rep 42:113573.
Chen R, Liu B, Jaślan D, Kucej L, Kudrina V, Warnke B, Klingl YE, Petrauskas A, Castro SP, Maeda K, Grimm C, Jäättelä M (2025) Lysosomal TMEM165 controls cellular ion homeostasis and survival by mediating lysosomal Ca2+ import and H+ efflux. Nat Commun 16:5209.
Chen X, Shi C, He M, Xiong S, Xia X (2023a) Endoplasmic reticulum stress: molecular mechanism and therapeutic targets. Signal Transduct Target Ther 8:352.
Choong CJ, Mochizuki H (2022) Neuropathology of α-synuclein in Parkinson's disease. Neuropathology 42:93-103.
Chow CY, Landers JE, Bergren SK, Sapp PC, Grant AE, Jones JM, Everett L, Lenk GM, McKenna-Yasek DM, Weisman LS, Figlewicz D, Brown RH, Meisler MH (2009) Deleterious variants of FIG4, a phosphoinositide phosphatase, in patients with ALS. Am J Hum Genet 84:85-88.
Christensen KA, Myers JT, Swanson JA (2002) pH-dependent regulation of lysosomal calcium in macrophages. J Cell Sci 115:599-607.
Cisneros J, Belton TB, Shum GC, Molakal CG, Wong YC (2022) Mitochondria-lysosome contact site dynamics and misregulation in neurodegenerative diseases. Trends Neurosci 45:312-322.
Cohen S, Valm AM, Lippincott-Schwartz J (2018) Interacting organelles. Curr Opin Cell Biol 53:84-91.
Concolino D, Deodato F, Parini R (2018) Enzyme replacement therapy: efficacy and limitations. Ital J Pediatr 44:120.
Cornejo VH, Hetz C (2013) The unfolded protein response in Alzheimer's disease. Semin Immunopathol 35:277-292.
Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, Krainc D (2006) Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 127:59-69.
Curcio-Morelli C, Charles FA, Micsenyi MC, Cao Y, Venugopal B, Browning MF, Dobrenis K, Cotman SL, Walkley SU, Slaugenhaupt SA (2010) Macroautophagy is defective in mucolipin-1-deficient mouse neurons. Neurobiol Dis 40:370-377.
Czeredys M, Maciag F, Methner A, Kuznicki J (2017) Tetrahydrocarbazoles decrease elevated SOCE in medium spiny neurons from transgenic YAC128 mice, a model of Huntington's disease. Biochem Biophys Res Commun 483:1194-1205.
Das E, Sahu KK, Roy I (2023) The functional role of Ire1 in regulating autophagy and proteasomal degradation under prolonged proteotoxic stress. FEBS J 290:3270-3289.
Date Y, Sasazawa Y, Kitagawa M, Gejima K, Suzuki A, Saya H, Kida Y, Imoto M, Itakura E, Hattori N, Saiki S (2024) Novel autophagy inducers by accelerating lysosomal clustering against Parkinson's disease. Elife 13:e98649.
de Duve C (2005) The lysosome turns fifty. Nat Cell Biol 7:847-849.
de la Mata M, Cotán D, Villanueva-Paz M, de Lavera I, Álvarez-Córdoba M, Luzón-Hidalgo R, Suárez-Rivero JM, Tiscornia G, Oropesa-Ávila M (2016) Mitochondrial dysfunction in lysosomal storage disorders. Diseases 4:31.
de Ridder I, Kerkhofs M, Lemos FO, Loncke J, Bultynck G, Parys JB (2023) The ER-mitochondria interface, where Ca2+ and cell death meet. Cell Calcium 112:102743.
Dematteis G, et al. (2024) ER-mitochondria distance is a critical parameter for efficient mitochondrial Ca2+ uptake and oxidative metabolism. Commun Biol 7:1294.
Di Marco G, Vallese F, Jourde B, Bergsdorf C, Sturlese M, De Mario A, Techer-Etienne V, Haasen D, Oberhauser B, Schleeger S, Minetti G, Moro S, Rizzuto R, De Stefani D, Fornaro M, Mammucari C (2020) A high-throughput screening identifies MICU1 targeting compounds. Cell Rep 30:2321-2331.
Di Paola S, Scotto-Rosato A, Medina DL (2018) TRPML1: the Ca(2+) retaker of the lysosome. Cell Calcium 69:112-121.
Dieterich DC, Karpova A, Mikhaylova M, Zdobnova I, König I, Landwehr M, Kreutz M, Smalla KH, Richter K, Landgraf P, Reissner C, Boeckers TM, Zuschratter W, Spilker C, Seidenbecher CI, Garner CC, Gundelfinger ED, Kreutz MR (2008) Caldendrin-Jacob: a protein liaison that couples NMDA receptor signalling to the nucleus. PLoS Biol 6:e34.
Diokmetzidou A, Scorrano L (2025) Mitochondria-membranous organelle contacts at a glance. J Cell Sci 138:jcs263895.
Dong XP, Shen D, Wang X, Dawson T, Li X, Zhang Q, Cheng X, Zhang Y, Weisman LS, Delling M, Xu H (2010) PI(3,5)P(2) controls membrane trafficking by direct activation of mucolipin Ca(2+) release channels in the endolysosome. Nat Commun 1:38.
Dreser A, Vollrath JT, Sechi A, Johann S, Roos A, Yamoah A, Katona I, Bohlega S, Wiemuth D, Tian Y, Schmidt A, Vervoorts J, Dohmen M, Beyer C, Anink J, Aronica E, Troost D, Weis J, Goswami A (2017) The ALS-linked E102Q mutation in Sigma receptor-1 leads to ER stress-mediated defects in protein homeostasis and dysregulation of RNA-binding proteins. Cell Death Differ 24:1655-1671.
Espina M, Di Franco N, Brañas-Navarro M, Navarro IR, Brito V, Lopez-Molina L, Costas-Insua C, Guzmán M, Ginés S (2023) The GRP78-PERK axis contributes to memory and synaptic impairments in Huntington's disease R6/1 mice. Neurobiol Dis 184:106225.
Fan H, Tan Y (2024) Lipid droplet-mitochondria contacts in health and disease. Int J Mol Sci 25:6878.
Fani G, Mannini B, Vecchi G, Cascella R, Cecchi C, Dobson CM, Vendruscolo M, Chiti F (2021) Aβ oligomers dysregulate calcium homeostasis by mechanosensitive activation of AMPA and NMDA receptors. ACS Chem Neurosci 12:766-781.
Fecto F, Yan J, Vemula SP, Liu E, Yang Y, Chen W, Zheng JG, Shi Y, Siddique N, Arrat H, Donkervoort S, Ajroud-Driss S, Sufit RL, Heller SL, Deng HX, Siddique T (2011) SQSTM1 mutations in familial and sporadic amyotrophic lateral sclerosis. Arch Neurol 68:1440-1446.
Fois G, Hobi N, Felder E, Ziegler A, Miklavc P, Walther P, Radermacher P, Haller T, Dietl P (2015) A new role for an old drug: Ambroxol triggers lysosomal exocytosis via pH-dependent Ca^{2+} release from acidic Ca^{2+} stores. Cell Calcium 58:628-637.
Franco-Iborra S, Plaza-Zabala A, Montpeyo M, Sebastian D, Vila M, Martinez-Vicente M (2021) Mutant HTT (huntingtin) impairs mitophagy in a cellular model of Huntington disease. Autophagy 17:672-689.
Gaja-Capdevila N, Hernández N, Navarro X, Herrando-Grabulosa M (2021) Sigma-1 receptor is a pharmacological target to promote neuroprotection in the SOD1G93A ALS mice. Front Pharmacol 12:780588.
Gao L, Liu F, Hou PP, Manaenko A, Xiao ZP, Wang F, Xu TL, Hu Q (2022) Neurons release injured mitochondria as "Help-Me" signaling after ischemic stroke. Front Aging Neurosci 14:785761.
Gelmetti V, De Rosa P, Torosantucci L, Marini ES, Romagnoli A, Di Rienzo M, Arena G, Vignone D, Fimia GM, Valente EM (2017) PINK1 and BECN1 relocalize at mitochondria-associated membranes during mitophagy and promote ER-mitochondria tethering and autophagosome formation. Autophagy 13:654-669.
Gerndt S, et al. (2020) Agonist-mediated switching of ion selectivity in TPC2 differentially promotes lysosomal function. Elife 9:e54712.
Ghosh C, Nandi A, Basu S (2019) Lipid nanoparticle-mediated induction of endoplasmic reticulum stress in cancer cells. ACS Biomater Sci Eng 2: 3992-4001.
Giaccio M, Monaco A, Galiano L, Parente A, Borzacchiello L, Rubino R, Klärner FG, Killa D, Perna C, Piccolo P, Marotta M, Pan X, Khijniak M, Siddique I, Schrader T, Pshezhetsky AV, Sorrentino NC, Bitan G, Fraldi A (2024) Anti-amyloid treatment is broadly effective in neuronopathic mucopolysaccharidoses and synergizes with gene therapy in MPS-IIIA. Mol Ther 32:4108-4121.
Gizatullina ZZ, Lindenberg KS, Harjes P, Chen Y, Kosinski CM, Landwehrmeyer BG, Ludolph AC, Striggow F, Zierz S, Gellerich FN (2006) Low stability of Huntington muscle mitochondria against Ca2+ in R6/2 mice. Ann Neurol 59:407-411.
Gómez-Suaga P, Bravo-San Pedro JM, González-Polo RA, Fuentes JM, Niso-Santano M (2018) ER-mitochondria signaling in Parkinson's disease. Cell Death Dis 9:337.
González-Rodríguez P, Zampese E, Stout KA, Guzman JN, Ilijic E, Yang B, Tkatch T, Stavarache MA, Wokosin DL, Gao L, Kaplitt MG, López-Barneo J, Schumacker PT, Surmeier DJ (2021) Disruption of mitochondrial complex I induces progressive parkinsonism. Nature 599:650-656.
Goode A, Butler K, Long J, Cavey J, Scott D, Shaw B, Sollenberger J, Gell C, Johansen T, Oldham NJ, Searle MS, Layfield R (2016) Defective recognition of LC3B by mutant SQSTM1/p62 implicates impairment of autophagy as a pathogenic mechanism in ALS-FTLD. Autophagy 12:1094-1104.
Grabowski GA (2012) Gaucher disease and other storage disorders. Hematology Am Soc Hematol Educ Program 2012:13-18.
Gregori M, Pereira GJS, Allen R, West N, Chau KY, Cai X, Bostock MP, Bolsover SR, Keller M, Lee CY, Lei SH, Harvey K, Bracher F, Grimm C, Hasan G, Gegg ME, Schapira AHV, Sweeney ST, Patel S (2025) Lysosomal TPC2 channels disrupt Ca2+ entry and dopaminergic function in models of LRRK2-Parkinson's disease. J Cell Biol 224:e202412055.
Gusella JF, Lee JM, MacDonald ME (2021) Huntington's disease: nearly four decades of human molecular genetics. Hum Mol Genet 30:R254-R263.
Han J, Back SH, Hur J, Lin YH, Gildersleeve R, Shan J, Yuan CL, Krokowski D, Wang S, Hatzoglou M, Kilberg MS, Sartor MA, Kaufman RJ (2013) ER-stress-induced transcriptional regulation increases protein synthesis leading to cell death. Nat Cell Biol 15:481-490.
Hassab LY, Abbas SS, Mohammed RA, Abdallah DM (2023) Dimethyl fumarate abrogates striatal endoplasmic reticulum stress in experimentally induced late-stage Huntington's disease: focus on the IRE1α/JNK and PERK/CHOP trajectories. Front Pharmacol 14:1133863.
Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, Ji X, Lo EH (2016) Transfer of mitochondria from astrocytes to neurons after stroke. Nature 535:551-555.
Hetz C, Saxena S (2017) ER stress and the unfolded protein response in neurodegeneration. Nat Rev Neurol 13:477-491.
Hönscher C, Mari M, Auffarth K, Bohnert M, Griffith J, Geerts W, van der Laan M, Cabrera M, Reggiori F, Ungermann C (2014) Cellular metabolism regulates contact sites between vacuoles and mitochondria. Dev Cell 30:86-94.
Hu M, Li P, Wang C, Feng X, Geng Q, Chen W, Marthi M, Zhang W, Gao C, Reid W, Swanson J, Du W, Hume RI, Xu H (2022) Parkinson's disease-risk protein TMEM175 is a proton-activated proton channel in lysosomes. Cell 185:2292-2308.
Huang DX, Yu X, Yu WJ, Zhang XM, Liu C, Liu HP, Sun Y, Jiang ZP (2022) Calcium signaling regulated by cellular membrane systems and calcium homeostasis perturbed in Alzheimer's disease. Front Cell Dev Biol 10:834962.
Huang P, Zou Y, Zhong XZ, Cao Q, Zhao K, Zhu MX, Murrell-Lagnado R, Dong XP (2014) P2X4 forms functional ATP-activated cation channels on lysosomal membranes regulated by luminal pH. J Biol Chem 289:17658-17667.
Ichas F, Jouaville LS, Mazat JP (1997) Mitochondria are excitable organelles capable of generating and conveying electrical and calcium signals. Cell 89:1145-1153.
Israelson A, Arbel N, Da Cruz S, Ilieva H, Yamanaka K, Shoshan-Barmatz V, Cleveland DW (2010) Misfolded mutant SOD1 directly inhibits VDAC1 conductance in a mouse model of inherited ALS. Neuron 67:575-587.
Jin Y, Wang X, Xu X, Zhou X, Wang Q, Zhang L, Li L, Jin M, Ni H (2025) Dimethyl malonate preserves brain and neurobehavioral phenotype following neonatal hypoxia-ischemia by inhibiting FTH1-mediated ferritinophagy. Redox Biol 86:103792.
Johnson KJ, Moy B, Rensing N, Robinson A, Ly M, Chengalvala R, Wong M, Galindo R (2022) Functional neuropathology of neonatal hypoxia-ischemia by single-mouse longitudinal electroencephalography. Epilepsia 63:3037-3050.
Keeney PM, Xie J, Capaldi RA, Bennett JP Jr (2006) Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled. J Neurosci 26:5256-5264.
Kim S, Kim DK, Jeong S, Lee J (2022) The common cellular events in the neurodegenerative diseases and the associated role of endoplasmic reticulum stress. Int J Mol Sci 23:5894.
Kim SD, Fung VS (2014) An update on Huntington's disease: from the gene to the clinic. Curr Opin Neurol 27:477-483.
Kinnear NP, Boittin FX, Thomas JM, Galione A, Evans AM (2004) Lysosome-sarcoplasmic reticulum junctions. A trigger zone for calcium signaling by nicotinic acid adenine dinucleotide phosphate and endothelin-1. J Biol Chem 279:54319-54326.
Kiselyov K, Jennigs JJ Jr, Rbaibi Y, Chu CT (2007) Autophagy, mitochondria and cell death in lysosomal storage diseases. Autophagy 3:259-262.
Klausen MK, et al. (2022) Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. JCI Insight 7:e159863.
Klivenyi P, Ferrante RJ, Matthews RT, Bogdanov MB, Klein AM, Andreassen OA, Mueller G, Wermer M, Kaddurah-Daouk R, Beal MF (1999) Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. Nat Med 5:347-350.
Korshunov KS, Prakriya M (2025) Store-operated calcium channels in the nervous system. Annu Rev Physiol 87:173-199.
Kostic M, Ludtmann MH, Bading H, Hershfinkel M, Steer E, Chu CT, Abramov AY, Sekler I (2015) PKA phosphorylation of NCLX reverses mitochondrial calcium overload and depolarization, promoting survival of PINK1-deficient dopaminergic neurons. Cell Rep 13:376-386.
La Russa D, Frisina M, Secondo A, Bagetta G, Amantea D (2020) Modulation of cerebral store-operated calcium entry-regulatory factor (SARAF) and peripheral orai1 following focal cerebral ischemia and preconditioning in mice. Neuroscience 441:8-21.
Lange I, Yamamoto S, Partida-Sanchez S, Mori Y, Fleig A, Penner R (2009) TRPM2 functions as a lysosomal Ca2+-release channel in beta cells. Sci Signal 2:ra23.
Leuner K, Schütt T, Kurz C, Eckert SH, Schiller C, Occhipinti A, Mai S, Jendrach M, Eckert GP, Kruse SE, Palmiter RD, Brandt U, Dröse S, Wittig I, Willem M, Haass C, Reichert AS, Müller WE (2012) Mitochondrion-derived reactive oxygen species lead to enhanced amyloid beta formation. Antioxid Redox Signal 16:1421-1433.
Li X, Li R, Lu L, Dhar A, Sheng H, Yang W (2022) Beneficial effects of neuronal ATF6 activation in permanent ischemic stroke. Front Cell Neurosci 16:1016391.

Lin CY, Wu HE, Weng EF, Wu HC, Su TP, Wang SM (2024) Fluvoxamine exerts sigma-1R to rescue autophagy via Pom121-mediated nucleocytoplasmic transport of TFEB. Mol Neurobiol 61:5282-5294.
Liu H, Jiang Y, Cong L, Zhang X, Zhou Y, Pan X, Liu S, Wang R, Cao X (2025) Intranasal insulin administration affecting perioperative neurocognitive dysfunction by regulating calcium transport protein complex IP3R/GRP75/VDAC1 on MAMs. Free Radic Biol Med 228:240-250.
Liu P, Xu J, Chen Y, Xu Q, Zhang W, Hu B, Li A, Zhu Q (2024) Electrophysiological signatures in global cerebral ischemia: neuroprotection via chemogenetic inhibition of CA1 pyramidal neurons in rats. J Am Heart Assoc 13:e036146.
Liu Y, Levine B (2015) Autosis and autophagic cell death: the dark side of autophagy. Cell Death Differ 22:367-376.
Lloyd-Evans E, Morgan AJ, He X, Smith DA, Elliot-Smith E, Sillence DJ, Churchill GC, Schuchman EH, Galione A, Platt FM (2008) Niemann-Pick disease type C1 is a sphingosine storage disease that causes deregulation of lysosomal calcium. Nat Med 14:1247-1255.
Loncke J, Kaasik A, Bezprozvanny I, Parys JB, Kerkhofs M, Bultynck G (2021) Balancing ER-mitochondrial Ca2+ fluxes in health and disease. Trends Cell Biol 31:598-612.
Lustbader JW, Cirilli M, Lin C, Xu HW, Takuma K, Wang N, Caspersen C, Chen X, Pollak S, Chaney M, Trinchese F, Liu S, Gunn-Moore F, Lue LF, Walker DG, Kuppusamy P, Zewier ZL, Arancio O, Stern D, Yan SS, Wu H (2004) ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. Science 304:448-452.
Magrì A, Lipari CLR, Caccamo A, Battiato G, Conti Nibali S, De Pinto V, Guarino F, Messina A (2024) AAV-mediated upregulation of VDAC1 rescues the mitochondrial respiration and sirtuins expression in a SOD1 mouse model of inherited ALS. Cell Death Discov 10:178.
Majewski L, Kuznicki J (2015) SOCE in neurons: Signaling or just refilling? Biochim Biophys Acta 1853:1940-1952.
Makio T, Simmen T (2024) Not so rare: diseases based on mutant proteins controlling endoplasmic reticulum-mitochondria contact (MERC) tethering. Contact (Thousand Oaks) 7:25152564241261228.
Mançano ASF, Pina JG, Froes BR, Sciani JM (2024) Autophagy-lysosomal pathway impairment and cathepsin dysregulation in Alzheimer's disease. Front Mol Biosci 11:1490275.
Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH (2006) Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. Hum Mol Genet 15:1437-1449.
Manczak M, Reddy PH (2012) Abnormal interaction between the mitochondrial fission protein Drp1 and hyperphosphorylated tau in Alzheimer's disease neurons: implications for mitochondrial dysfunction and neuronal damage. Hum Mol Genet 21:2538-2547.
Markovinovic A, Greig J, Martín-Guerrero SM, Salam S, Paillusson S (2022) Endoplasmic reticulum-mitochondria signaling in neurons and neurodegenerative diseases. J Cell Sci 135:jcs248534.
Marmolejo-Garza A, Krabbendam IE, Luu MDA, Brouwer F, Trombetta-Lima M, Unal O, O'Connor SJ, Majerníková N, Elzinga CRS, Mammucari C, Schmidt M, Madesh M, Boddeke E, Dolga AM (2023) Negative modulation of mitochondrial calcium uniporter complex protects neurons against ferroptosis. Cell Death Dis 14:772.
Márta K, Hasan P, Rodríguez-Prados M, Paillard M, Hajnóczky G (2021) Pharmacological inhibition of the mitochondrial Ca2+ uniporter: relevance for pathophysiology and human therapy. J Mol Cell Cardiol 151:135-144.
Martin LJ, Fancelli D, Wong M, Niedzwiecki M, Ballarini M, Plyte S, Chang Q (2014) GNX-4728, a novel small molecule drug inhibitor of mitochondrial permeability transition, is therapeutic in a mouse model of amyotrophic lateral sclerosis. Front Cell Neurosci 8:433.
Martinez-Vicente M, Talloczy Z, Wong E, Tang G, Koga H, Kaushik S, de Vries R, Arias E, Harris S, Sulzer D, Cuervo AM (2010) Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. Nat Neurosci 13:567-576.
McColgan P, Tabrizi SJ (2018) Huntington's disease: a clinical review. Eur J Neurol 25:24-34.
McLelland GL, Lee SA, McBride HM, Fon EA (2016) Syntaxin-17 delivers PINK1/parkin-dependent mitochondrial vesicles to the endolysosomal system. J Cell Biol 214:275-291.
Medina DL, Di Paola S, Peluso I, Armani A, De Stefani D, Venditti R, Montefusco S, Scotto-Rosato A, Prezioso C, Forrester A, Settembre C, Wang W, Gao Q, Xu H, Sandri M, Rizzuto R, De Matteis MA, Ballabio A (2015) Lysosomal calcium signalling regulates autophagy through calcineurin and TFEB. Nat Cell Biol 17:288-299.
Medina DL, Fraldi A, Bouche V, Annunziata F, Mansueto G, Spampanato C, Puri C, Pignata A, Martina JA, Sardiello M, Palmieri M, Polishchuk R, Puertollano R, Ballabio A (2011) Transcriptional activation of lysosomal exocytosis promotes cellular clearance. Dev Cell 21:421-430.
Meissner WG, et al. (2024) Trial of lixisenatide in early Parkinson's disease. N Engl J Med 390:1176-1185.
Messak M, Abdelmageed A, Senbel AA, Khattab YA, Mandour Y, Shaker O, Rehan AH, Oransa S, Nasr M, Shabeeb A E, Rezq Z, Hossam F, Abouelmagd ME. (2025) Efficacy and safety of GLP-1 agonists in Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. Naunyn Schmiedebergs Arch Pharmacol 398:9721-9736.
Mikhaylova M, Reddy PP, Munsch T, Landgraf P, Suman SK, Smalla KH, Gundelfinger ED, Sharma Y, Kreutz MR (2009) Calneurons provide a calcium threshold for trans-Golgi network to plasma membrane trafficking. Proc Natl Acad Sci U S A 106:9093-9098.
Milakovic T, Quintanilla RA, Johnson GV (2006) Mutant huntingtin expression induces mitochondrial calcium handling defects in clonal striatal cells: functional consequences. J Biol Chem 281:34785-34795.
Mimori S, Okuma Y, Kaneko M, Kawada K, Hosoi T, Ozawa K, Nomura Y, Hamana H (2012) Protective effects of 4-phenylbutyrate derivatives on the neuronal cell death and endoplasmic reticulum stress. Biol Pharm Bull 35:84-90.
Mishra S, Morshed N, Sidhu SB, Kinoshita C, Stevens B, Jayadev S, Young JE (2025) The Alzheimer's disease gene SORL1 regulates lysosome function in human microglia. Glia 73:1329-1348.
Mizuno Y, Ohta S, Tanaka M, Takamiya S, Suzuki K, Sato T, Oya H, Ozawa T, Kagawa Y (1989) Deficiencies in complex I subunits of the respiratory chain in Parkinson's disease. Biochem Biophys Res Commun 163:1450-1455.
Morcillo P, Kabra K, Velasco K, Cordero H, Jennings S, Yun TD, Larrea D, Akman HO, Schon EA (2024) Aberrant ER-mitochondria communication is a common pathomechanism in mitochondrial disease. Cell Death Dis 15:405.
Morgan AJ, Platt FM, Lloyd-Evans E, Galione A (2011) Molecular mechanisms of endolysosomal Ca2+ signalling in health and disease. Biochem J 439:349-374.
Mustaly-Kalimi S, Gallegos W, Steinbrenner D, Gupta S, Houcek AJ, Bennett DA, Marr RA, Peterson DA, Sekler I, Stutzmann GE (2025) Mitochondrial dysfunction mediated by ER-calcium dysregulation in neurons derived from Alzheimer's disease patients. Acta Neuropathol Commun 13:165.
Navarro-Romero A, Montpeyó M, Martinez-Vicente M (2020) The emerging role of the lysosome in Parkinson's disease. Cells 9:2399.
Nguyen KT, Barrett JN, García-Chacón L, David G, Barrett EF (2011) Repetitive nerve stimulation transiently opens the mitochondrial permeability transition pore in motor nerve terminals of symptomatic mutant SOD1 mice. Neurobiol Dis 42:381-390.
Ni J, Zhao J, Zhang X, Reinheckel T, Turk V, Nakanishi H (2021) Cathepsin H deficiency decreases hypoxia-ischemia-induced hippocampal atrophy in neonatal mice through attenuated TLR3/IFN-β signaling. J Neuroinflammation 18:176.
Nixon RA (2024) Autophagy-lysosomal-associated neuronal death in neurodegenerative disease. Acta Neuropathol 148:42.
Nixon RA, Rubinsztein DC (2024) Mechanisms of autophagy-lysosome dysfunction in neurodegenerative diseases. Nat Rev Mol Cell Biol 25:926-946.
Novorolsky RJ, Nichols M, Kim JS, Pavlov EV, J Woods J, Wilson JJ, Robertson GS (2020) The cell-permeable mitochondrial calcium uniporter inhibitor Ru265 preserves cortical neuron respiration after lethal oxygen glucose deprivation and reduces hypoxic/ischemic brain injury. J Cereb Blood Flow Metab 40:1172-1181.
Onyango IG, Dennis J, Khan SM (2016) Mitochondrial dysfunction in Alzheimer's disease and the rationale for bioenergetics based therapies. Aging Dis 7:201-214.
Osellame LD, Rahim AA, Hargreaves IP, Gegg ME, Richard-Londt A, Brandner S, Waddington SN, Schapira AHV, Duchen MR (2013) Mitochondria and quality control defects in a mouse model of Gaucher disease--links to Parkinson's disease. Cell Metab 17:941-953.
Osmanovic A, Rangnau I, Kosfeld A, Abdulla S, Janssen C, Auber B, Raab P, Preller M, Petri S, Weber RG (2017) FIG4 variants in central European patients with amyotrophic lateral sclerosis: a whole-exome and targeted sequencing study. Eur J Hum Genet 25:324-331.
Paillusson S, Stoica R, Gomez-Suaga P, Lau DHW, Mueller S, Miller T, Miller CCJ (2016) There's something wrong with my MAM; the ER-mitochondria axis and neurodegenerative diseases. Trends Neurosci 39:146-157.
Palmieri M, Pal R, Nelvagal HR, Lotfi P, Stinnett GR, Seymour ML, Chaudhury A, Bajaj L, Bondar VV, Bremner L, Saleem U, Tse DY, Sanagasetti D, Wu SM, Neilson JR, Pereira FA, Pautler RG, Rodney GG, Cooper JD, Sardiello M (2017) mTORC1-independent TFEB activation via Akt inhibition promotes cellular clearance in neurodegenerative storage diseases. Nat Commun 8:14338.
Panagaki T, Randi EB, Szabo C, Hölscher C (2023) Incretin mimetics restore the ER-mitochondrial axis and switch cell fate towards survival in LUHMES dopaminergic-like neurons: implications for novel therapeutic strategies in Parkinson's disease. J Parkinsons Dis 13:1149-1174.
Pani B, Ong HL, Liu X, Rauser K, Ambudkar IS, Singh BB (2008) Lipid rafts determine clustering of STIM1 in endoplasmic reticulum-plasma membrane junctions and regulation of store-operated Ca2+ entry (SOCE). J Biol Chem 283:17333-17340.
Pannaccione A, Piccialli I, Secondo A, Ciccone R, Molinaro P, Boscia F, Annunziato L (2020) The Na+/Ca2+exchanger in Alzheimer's disease. Cell Calcium 87:102190.
Park HJ, Kim J, Choi J, Ryou C, Shin E, Lee JY (2025) Targeted genome editing of ZKSCAN3 mitigates the neurotoxicity caused by mutant HTT (huntingtin) in a Huntington disease animal model and three-dimensional cell culture of Huntington disease. Autophagy 10:1-15.
Park JS, Davis RL, Sue CM (2018) Mitochondrial dysfunction in Parkinson's disease: new mechanistic insights and therapeutic perspectives. Curr Neurol Neurosci Rep 18:21.
Patel S, Docampo R (2010) Acidic calcium stores open for business: expanding the potential for intracellular Ca2+ signaling. Trends Cell Biol 20:277-286.
Patterson MC, Hendriksz CJ, Walterfang M, Sedel F, Vanier MT, Wijburg F; NP-C Guidelines Working Group (2012) Recommendations for the diagnosis and management of Niemann-Pick disease type C: an update. Mol Genet Metab 106:330-344.
Pchitskaya E, Popugaeva E, Bezprozvanny I (2018) Calcium signaling and molecular mechanisms underlying neurodegenerative diseases. Cell Calcium 70:87-94.
Peng W, Schröder LF, Song P, Wong YC, Krainc D (2023) Parkin regulates amino acid homeostasis at mitochondria-lysosome (M/L) contact sites in Parkinson's disease. Sci Adv 9:eadh3347.
Pereira AC, De Pascale J, Resende R, Cardoso S, Ferreira I, Neves BM, Carrascal MA, Zuzarte M, Madeira N, Morais S, Macedo A, do Carmo A, Moreira PI, Cruz MT, Pereira CF (2022) ER-mitochondria communication is involved in NLRP3 inflammasome activation under stress conditions in the innate immune system. Cell Mol Life Sci 79:213.
Petrozziello T, Secondo A, Tedeschi V, Esposito A, Sisalli M, Scorziello A, Di Renzo G, Annunziato L (2017) ApoSOD1 lacking dismutase activity neuroprotects motor neurons exposed to beta-methylamino-L-alanine through the Ca2+/Akt/ERK1/2 prosurvival pathway. Cell Death Differ 24:511-522.
Pierzynowska K, Gaffke L, Cyske Z, Węgrzyn G, Buttari B, Profumo E, Saso L (2021) Oxidative stress in mucopolysaccharidoses: pharmacological implications. Molecules 26:5616.
Pilotto F, Smeele PH, Scheidegger O, Diab R, Schobesberger M, Sierra-Delgado JA, Saxena S (2025) Kaempferol enhances ER-mitochondria coupling and protects motor neurons from mitochondrial dysfunction and ER stress in C9ORF72-ALS. Acta Neuropathol Commun 13:21.
Pittalà MGG, Reina S, Nibali SC, Cucina A, Cubisino SAM, Cunsolo V, Amodeo GF, Foti S, De Pinto V, Saletti R, Messina A (2022) Specific post-translational modifications of VDAC3 in ALS-SOD1 model cells identified by high-resolution mass spectrometry. Int J Mol Sci. 23:15853.
Platt FM, d'Azzo A, Davidson BL, Neufeld EF, Tifft CJ (2018) Lysosomal storage diseases. Nat Rev Dis Primers 4:27.
Popugaeva E, Vlasova OL, Bezprozvanny I (2015) Restoring calcium homeostasis to treat Alzheimer's disease: a future perspective. Neurodegener Dis Manag 5:395-398.
Pottier C, et al. (2012). High frequency of potentially pathogenic SORL1 mutations in autosomal dominant early-onset Alzheimer disease. Mol Psychiatry 17:875-879.
Quintanilla RA, Johnson GV (2009) Role of mitochondrial dysfunction in the pathogenesis of Huntington's disease. Brain Res Bull 80:242-247.
Rahi V, Kaundal RK (2025) A small-molecule activator of sarco/endoplasmic reticulum Ca2+-ATPase attenuates cerebral ischemia-reperfusion injury by suppressing endoplasmic reticulum stress and apoptosis. ACS Pharmacol Transl Sci 8:2953-2963.
Rai SN, Singh C, Singh A, Singh MP, Singh BK (2020) Mitochondrial dysfunction: a potential therapeutic target to treat Alzheimer's disease. Mol Neurobiol 57:3075-3088.
Ranjan AK, Gulati A (2023) Advances in therapies to treat neonatal hypoxic-ischemic encephalopathy. J Clin Med 12:6653.
Rashid HO, Yadav RK, Kim HR, Chae HJ (2015) ER stress: autophagy induction, inhibition and selection. Autophagy 11:1956-1977.
Raymond LA (2017) Striatal synaptic dysfunction and altered calcium regulation in Huntington disease. Biochem Biophys Res Commun 483:1051-1062.
Reilmann R, Feigin A, Rosser AE, Kostyk SK, Saft C, Cohen Y, Schuring H, Hand R, Tan A M, Chen K, Feng W, Navon-Perry L, Cruz-Herranz A, Syltevik C, Boot D, Squitieri F, Kayson E, Mehra M, Goldberg YP, Geva M, Hayden MR (2025) Pridopidine in early-stage manifest Huntington's disease: a phase 3 trial. Nature Medicine 31: 3780-3789.
Rizzollo F, Agostinis P (2025) Mitochondria-lysosome contact sites: emerging players in cellular homeostasis and disease. Contact (Thousand Oaks) 8:25152564251329250.
Romero-Sanz S, Caldero-Escudero E, Álvarez-Illera P, Santo-Domingo J, Fonteriz RI, Montero M, Álvarez J (2023) SERCA inhibition improves lifespan and healthspan in a chemical model of Parkinson disease in Caenorhabditis elegans. Front Pharmacol 14:1182428.
Rusmini P, et al. (2025) Impairment of lysosomal quality control in Huntington disease. Cell Death Dis 16:762.
Ryskamp D, Wu J, Geva M, Kusko R, Grossman I, Hayden M, Bezprozvanny I (2017) The sigma-1 receptor mediates the beneficial effects of pridopidine in a mouse model of Huntington disease. Neurobiol Dis 97:46-59.
Saito R, Mu Q, Yuan Y, Rubio-Alarcón M, Eznarriaga M, Zhao P, Gunaratne G, Kumar S, Keller M, Bracher F, Grimm C, Brailoiu E, Marchant JS, Rahman T, Patel S (2023) Convergent activation of Ca2+ permeability in two-pore channel 2 through distinct molecular routes. Sci Signal 16:eadg0661.
Sakai S, Watanabe S, Komine O, Sobue A, Yamanaka K (2021) Novel reporters of mitochondria-associated membranes (MAM), MAMtrackers, demonstrate MAM disruption as a common pathological feature in amyotrophic lateral sclerosis. FASEB J 35:e21688.
Samie M, et al. (2013) A TRP channel in the lysosome regulates large particle phagocytosis via focal exocytosis. Dev Cell 26:511-524.
Sardiello M, Palmieri M, di Ronza A, Medina DL, Valenza M, Gennarino VA, Di Malta C, Donaudy F, Embrione V, Polishchuk RS, Banfi S, Parenti G, Cattaneo E, Ballabio A (2009) A gene network regulating lysosomal biogenesis and function. Science 325:473-477.
Sassano ML, Felipe-Abrio B, Agostinis P (2022) ER-mitochondria contact sites; a multifaceted factory for Ca2+ signaling and lipid transport. Front Cell Dev Biol 10:988014.
Saxena S, Cabuy E, Caroni P (2009) A role for motoneuron subtype-selective ER stress in disease manifestations of FALS mice. Nat Neurosci 12:627-636.
Schampel A, Kuerten S (2017) Danger: high voltage-the role of voltage-gated calcium channels in central nervous system pathology. Cells 6:43.
Schapira AH, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD (1990) Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem 54:823-827.
Schneider JL, Cuervo AM (2014) Autophagy and human disease: emerging themes. Curr Opin Genet Dev 26:16-23.
Scott HS, Bunge S, Gal A, Clarke LA, Morris CP, Hopwood JJ (1995) Molecular genetics of mucopolysaccharidosis type I: diagnostic, clinical, and biological implications. Hum Mutat 6:288-302.
Secondo A, Bagetta G, Amantea D (2018) On the role of store-operated calcium entry in acute and chronic neurodegenerative diseases. Front Mol Neurosci 11:87.
Secondo A, Petrozziello T, Tedeschi V, Boscia F, Vinciguerra A, Ciccone R, Pannaccione A, Molinaro P, Pignataro G, Annunziato L (2019) ORAI1/STIM1 interaction intervenes in stroke and in neuroprotection induced by ischemic preconditioning through store-operated calcium entry. Stroke 50:1240-1249.
Settembre C, Di Malta C, Polito VA, Garcia Arencibia M, Vetrini F, Erdin S, Erdin SU, Huynh T, Medina D, Colella P, Sardiello M, Rubinsztein DC, Ballabio A (2011) TFEB links autophagy to lysosomal biogenesis. Science 332:1429-1433.
Settembre C, Fraldi A, Jahreiss L, Spampanato C, Venturi C, Medina D, de Pablo R, Tacchetti C, Rubinsztein DC, Ballabio A (2008b) A block of autophagy in lysosomal storage disorders. Hum Mol Genet 17:119-129.

Settembre C, Fraldi A, Medina DL, Ballabio A (2013) Signals from the lysosome: a control centre for cellular clearance and energy metabolism. Nat Rev Mol Cell Biol 14:283-296.
Settembre C, Fraldi A, Rubinsztein DC, Ballabio A (2008a) Lysosomal storage diseases as disorders of autophagy. Autophagy 4:113-114.
Shang S, et al. (2016) Intracellular TRPA1 mediates Ca2+ release from lysosomes in dorsal root ganglion neurons. J Cell Biol 215:369-381.
Shi M, Chai Y, Zhang J, Chen X (2022) Endoplasmic reticulum stress-associated neuronal death and innate immune response in neurological diseases. Front Immunol 12:794580.
Shteinfer-Kuzmine A, Argueti-Ostrovsky S, Leyton-Jaimes MF, Anand U, Abu-Hamad S, Zalk R, Shoshan-Barmatz V, Israelson A (2022) Targeting the mitochondrial protein VDAC1 as a potential therapeutic strategy in ALS. Int J Mol Sci 23:9946.
Silveira CRA, et al. (2025) Ambroxol as a treatment for Parkinson disease dementia: a randomized clinical trial. JAMA Neurol 82:797-807.
Sirabella R, Secondo A, Pannaccione A, Scorziello A, Valsecchi V, Adornetto A, Bilo L, Di Renzo G, Annunziato L (2009) Anoxia-induced NF-kappaB-dependent upregulation of NCX1 contributes to Ca2+ refilling into endoplasmic reticulum in cortical neurons. Stroke 40:922-929.
Sirabella R, Sisalli MJ, Costa G, Omura K, Ianniello G, Pinna A, Morelli M, Di Renzo GM, Annunziato L, Scorziello A (2018) NCX1 and NCX3 as potential factors contributing to neurodegeneration and neuroinflammation in the A53T transgenic mouse model of Parkinson's Disease. Cell Death Dis 9:725.
Sisalli MJ, Secondo A, Esposito A, Valsecchi V, Savoia C, Di Renzo GF, Annunziato L, Scorziello A (2014) Endoplasmic reticulum refilling and mitochondrial calcium extrusion promoted in neurons by NCX1 and NCX3 in ischemic preconditioning are determinant for neuroprotection. Cell Death Differ 21:1142-1149.
Solana-Manrique C, Muñoz-Soriano V, Sanz FJ, Paricio N (2021) Oxidative modification impairs SERCA activity in Drosophila and human cell models of Parkinson's disease. Biochim Biophys Acta Mol Basis Dis 1867:166152.
Somogyi A, Kirkham ED, Lloyd-Evans E, Winston J, Allen ND, Mackrill JJ, Anderson KE, Hawkins PT, Gardiner SE, Waller-Evans H, Sims R, Boland B, O'Neill C (2023) The synthetic TRPML1 agonist ML-SA1 rescues Alzheimer-related alterations of the endosomal-autophagic-lysosomal system. J Cell Sci 136:jcs259875.
Sood A, Jeyaraju DV, Prudent J, Caron A, Lemieux P, McBride HM, Laplante M, Tóth K, Pellegrini L (2014) A mitofusin-2-dependent inactivating cleavage of Opa1 links changes in mitochondria cristae and ER contacts in the postprandial liver. Proc Natl Acad Sci U S A 111:16017-16022.
Sorrentino NC, Cacace V, De Risi M, Maffia V, Strollo S, Tedesco N, Nusco E, Romagnoli N, Ventrella D, Huang Y, Liu N, Kalled SL, Choi VW, De Leonibus E, Fraldi A (2019) Enhancing the therapeutic potential of sulfamidase for the treatment of mucopolysaccharidosis IIIA. Mol Ther Methods Clin Dev 15:333-342.
Sosunov S, Bhutada A, Niatsetskaya Z, Starkov A, Ten V (2022) Mitochondrial calcium buffering depends upon temperature and is associated with hypothermic neuroprotection against hypoxia-ischemia injury. PLoS One 17:e0273677.
Sugiura A, McLelland GL, Fon EA, McBride HM (2014) A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. EMBO J 33:2142-2156.
Sun M, Goldin E, Stahl S, Falardeau JL, Kennedy JC, Acierno JS Jr, Bove C, Kaneski CR, Nagle J, Bromley MC, Colman M, Schiffmann R, Slaugenhaupt SA (2000) Mucolipidosis type IV is caused by mutations in a gene encoding a novel transient receptor potential channel. Hum Mol Genet 9:2471-2478.
Szabadkai G, Bianchi K, Várnai P, De Stefani D, Wieckowski MR, Cavagna D, Nagy AI, Balla T, Rizzuto R (2006) Chaperone-mediated coupling of endoplasmic reticulum and mitochondrial Ca2+ channels. J Cell Biol 175:901-911.
Tabrizi SJ, Workman J, Hart PE, Mangiarini L, Mahal A, Bates G, Cooper JM, Schapira AH (2000) Mitochondrial dysfunction and free radical damage in the Huntington R6/2 transgenic mouse. Ann Neurol 47:80-86.
Tagashira H, Bhuiyan MS, Shinoda Y, Kawahata I, Numata T, Fukunaga K (2023) Sigma-1 receptor is involved in modification of ER-mitochondria proximity and Ca2+ homeostasis in cardiomyocytes. J Pharmacol Sci 151:128-133.
Tang T, Jian B, Liu Z (2023) Transmembrane protein 175, a lysosomal ion channel related to Parkinson's disease. Biomolecules 13:802.
Tang TS, Slow E, Lupu V, Stavrovskaya IG, Sugimori M, Llinás R, Kristal BS, Hayden MR, Bezprozvanny I (2005) Disturbed Ca2+ signaling and apoptosis of medium spiny neurons in Huntington's disease. Proc Natl Acad Sci U S A 102:2602-2607.
Tang TS, Guo C, Wang H, Chen X, Bezprozvanny I (2009) Neuroprotective effects of inositol 1,4,5-trisphosphate receptor C-terminal fragment in a Huntington's disease mouse model. J Neurosci 29:1257-1266.
Tedeschi V, Ciancio R, Magliocca G, Esposito E, Piccirillo S, Rubino V, Preziuso A, Spadoni T, Muraglia ND, Ruggiero G, Pannaccione A, Secondo A (2025b) Lysosomal TPC2 channel as a new target of chlorpromazine and clomipramine to induce protective autophagy in L-BMAA-induced neurodegeneration. Biochem Pharmacol 242:117219.
Tedeschi V, La Russa D, Franco C, Vinciguerra A, Amantea D, Secondo A (2021) Plasma membrane and organellar targets of STIM1 for intracellular calcium handling in health and neurodegenerative diseases. Cells 10:2518.
Tedeschi V, Nele V, Valsecchi V, Anzilotti S, Vinciguerra A, Zucaro L, Sisalli MJ, Cassiano C, De Iesu N, Pignataro G, Canzoniero LMT, Pannaccione A, De Rosa G, Secondo A (2024) Nanoparticles encapsulating phosphatidylinositol derivatives promote neuroprotection and functional improvement in preclinical models of ALS via a long-lasting activation of TRPML1 lysosomal channel. Pharmacol Res 210:107491.
Tedeschi V, Petrozziello T, Sisalli MJ, Boscia F, Canzoniero LMT, Secondo A (2019) The activation of mucolipin TRP channel 1 (TRPML1) protects motor neurons from L-BMAA neurotoxicity by promoting autophagic clearance. Sci Rep 9:10743.
Tedeschi V, Sapienza S, Ciancio R, Canzoniero LMT, Pannaccione A, Secondo A (2025a) Lysosomal channels as new molecular targets in the pharmacological therapy of neurodegenerative diseases via autophagy regulation. Curr Neuropharmacol 23:375-383.
Tedeschi V, Vinciguerra A, Sisalli MJ, Pignataro G, Secondo A (2023) Pharmacological inhibition of lysosomal two-pore channel 2 (TPC2) confers neuroprotection in stroke via autophagy regulation. Neurobiol Dis 178:106020.
Teyssou E, Takeda T, Lebon V, Boillée S, Doukouré B, Bataillon G, Sazdovitch V, Cazeneuve C, Meininger V, LeGuern E, Salachas F, Seilhean D, Millecamps S (2013) Mutations in SQSTM1 encoding p62 in amyotrophic lateral sclerosis: genetics and neuropathology. Acta Neuropathol 125:511-522.
Theurey P, Tubbs E, Vial G, Jacquemetton J, Bendridi N, Chauvin MA, Alam MR, Le Romancer M, Vidal H, Rieusset J (2016) Mitochondria-associated endoplasmic reticulum membranes allow adaptation of mitochondrial metabolism to glucose availability in the liver. J Mol Cell Biol 8:129-143.
Tian X, Gala U, Zhang Y, Shang W, Nagarkar Jaiswal S, di Ronza A, Jaiswal M, Yamamoto S, Sandoval H, Duraine L, Sardiello M, Sillitoe RV, Venkatachalam K, Fan H, Bellen HJ, Tong C (2015) A voltage-gated calcium channel regulates lysosomal fusion with endosomes and autophagosomes and is required for neuronal homeostasis. PLoS Biol 13:e1002103.
Tong H, Yang T, Xu S, Li X, Liu L, Zhou G, Yang S, Yin S, Li XJ, Li S (2024) Huntington's disease: complex pathogenesis and therapeutic strategies. Int J Mol Sci 25:3845.
Tsunemi T, Ashe TD, Morrison BE, Soriano KR, Au J, Roque RA, Lazarowski ER, Damian VA, Masliah E, La Spada AR (2012) PGC-1α rescues Huntington's disease proteotoxicity by preventing oxidative stress and promoting TFEB function. Sci Transl Med 4:142ra97.
Uchiyama Y, Koike M, Shibata M (2008) Autophagic neuron death in neonatal brain ischemia/hypoxia. Autophagy 4:404-408.
van der Vlag M, Havekes R, Heckman PRA (2020) The contribution of Parkin, PINK1 and DJ-1 genes to selective neuronal degeneration in Parkinson's disease. Eur J Neurosci 52:3256-3268.
van Gool R, Golden E, Goodlett B, Zhang F, Vogel AP, Tourville JA, Yao K, Cay M, Tiwari S, Yang E, Zekelman LR, Todd N, O'Donnell LJ, Ren B, Bodamer OA, Al-Hertani W, Upadhyay J (2024) Characterization of central manifestations in patients with Niemann-Pick disease type C. Genet Med 26:101053.
Vance JE (1990) Phospholipid synthesis in a membrane fraction associated with mitochondria. J Biol Chem 265:7248-7256.
Vance JE (2020) Inter-organelle membrane contact sites: implications for lipid metabolism. Biol Direct 15:24.
Vanier MT (2010) Niemann-Pick disease type C. Orphanet J Rare Dis 5:16.
Venkatachalam K (2022) Regulation of aging and longevity by ion channels and transporters. Cells 11:1180.
Venkatachalam K, Wong CO, Zhu MX (2015) The role of TRPMLs in endolysosomal trafficking and function. Cell Calcium 58:48-56.
Vergarajauregui S, Puertollano R (2008) Mucolipidosis type IV: the importance of functional lysosomes for efficient autophagy. Autophagy 4:832-834.
Verkhratsky A, Shmigol A (1996) Calcium-induced calcium release in neurones. Cell Calcium 19:1-14.
Vigont V, Kolobkova Y, Skopin A, Zimina O, Zenin V, Glushankova L, Kaznacheyeva E (2015) Both Orai1 and TRPC1 are involved in excessive store-operated calcium entry in striatal neurons expressing mutant Huntingtin exon 1. Front Physiol 6:337.
Vigont VA, Zimina OA, Glushankova LN, Kolobkova JA, Ryazantseva MA, Mozhayeva GN, Kaznacheyeva EV (2014) STIM1 protein activates store-operated calcium channels in cellular model of Huntington's disease. Acta Naturae 6:40-47.
Walker AK, Farg MA, Bye CR, McLean CA, Horne MK, Atkin JD (2010) Protein disulphide isomerase protects against protein aggregation and is S-nitrosylated in amyotrophic lateral sclerosis. Brain 133:105-116.
Wang B, Abraham N, Gao G, Yang Q (2016) Dysregulation of autophagy and mitochondrial function in Parkinson's disease. Transl Neurodegener 5:19.
Wang J, Li X, Yang F, Guo P, Ren C, Duan Z, Bi M, Kong Y, Zhang Y, Lu J (2025a) Exploration of endoplasmic reticulum stress-related gene markers in amyotrophic lateral sclerosis: a comprehensive analysis of bioinformatics and machine learning. Anal Biochem 707:115969.
Wang M, Zhang H, Liang J, Huang J, Wu T, Chen N (2025b) Calcium signaling hypothesis: a non-negligible pathogenesis in Alzheimer's disease. J Adv Res 8:S2090-1232(25)00026-8.
Wang S, Jiang Q, Zheng X, Wei Q, Lin J, Yang T, Xiao Y, Li C, Shang H (2024) Genotype-phenotype correlation of SQSTM1 variants in patients with amyotrophic lateral sclerosis. J Med Genet 61:966-972.
Wang W, Zhao F, Ma X, Perry G, Zhu X (2020) Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. Mol Neurodegener 15:30.
Watanabe S, Ilieva H, Tamada H, Nomura H, Komine O, Endo F, Jin S, Mancias P, Kiyama H, Yamanaka K (2016) Mitochondria-associated membrane collapse is a common pathomechanism in SIGMAR1- and SOD1-linked ALS. EMBO Mol Med 8:1421-1437.
Wegierski T, Kuznicki J (2018) Neuronal calcium signaling via store-operated channels in health and disease. Cell Calcium 74:102-111.
Wen D, Ji Y, Li Y, Duan W, Wang Y, Li Z, Tao M, Liu Y (2024) OPTN gene therapy increases autophagy and protects mitochondria in SOD1-G93A-expressing transgenic mice and cells. FEBS J 291:795-813.
Wilson EL, Metzakopian E (2021) ER-mitochondria contact sites in neurodegeneration: genetic screening approaches to investigate novel disease mechanisms. Cell Death Differ 28:1804-1821.
Wiseman RL, Mesgarzadeh JS, Hendershot LM (2022) Reshaping endoplasmic reticulum quality control through the unfolded protein response. Mol Cell 82:1477-1491.
Wong YC, Holzbaur EL (2014) Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. Proc Natl Acad Sci U S A 111:E4439-4448.
Woods JJ, Nemani N, Shanmughapriya S, Kumar A, Zhang M, Nathan SR, Thomas M, Carvalho E, Ramachandran K, Srikantan S, Stathopulos PB, Wilson JJ, Madesh M (2019) A selective and cell-permeable mitochondrial calcium uniporter (MCU) inhibitor preserves mitochondrial bioenergetics after hypoxia/reoxygenation injury. ACS Cent Sci 5:153-166.
Wu CK, Fuh JL (2025) A 2025 update on treatment strategies for the Alzheimer's disease spectrum. J Chin Med Assoc 88:495-502.
Wu J, Ryskamp DA, Liang X, Egorova P, Zakharova O, Hung G, Bezprozvanny I (2016) Enhanced store-operated calcium entry leads to striatal synaptic loss in a Huntington's disease mouse model. J Neurosci 36:125-141.
Wu L, Chang E, Zhao H, Ma D (2024) Regulated cell death in hypoxic-ischaemic encephalopathy: recent development and mechanistic overview. Cell Death Discov 10:277.
Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, Troy A, Cinti S, Lowell B, Scarpulla RC, Spiegelman BM (1999) Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell 98:115-124.
Yang DS, et al. (2011) Reversal of autophagy dysfunction in the TgCRND8 mouse model of Alzheimer's disease ameliorates amyloid pathologies and memory deficits. Brain 134:258-277.
Yang J, Zhang C (2023) Targeting the autophagy-lysosomal pathway in Huntington disease: a pharmacological perspective. Front Aging Neurosci 15:1175598.
Yang M, Liu B, Chen B, Shen Y, Liu G (2025) Cerebral ischemia-reperfusion injury: mechanisms and promising therapies. Front Pharmacol 16:1613464.
Yi J, Ma C, Li Y, Weisleder N, Ríos E, Ma J, Zhou J (2011) Mitochondrial calcium uptake regulates rapid calcium transients in skeletal muscle during excitation-contraction (E-C) coupling. J Biol Chem 286:32436-32443.
Yi M, Weaver D, Hajnóczky G (2004) Control of mitochondrial motility and distribution by the calcium signal: a homeostatic circuit. J Cell Biol 167:661-672.
Young PA, Senkal CE, Suchanek AL, Grevengoed TJ, Lin DD, Zhao L, Crunk AE, Klett EL, Füllekrug J, Obeid LM, Coleman RA (2018) Long-chain acyl-CoA synthetase 1 interacts with key proteins that activate and direct fatty acids into niche hepatic pathways. J Biol Chem 293:16724-16740.
Yu CH, et al. (2020) TDP-43 triggers mitochondrial DNA release via mPTP to activate cGAS/STING in ALS. Cell 183:636-649.
Yuan Z, Lu L, Lian Y, Zhao Y, Tang T, Xu S, Yao Z, Yu Z (2022) AA147 ameliorates post-cardiac arrest cerebral ischemia/reperfusion injury through the co-regulation of the ATF6 and Nrf2 signaling pathways. Front Pharmacol 13:1028002.
Zaidi A, Adewale M, McLean L, Ramlow P (2018) The plasma membrane calcium pumps-The old and the new. Neurosci Lett 663:12-17.
Zhang H, Tian Y, Yu W, Tong D, Ji Y, Qu X, Deng T, Li X, Xu Y (2023a) TMEM175 downregulation participates in impairment of the autophagy related lysosomal dynamics following neonatal hypoxic-ischemic brain injury. J Cell Physiol 238:2512-2527.
Zhang H, Xie W, Feng Y, Wei J, Yang C, Luo P, Yang Y, Zhao P, Jiang X, Liang W, Dai S, Li X (2023b) Stromal interaction molecule 1-mediated store-operated calcium entry promotes autophagy through AKT/mammalian target of rapamycin pathway in hippocampal neurons after ischemic stroke. Neuroscience 514:67-78.
Zhang I, Hu H (2020) Store-operated calcium channels in physiological and pathological states of the nervous system. Front Cell Neurosci 14:600758.
Zhang L, Fang Y, Cheng X, Lian Y, Xu H (2022) Interaction between TRPML1 and p62 in regulating autophagosome-lysosome fusion and impeding neuroaxonal dystrophy in Alzheimer's disease. Oxid Med Cell Longev 2022:8096009.
Zhang X, Cheng X, Yu L, Yang J, Calvo R, Patnaik S, Hu X, Gao Q, Yang M, Lawas M, Delling M, Marugan J, Ferrer M, Xu H (2016) MCOLN1 is a ROS sensor in lysosomes that regulates autophagy. Nat Commun 7:12109.
Zheng Y, Na Y, Qilian M, Fan C, Ningning L, Xuechu Z (2023) Targeted to neuronal organelles for CNS drug development. Adv Drug Deliv Rev 200 115025.
Zhu C, Li H, Kong X, Wang Y, Sun T, Wang F (2022a) Possible mechanisms underlying the effects of glucagon-like peptide-1 receptor agonist on cocaine use disorder. Front Pharmacol 13:819470.
Zhu J, Chu SF, Peng Y, Liu DD, Chen C, Jian WX, Sun HS, Feng ZP, Zhang Z, Chen NH (2022b) Pyk2 inhibition attenuates hypoxic-ischemic brain injury in neonatal mice. Acta Pharmacol Sin 43:797-810.
Zhu Y, Yu J, Gong J, Shen J, Ye D, Cheng D, Xie Z, Zeng J, Xu K, Shen J, Zhou H, Weng Y, Pan J, Zhan R (2021) PTP1B inhibitor alleviates deleterious microglial activation and neuronal injury after ischemic stroke by modulating the ER stress-autophagy axis via PERK signaling in microglia. Aging (Albany NY) 13:3405-3427.
Zong P, Feng J, Yue Z, Li Y, Wu G, Sun B, He Y, Miller B, Yu AS, Su Z, Xie J, Mori Y, Hao B, Yue L (2022) Functional coupling of TRPM2 and extrasynaptic NMDARs exacerbates excitotoxicity in ischemic brain injury. Neuron 110:1944-1958.
Zong P, Feng J, Legere N, Li Y, Yue Z, Li CX, Mori Y, Miller B, Hao B, Yue L (2024) TRPM2 enhances ischemic excitotoxicity by associating with PKCγ. Cell Rep 43:113722.
Zou J, Hu B, Arpag S, Yan Q, Hamilton A, Zeng YS, Vanoye CG, Li J (2015) Reactivation of lysosomal Ca2+ efflux rescues abnormal lysosomal storage in FIG4-deficient cells. J Neurosci 35:6801-6812.

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