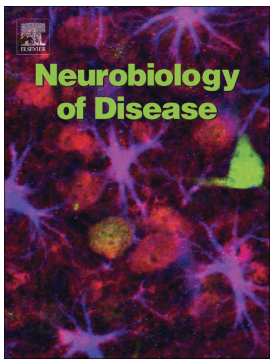

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Role of endolysosomes and inter-organellar signaling in brain disease

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Abstract: Endosomes and lysosomes (endolysosomes) are membrane bounded organelles that play a key role in cell survival and cell death. These acidic intracellular organelles are the principal sites for intracellular hydrolytic activity required for the maintenance of cellular homeostasis. Endolysosomes are involved in the degradation of plasma membrane components, extracellular macromolecules as well as intracellular macromolecules and cellular fragments. Understanding the physiological significance and pathological relevance of endolysosomes is now complicated by relatively recent findings of physical and functional interactions between endolysosomes with other intracellular organelles including endoplasmic reticulum, mitochondria, plasma membranes, and peroxisomes. Indeed, evidence clearly indicates that endolysosome dysfunction and inter-organellar signaling occurs in different neurodegenerative diseases including Alzheimer's disease (AD) and HIV-1 associated neurocognitive disease (HAND), Parkinson's disease (PD) as well as various forms of brain cancer such as glioblastoma multiforme (GBM). These findings open new areas of cell biology research focusing on understanding the physiological actions and pathophysiological consequences of inter-organellar communication. Here, we will review findings of others and us that endolysosome de-acidification and dysfunction coupled with impaired inter-organellar signaling is involved in the pathogenesis of AD, HAND, PD, and GBM. A more comprehensive appreciation of cell biology and inter-organellar signaling could lead to the development of new drugs to prevent or cure these diseases.

Introduction: Endosomes and lysosomes (hereafter referred to as endolysosomes) are acidic organelles that degrade plasma membrane components, extracellular macromolecules, intracellular macromolecules, and cellular fragments (Orr and Oddo, 2013; Pryor and Luzio, 2009). Endolysosomes help to maintain homeostasis of cells through their degradative roles. These organelles are considered as energy sparing organelles because they provide amino acids, fatty acids and simple sugars (Dugail, 2014), and these digestive organelles participate in immune responses through their proteolytic functions that provide degradation products presented by major histocompatibility complex (MHC) class II molecules (Munz, 2012). Beyond their degradative functions, endolysosomes are involved in membrane resealing (Perera and Zoncu, 2016) and apoptosis through mitochondrial destabilization (Repnik and Turk, 2010). Structural and functional changes to endolysosomes have been implicated in the pathogenesis of neurodegenerative diseases and cancer (Colacurcio and Nixon, 2016; Kroemer and Jäättelä, 2005; Olson and Joyce, 2015). The growing interest in the physical and functional interactions between organelles has led to increased efforts to understand better how inter-organellar signaling plays a role in disease progression especially neurodegenerative diseases and different types of cancer. Accordingly, we discuss here evidence suggesting that endolysosomes participate in early and upstream pathological signaling events that are triggered by various disease-relevant insults (Table 1).

Endolysosome calcium storage and signaling: Endolysosomes contain many biologically important substances including divalent cations. Calcium is known as a

universally important signaling cation that is contained in the lumen of endolysosomes at concentrations estimated to be about 500 µM; levels approaching those found in endoplasmic reticulum (ER) (Christensen et al., 2002; Patel and Cai, 2015). Others and we have shown that endolysosome stores of calcium are readily releasable (Christensen et al., 2002; Hui et al., 2015; Shen et al., 2012). The release of endolysosome calcium is mediated by various transporters including two-pore channels (TPCs) (Penny et al., 2015). And, calcium released following activation of TPC2 has been shown to trigger the release of calcium from ER-resident inositol trisphosphate receptors (IP_3Rs) and/or ryanodine receptors (RyRs) (Penny et al., 2015) (Fig. 1). Moreover, we have shown that calcium released from endolysosomes can enhance extracellular calcium influx through N-type calcium channels (NTCCs); a phenomenon we termed “acidic store-operated calcium entry (aSOCE)” (Hui et al., 2015) (Fig. 1). Thus, accumulating evidence suggests that endolysosome-based events are early and upstream of many downstream signaling pathways in cells and that calcium is involved.

Acidic nature of endolysosomes: An important hallmark of endolysosomes is their acidic luminal pH, which is maintained by different mechanisms such as electrogenic pumping of protons by vacuolar-ATPase (v-ATPase) in conjunction with vesicular chloride transporters that effectively shunt membrane potentials to allow a build-up of luminal protons (Ishida et al., 2013). v-ATPase activity is important not only for the maintenance of the acidic environment of endolysosomes, but also cytosolic and extracellular pH (Halcrow et al., 2019). v-ATPases are multi-subunit complexes composed of two major domains; a peripheral V1 domain that contains 8 subunits and

hydrolyzes ATP, and an integral membrane V0 domain that contains 5 subunits and transports H^+ (Marshansky et al., 2014; McGuire et al., 2016). The acidic pH of endolysosomes is critical for the activity of up to 60 different pH-sensitive hydrolytic enzymes including proteases, lipases, glycosidases, and nucleases thus enabling the endolysosomes to break down a wide range of endogenous and exogenous cargo (Xu and Ren, 2015). Endolysosome pH is very tightly controlled because de-acidification can inhibit the activity of hydrolases that function optimally at acidic pH and can promote the activity of other hydrolases that function optimally at pH values closer to neutral (Colacurcio and Nixon, 2016). Endolysosome de-acidification can increase the generation of undigested substrates, toxic products, and/or semi-digested intermediates (Colacurcio and Nixon, 2016). De-acidification of endolysosomes can also cause the release of various cations including calcium from the lumen into the cytoplasm (Penny et al., 2015). In addition to the critical role in regulating the activity levels of hydrolytic enzymes, low pH is important for fusion between lysosomes and autophagosomes to yield autophagolysosomes.

An ever-increasing number of compounds and conditions are now known to cause endolysosome de-acidification. De-acidification occurs by basic and weakly-basic drugs, compounds including ammonium chloride, the anti-malarial drug chloroquine, as well as by the selective v-ATPase inhibitor, bafilomycin A1; consequences of which include the release of calcium from endolysosomes (Chen et al., 2018; Hui et al., 2015; Johannessen et al., 2019) and the suppression of autophagosome-lysosome fusion (Kawai et al., 2007). Altered endolysosome pH has been implicated in a growing

number of therapeutic drugs' actions and human diseases including AD, PD, HAND, and different types of cancers including GBM (Avrahami et al., 2013; Cai et al., 2012; Chen et al., 2013; Dehay et al., 2012; Di Cristofori et al., 2015; Feng et al., 2013; Hui et al., 2012b; Wolfe et al., 2013).

Alzheimer's disease (AD): AD is the leading cause of dementia worldwide in people older than 65 years of age and currently there are no effective treatments capable of preventing or reversing the ravages of the disease. AD is characterized clinically by progressive memory loss and cognitive impairments. Pathologically, AD is characterized by the presence of extracellular senile plaques composed of amyloid β (Aβ) protein, intracellular neurofibrillary tangles composed of hyperphosphorylated tau (P-Tau) protein, synaptic and neuronal loss, and increased levels of reactive oxygen species (ROS) (Alzheimer's Association, 2016; De Strooper and Karran, 2016; Pohanka, 2018; Tarawneh and Holtzman, 2012). At the subcellular level organelles including endolysosomes, mitochondria, and ER as well as the process of autophagy appear to play important roles in AD pathogenesis (Avrahami et al., 2013; Ferreiro et al., 2012).

Endolysosomes in AD: Although the pathogenesis of AD remains elusive, growing evidence has linked endolysosome dysfunction to accelerated amyloidogenesis, tauopathy, and neurite dystrophy to the development of AD (Nixon, 2017). Amyloid-β precursor protein (AβPP) metabolism is catalyzed by the amyloidogenic enzymes β- and γ-secretase, and the non-amyloidogenic enzymes α- and γ-secretase (Zhang et al., 2011). β- and γ-secretases are mainly localized to endolysosomes and endolysosome

deacidification increases while endolysosome acidification decreases the activity of BACE1, the rate limiting enzyme that controls amyloidogenesis. Endolysosome deacidification with low-density lipoprotein (LDL) cholesterol enhanced β-secretase activity levels as well as secreted and intraneuronal levels of $A\beta_{1-40}$ and $A\beta_{1-42}$; effects that were blocked by mucolipin synthetic agonist MLSA-1 activation of TRPM1 channels and endolysosome acidification (Hui et al., 2012a; Hui et al., 2019a; Hui et al., 2019b; Khan et al., 2019). It is doubtful that this effect was unique to LDL cholesterol because, for example, HIV-1 Tat protein also deacidified endolysosomes, increased the activity of β-secretase, and increased neuronal levels of Aβ (Chen et al., 2013). Indeed, endolysosome deacidification increases γ-secretase activity and the production of $A\beta_{1-40}$ and $A\beta_{1-42}$ (McLendon et al., 2000). However, considering that AβPP cleavage occurs mainly on the cell surface (Parvathy et al., 1999) and not in endolysosomes, pH changes are not expected to affect non-amyloidogenic metabolism of AβPP.

Because the acidic pH of endolysosomes is critical for the activity of pH-sensitive β- and γ-secretases and as well as the degradation of Aβ and aggregated tau, even subtle alkalization (de-acidification) can increase levels of aggregated Aβ and Tau (Aufschnaiter et al., 2017; Chesser et al., 2013a; Di Domenico et al., 2016; Soliman et al., 2017). Furthermore, because neurons are extraordinarily polarized cells with extensive processes that require constant movement of endolysosomes for membrane trafficking and for the maintenance of synaptic plasticity, (Nixon, 2017; Nixon and Cataldo, 1995; Nixon and Cataldo, 2006), and because changes in endolysosome pH have been shown to affect markedly the movement of endolysosomes in cells, dysregulation of endolysosome trafficking due to de-acidification could lead to impaired

synaptic integrity (Chen et al., 2013; Eitan et al., 2016; Hui et al., 2012a; Hui et al., 2012b; Hui et al., 2019a; Jia et al., 2017; Johnson et al., 2016; Korolchuk et al., 2011; Michael et al., 2018; Shea et al., 2016).

Associated with AD are findings of endolysosome enlargement, redistribution of endolysosomes in neurons, and accumulation of endolysosome substrates in brain (Cataldo et al., 2008; Cataldo et al., 2004; Chen et al., 2010; Colacurcio et al., 2018; Li et al., 1993; Kim et al., 2016; Nakamura et al., 1991; Nixon, 2017; Whyte et al., 2017). Because neurons are long-lived post-mitotic cells and thus cannot get rid of waste materials via cell division, endolysosomes are especially important for the health and demise of neurons (Nixon and Cataldo, 2006). Endolysosome dysfunction also appears to play an early pathogenic role in AD; endolysosome de-acidification and dysfunction was found in cultured cell models of AD, brains of AD mouse models, and fibroblasts from AD patients (Avrahami et al., 2013; Hui et al., 2019a; McBrayer and Nixon, 2013; Wolfe et al., 2013).

Acidifying endolysosomes by, for example, inhibition of glycogen synthase kinase 3β (GSK-3β) increased Aβ clearance and improved behavior in 5xFAD mice (Avrahami et al., 2013). Inhibition of GSK-3β can restore the activity of the classical autophagy suppressor mammalian target of rapamycin (mTOR) in 5xFAD mouse brain, inhibit autophagy, and acidify endolysosomes (Avrahami et al., 2013). Presenilin1 (PSEN1) is an ER chaperone involved in the maturation and targeting of the V0a1 subunit of v-ATPase to lysosome membranes. N-glycosylation of V0a1 is essential for transferring

the subunit from the ER to lysosomes and the subsequent lysosome acidification; this effect is blocked by PSEN1 ablation and dysfunction (Lee et al., 2010). GSK-3β inhibition also increased N-glycosylation of V0a1, a modification required for lysosomal acidification in PSEN1/PSEN2 mutants (Avrahami et al., 2013). Given that P-Tau tends to aggregate and that aggregated P-Tau requires lysosome degradation via autophagy (Chesser et al., 2013b; Guo et al., 2016), endolysosome acidification as a result of GSK-3β inhibition may also enhance the ability of lysosome to degrade P-Tau aggregates.

As mentioned, endolysosome pH is maintained mainly through the activity of v-ATPase. v-ATPase activity is regulated by different mechanisms such as reversible assembly of the V1 and V0 domains (McGuire et al., 2017). In an animal study on the effects of modulating GSK-3β activity on endolysosome acidity and AD pathology, post transcriptional modifications of v-ATPase were found to play an important role in regulating endolysosome pH (Avrahami et al., 2013). Indeed, in 5xFAD mice N-glycosylation of the V0a1 subunit of v-ATPase was decreased and endolysosomes were de-acidified. In contrast, endolysosome acidification via inhibition of GSK-3β led to an increase in Aβ clearance and improvement in 5xFAD mouse behavior (Avrahami et al., 2013). Furthermore, GSK-3β inhibition decreased Aβ generation (Cai et al., 2012) and increased levels of cathepsin D (CatD); a proteolytic enzyme that controls Aβ and Tau degradation (Aufschnaiter et al., 2017; Avrahami et al., 2013; Di Domenico et al., 2016; Soliman et al., 2017).

Disrupted cholesterol homeostasis and elevated levels of plasma LDL cholesterol is a robust risk factor for developing AD pathogenesis (Fiorenza et al., 2013). Considering that the presence of apolipoprotein E4 (apoE4) allele is the strongest risk factor for developing sporadic AD and the fact that APOE protein is a major transporter of LDL cholesterol in brain, the relationship between APOE, LDL cholesterol level, and AD pathology is receiving fresh attention in AD research (Chen et al., 2014; Coon et al., 2007; Dhiman et al., 2019; Leduc et al., 2010). Although the exact mechanism by which APOE4 is involved in AD pathogenesis remains elusive, studies suggest APOE4 is clearly associated with elevated levels of LDL cholesterol (Cahua-Pablo et al., 2016). Also, elevated levels of LDL cholesterol independent of APOE genotypes are associated with developing AD pathology such as increased levels of Aβ deposition in brain and/or tau pathology, and memory impairment in animal models for AD (Chen et al., 2010; Thirumangalakudi et al., 2008). Moreover, we have shown that increased levels of circulating cholesterol which is a risk factor for developing sporadic AD is associated with endolysosome deacidification (Hui et al., 2012a; Hui et al., 2019a). LDL cholesterol caused accumulation of β-secretase-1 (BACE-1) in endolysosomes, increased BACE-1 activity levels, and increased amyloidogenesis; these effects were blocked by activating TRPML1 cation channels and acidifying endolysosomes (Hui et al., 2012a; Hui et al., 2019a). Therefore, treatments that promote v-ATPase activity and acidify endolysosomes might have protective effects against development of AD pathological hallmarks.

Besides impaired BACE-1 activity, disruption in endolysosome trafficking of BACE1 can also occur in AD. Under normal conditions AβPP processing by BACE1 occurs mainly in early endosomes (Rajendran et al., 2006), but trafficking of AβPP and/or BACE1 can be impaired because of changes in the levels of cargo receptors and/or retromer core components. Accordingly, BACE1 and AβPP may reside longer in early endosomes and the subsequent increase in the β-amyloidogenic processing of AβPP could lead to an increase in Aβ (Toh and Gleeson, 2016).

Changes in endolysosome morphology and impaired endolysosome function have also been reported in other animal models for AD. In olfactory bulbs of rabbits fed a cholesterol-enriched diet, a model of sporadic AD, there were decreases in specific activity levels of acid phosphatase and CatD as well as decreases in synaptic area. We also observed increased sizes of endolysosomes, and increased levels of Aβ, phosphorylated tau, and ApoB-containing cholesterol. Considering the role of endolysosomes in the degradation of tau protein, tau-pathology observed in neurons of olfactory bulb indicated impaired endolysosome function (Chen et al., 2010). We have also found morphological changes in endolysosomes and endolysosome dysfunction in skeletal muscles of cholesterol-fed rabbits. Deficits in skeletal muscles are involved in progressive functional problems in AD patients (Chen et al., 2016) and we observed enlarged endolysosomes containing accumulations of free cholesterol, Aβ, P-Tau and ubiquitin.

Impaired lysosomal protein expression and integrity has also been shown in post-mortem brain of patients with early-onset familial AD; there were increased levels of lysosomal-associated membrane protein 1 (LAMP1) and a diffuse spread of CatD (Piras et al., 2016). Dysregulation of the autophagy-lysosomal pathway was also observed; increased accumulations of the autophagic marker microtubule-associated protein 1A/1B-light chain 3 (LC3) were observed in LC3-positive vesicles in frontal cortex localized with P-Tau (Piras et al., 2016). Nevertheless, relatively little is known about mechanistic links between endolysosome dysfunction and AD pathogenesis and better understanding of such mechanisms may provide new insight into AD pathogenesis and potentially new therapeutic strategies.

Inter-organellar signaling in AD: The mechanisms involved in AD pathogenesis are complex and anti-amyloidogenic treatments have failed in clinical trials (Cavanaugh et al., 2014; Selkoe and Hardy, 2016). Of course, there are many possible reasons for clinical trial failures, but increasingly other morphological and biochemical changes in AD have been targeted that might lead to earlier interventions against AD even before the formation of plaques and neurofibrillary tangles (Area-Gomez and Schon, 2017). Accordingly, there has been a growing interest in studying other morphological and biochemical changes in AD such as altered phospholipid, calcium, and cholesterol metabolism.

Mitochondrial dysfunction continues to be implicated in the pathogenesis of AD. Changes to mitochondrial function have been reported in sporadic and early onset AD

including decreased numbers, decreased axonal transport of mitochondria, impairments in mitochondrial fusion and fission, and morphological changes such as decreased length and increased overall sizes (Albensi, 2019; Lazarov et al., 2007; Lunnon et al., 2012; Wang et al., 2009; Wang et al., 2008; Zhu et al., 2013). Dysfunctions in mitochondrial respiratory complexes I and IV have been reported in AD (Eckert et al., 2011) and such abnormal mitochondrial electron activities could lead to disruption in mitochondrial membrane potentials, decreases in the production of ATP, and increases in the levels of ROS (Eckert et al., 2011). Opening of mPTPs have been implicated in AD in part because they are affected by ROS generation, changes in membrane potential, increases in levels of intracellular calcium, and the release of pro-apoptotic factors; all of which can lead to cell death (Albensi, 2019; Du and Yan, 2010). Indeed, it has been suggested that mPTP inhibitors may serve as potential therapeutic strategies in AD treatment (Albensi, 2019; Du and Yan, 2010).

Enhanced functions of mitochondria-associated membranes (MAM) have been observed in cells from AD patients as well as in cellular and animal models of AD (Area-Gomez and Schon, 2017). MAMs are specialized lipid raft-like subdomains of ER that physically link mitochondria to ER and increased MAM connections between ER and mitochondria may be involved in AD pathogenesis (Area-Gomez and Schon, 2017). Because MAMs are involved in calcium transmission between ER and mitochondria (Hayashi et al., 2009), up-regulation of MAM function could lead to calcium dysregulation in AD (Schon and Area-Gomez, 2013). Endolysosome calcium dysregulation can lead to altered calcium levels in the cytoplasm, calcium release from

ER, calcium influx through cell surface calcium channels, and Ca^{2+} overload in mitochondria (Hui et al., 2015; Penny et al., 2015; Supnet and Bezprozvanny, 2010a).

Intracellular levels of calcium help regulate many different signaling pathways and is subject to complex spatial and temporal control. Altered calcium signaling and the involvement of intracellular calcium stores have long been described for AD pathogenesis (Magi et al., 2016; Supnet and Bezprozvanny, 2010a). Calcium dysregulation in neuronal cells and changes in protein levels of proteins involved in Ca^{2+} signaling have been shown in animal models of familial AD and in brain of AD patients (Bekris et al., 2010; Bezprozvanny and Mattson, 2008; Stutzmann et al., 2006; Supnet and Bezprozvanny, 2010b; Veinbergs et al., 2002). The two major readily releasable stores of intracellular calcium are ER and endolysosomes; both contain concentrations of calcium approaching about 500 µM (Christensen et al., 2002; Patel and Cai, 2015). Impaired calcium homeostasis occurs in aging and even subtle changes in calcium homeostasis can lead to age-related neuronal dysfunction (Supnet and Bezprozvanny, 2010b; Toescu and Verkhratsky, 2007). Endolysosome de-acidification results in the release of calcium from endolysosomes and the resulting increased levels of calcium in the cytoplasm can trigger downstream pathways as well as the release of calcium from ER (Penny et al., 2015). In a study on calcium signaling in familial AD, enhanced IP_3 mediated Ca^{2+} release from ER has been reported in skin fibroblasts from AD patients (Ito et al., 1994). In addition, fibroblasts from asymptomatic patients at risk for AD showed enhanced release of ER calcium following activation of IP_3 receptors (Etcheberrigaray et al., 1998). Such high levels of cytosolic calcium can activate the

Ca^{2+}-dependent protein phosphatase calcineurin (CaN) and such Ca^{2+}-dependent proteases as calpains and can lead to modification of neuronal cytoskeleton, inhibition of long-term potentiation, neuritic atrophy, and synaptic loss (Fig. 1). Indeed, Ca^{2+} signaling remodeling may be involved in erasing memory by enhancing the process of long-term depression (Berridge, 2010; Supnet and Bezprozvanny, 2010a; Trinchese et al., 2008; Vosler et al., 2008).

Mitochondria also are involved in the control of intracellular calcium levels and do so by accumulating Ca^{2+} from cytoplasm or ER through the outer mitochondrial membrane (OMM) likely via the voltage-dependent anion channel (VDAC) (Fig. 1). Excessive Ca^{2+} taken up by mitochondria (calcium overload) can result in calcium being released through opening of mitochondrial permeability-transition pores (MPTP); a process linked to initiation of cell death signaling cascades (Giacomello et al., 2007; Supnet and Bezprozvanny, 2010a; Supnet and Bezprozvanny, 2010b). Because disturbances in cytosolic and mitochondrial calcium can affect multiple calcium signaling pathways, mitochondrial pools of calcium have been regarded as good targets against which therapeutic strategies might be developed for AD treatment (Supnet and Bezprozvanny, 2010a; Supnet and Bezprozvanny, 2010b). Dysregulation of neuronal Ca^{2+} in AD impairs Ca^{2+} signaling in mitochondria and leads to mitochondrial dysfunction and impaired neuronal function (Supnet and Bezprozvanny, 2010b). Abnormal calcium signaling has also been reported through the binding of Aβ to AβPP protein. Under normal conditions AβPP protein binds to G-proteins and stays inactive. However, increased levels of Aβ in AD brain can induce the release of G protein from AβPP.

Activated G-protein in turn induces calcium dysregulation possibly through regulating the receptors on ER and plasma membrane leading to influx of calcium from ER stores or from the extracellular space resulting in cell death (Shaked et al., 2009). Decreasing calcium uptake by mitochondria using anti-inflammatory drugs (NSAIDs) was suggested to be protective against AD by inhibiting Ca^{2+} overload in mitochondria and subsequent cytochrome c release, and apoptosis and cell death induced by Aβ (Sanz-Blasco et al., 2008).

Oxidative stress is also involved in AD pathogenesis through altering AβPP processing by increasing the levels of BACE-1 through activation of c-Jun amino-terminal kinase and p38 mitogen-activated protein kinase (MAPK) or increasing P-Tau by activation of GSK-3β (Lin and Beal, 2006; Lovell et al., 2004; Tamagno et al., 2005).

Presenilin mutations can impair intracellular function and communication. Presenilins are transmembrane proteins that play a key role in regulating ER-calcium dynamics through different mechanisms including activation of sarco/endoplasmic reticulum Ca^{2+}-ATPase SERCA pump, and via IP_3Rs and RyRs (Corona et al., 2011). Presenilin2 (PSEN2) is involved in transferring calcium between ER and mitochondria, a process that is enhanced in cells expressing PSEN2 mutants (Zampese et al., 2011). Brains of zebrafish harboring a single early onset AD (EOAD)-like mutation in their PSEN1-orthologous gene displayed profound effects on cellular components including plasma membranes, mitochondria, and membrane transporter activity particularly v-ATPases (Newman et al., 2019).

PSEN2 plays a critical role in modulating intracellular Ca^{2+} homeostasis independently of its γ-secretase activity. PSEN2 mutants show disruptions in autophagy resulting from a reduction in recruitment of the GTPase Rab7 to autophagosomes and impairment of autophagosome-lysosome fusion. Moreover, the effect of FAD-PSEN2 mutants on autophagy is related to its ability to partially deplete ER Ca^{2+} and decrease levels of cytosolic Ca^{2+} following IP_3-linked cell stimulations (Fedeli et al., 2019; Zatti et al., 2004). It has been suggested that PSEN mutations might enhance IP_3R- and RyR-mediated Ca^{2+} efflux as a compensatory response for increased levels of ER Ca^{2+} (Wang and Zheng, 2019). Ca^{2+} channels on plasma membranes also could be affected by PSEN mutations; PSEN 1 mutants cleave stromal interaction molecule 1 (STIM1) and cause dysfunctions in store-operated calcium entry (SOCE) (Tong et al., 2016). Mutations in PSEN can also impair mitochondrial/ER interactions by targeting MAMs and inducing the transfer of Ca^{2+} between ER and mitochondria (Wang and Zheng, 2019).

Based on the findings of us and others, endolysosome dysfunction and altered inter-organellar signaling might be considered to be early and upstream trigger in the development of pathological changes associated with AD.

HIV-1 associated neurocognitive disorder (HAND): Nearly 40 million people were living worldwide with HIV-1 (human immunodeficiency virus) in 2017 (Global HIV & AIDS statistics, 2018). People living with HIV-1 (PLWH) who have been taking

antiretroviral therapeutic (ART) drugs are now living almost full life-spans and fewer PLWH are dying from acquired immunodeficiency disease (AIDS) (Saylor et al., 2016). However, 40–50% of PLWH suffer from HIV-associated neurocognitive disorders (HAND) that varies in intensity from so-called asymptomatic HAND to HIV-1 associated dementia (Ghosh et al., 2017). Although the pathogenesis of HAND is not entirely clear, others and we have demonstrated the involvement of such virotoxins as HIV-1 transactivator of transcription protein (Tat), envelope glycoprotein gp120, negative factor (Nef), and viral protein r (Vpr) (Buscemi et al., 2007; Chen et al., 2013; Datta et al., 2019; Haughey and Mattson, 2002; Hui et al., 2012b; King et al., 2006; Kovalevich and Langford, 2012). Tat is a well-studied HIV-1 viral protein that has been found to be present in the CSF of even virally-suppressed patients and that induces neuronal excitation and calcium release from intracellular stores leading to disruption of calcium homeostasis in neuronal cells and neurotoxicity (Haughey et al., 1999; Haughey and Mattson, 2002; Hui et al., 2012b; Johnson et al., 2013).

Endolysosomes in HAND: Changes in pH, membrane integrity, and morphology of endolysosomes have been considered by others and us as pathological features in HAND (Achim et al., 2009; Hui et al., 2012b). As is typical of agents that de-acidify endolysosomes, treatment of primary rat hippocampal neurons with HIV-1 Tat resulted in endolysosomes being larger and prone to increased clumping (Chen et al., 2013; Hui et al., 2012b). Distribution of endolysosomes within cells is affected by HIV-1 Tat. While control cells displayed a perinuclear and evenly distributed puncta pattern for endolysosomes, cells treated with HIV-1 Tat showed a diffuse pattern in the cytoplasm

(Hui et al., 2012b). Moreover, HIV-1 Tat-induced impairment of endolysosome membrane integrity and endolysosome de-acidification was also reported by others and us (Chen et al., 2013; El-Hage et al., 2015; Hui et al., 2012b).

The underlying mechanisms involved in endolysosome de-acidification by HIV-1 Tat are not well understood, but may include the arginine-rich sequence of HIV-1 Tat protein and the effects of Tat on endolysosome membrane integrity. HIV-1 Tat has an arginine-rich domain between amino acid residues 49 and 57, and other arginine-rich peptides such as penetratin, Antennapedia protein, and oligoarginines have all been found to deacidify endolysosomes (L. Hui, X. Chen and J. D. Geiger, unpublished data). Disrupting the membrane integrity of endolysosomes is another mechanism whereby HIV-1 Tat could induce endolysosome deacidification (Hui et al., 2012b). Moreover, enlarged and clustered lysosomes and autophagosomes have been observed in brain of HIV-infected patients who were taking ART (Achim et al., 2009). Interestingly, these lysosomal-autophagic structures exhibited a significant accumulation of Aβ in neurons from the frontal cortex suggesting disturbed Aβ clearance in these cells which might result in cognitive impairment in older PLWH (Achim et al., 2009). Prolonged ART may contribute to elevated levels of Aβ deposition; implicated mechanisms include disrupted axonal transport of AβPP, inhibition of insulin degradation enzyme (IDE), or suppression of the major Aβ degrading enzyme neprilysin (Daily et al., 2006; Green et al., 2005). In brain of HIV-1 infected patients there was an accumulation of lysosomes in macrophages, astrocytes, microglial and glial cells (Gelman et al., 2005; Gelman et al., 1997). In patients with HIV-1 associated dementia, lysosome expansion was noted in

subcortical white matter (Gelman et al., 2005; Gelman et al., 1997). Thus, endolysosomes are impaired in HAND and more studies are needed to clarify the mechanisms involved in endolysosome dysfunction in the pathogenesis of HAND.

Inter-organellar signaling in HAND: A limited number of studies have been published regarding the role of inter-organellar signaling in HAND. The HIV protein Vpr is transported from ER to mitochondria via MAMs where it leads to an increase in the permeability of mitochondrial outer membranes, mitochondrial deformation, increase in bulging in MAMs, and a loss in mitochondrial membrane potential (Huang et al., 2012). The possible role of ER stress and mitochondrial dysfunction has been also studied in primary human astrocytes exposed to HAND-relevant stimuli (HIV-1 virions, inflammatory stimuli, and ARTs); the observed increases in intracellular calcium signaling in cells treated with IL-1β and the nucleoside reverse transcriptase inhibitor abacavir involved calcium release from ER. The subsequent mitochondrial permeability transition pore (mPTP) opening observed in these cells demonstrated that ER stress was upstream of mitochondrial depolarization which could lead to apoptosis (Nooka and Ghorpade, 2017). Calcium regulation in HAND (Haughey and Mattson, 2002) might now be reevaluated from the context of inter-organellar signaling especially because of findings that significant reductions in lysosomal calcium stores as a result of accumulation of sphingosine leads to impaired endocytic fusion and trafficking (Lloyd-Evans et al., 2008) and can lead to dysregulation of calcium homeostasis in ER by affecting the function of calcium channels (Platt et al., 2012).

Endolysosomes in Parkinson's disease (PD): Parkinson's disease is the second-most common neurodegenerative disorder pathologically characterized by death of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies (Dehay et al., 2012; Poewe et al., 2017). Impaired lysosomal acidification and function including decreased degradation of lysosomal substrates and reductions in proteolytic enzyme activity of CatD has been shown in fibroblasts derived from patients with PD harboring ATP13A2 mutations and in stable ATP13A2-knockdown dopaminergic cell lines. ATP13A2 is a lysosomal type 5 P-type ATPase linked to autosomal recessive familial parkinsonism; there are reduced levels in dopaminergic nigral neurons derived from PD patients with a high-level of accumulation in Lewy bodies. Restoring the protein level of ATP13A2 in ATP13A2-mutant/depleted cells rescued lysosomal function and resulted in decreased cell death (Dehay et al., 2012). Endolysosome dysfunction in PD has also been linked to the gene encoding leucine-rich repeat kinase 2 (LRRK2) (Vidyadhara et al., 2019). LRRK2 is involved in different intracellular vesicular trafficking pathways such as endolysosomal degradative pathways (Gomez-Suaga et al., 2014). For example, degradation of epidermal growth factor receptor (EGFR) is regulated by LRRK2 and is impaired in cells expressing LRRK2 pathogenic variants. LRRK2-mediated deficit in EGF degradation and endolysosomal membrane trafficking were rescued through expression of active Rab8A membrane protein, a substrate for LRRK2 (Rivero-Rios et al., 2019). Lysosome dysfunction in PD has also been linked to mutations in GBA1 gene (Bae et al., 2015); GBA1 encodes β-glucocerebrosidase 1 (GCase 1) and is a significant genetic risk factor for PD (O'Regan et al., 2017). Indeed deficiency of GCase 1, a lysosomal hydrolase, is

sufficient to cause accumulation of α-synuclein aggregates and lysosomal dysfunction including accumulation of lysosomal substrates and accumulation of enlarged vacuolar structures in human neuroblastoma cell lines (Bae et al., 2015). Moreover, lysosomal accumulation of cholesterol has been reported in fibroblasts from PD patients harboring N370S-GBA1 mutation (Garcia-Sanz et al., 2017).

Inter-organellar signaling in PD: Mutations in PTEN-induced putative kinase (PINK)1, Parkin and DJ-1 are associated with PD pathogenesis (Bonifati et al., 2004; Cookson et al., 2008; Pilsl and Winklhofer, 2012; Scarffe et al., 2014). DJ-1 is a multifunctional protein that plays a key role in protecting cells against oxidative stress (van der Merwe et al., 2015) and inhibiting the formation of α-synuclein aggregates; mutant forms of DJ-1 have been linked to autosomal recessive early onset PD (Bonifati et al., 2003a; Bonifati et al., 2003b; Shendelman et al., 2004). Mitochondrial kinase PINK1 is involved in recruiting Parkin from cytosol to mitochondria, inducing Parkin-mediated mitophagy and increasing the ubiquitination activity of Parkin (Lazarou et al., 2013). When mitochondria become depolarized, PINK1 accumulates at the OMM where it causes the ubiquitination of mitochondrial substrates and subsequent mitophagy initiation (Liu et al., 2019; van der Merwe et al., 2015). The interactions of Parkin with DJ-1 at the OMM helps control oxidative stress (van der Merwe et al., 2015).

ER–mitochondria associations are altered in PD. Further, PD-related mutations in genes encoding proteins localized in mitochondria and MAMs may be involved in dysregulation of ER-mitochondria signaling (Gómez-Suaga et al., 2018). PINK1 and

Parkin both localize to MAMs upon mitochondrial depolarization (Gelmetti et al., 2017). Location of PINK1 to MAMs may be important for recruitment of autophagy machinery, while excitotoxicity in neurons triggers the translocation of Parkin into mitochondrial/ER junctions (Gómez-Suaga et al., 2018; Van Laar et al., 2015). Moreover, mutations in DJ-1 gene have been linked to autosomal recessive early-onset parkinsonism (Klein and Westenberger, 2012). DJ-1 protein is localized to MAMs and DJ-1 overexpression increases mitochondrial Ca^{2+} uptake and ER–mitochondria associations (Ottolini et al., 2013). On the other hand, decreased DJ-1 levels reduces mitochondrial Ca^{2+} uptake and induces mitochondria fragmentation (Ottolini et al., 2013).

Mutations in the gene encoding Parkin protein are involved in the pathogenesis of autosomal recessive early-onset PD (Hunn et al., 2015). Parkin, an E3 ubiquitin ligase, regulates endolysosomes by modulating tubular and multivesicular regions as well as exosome secretion (Song et al., 2016). Parkin also stabilizes and activates Rab7 thus suggesting that Rab7 deregulation may be involved in the increased exosome secretion observed in Parkin-deficient cells (Song et al., 2016).

Synucleinopathy is caused by abnormal accumulations of aggregated alpha-synuclein protein (McCann et al., 2014). Synucleinopathy can result from synuclein alpha (SNCA) gene triplication (Singleton et al., 2003) as well as from lysosome dysfunction as observed in the lysosomal storage disease known as Gaucher disease. Thus, similar mechanisms might be involved in PD pathogenesis (Mazzulli et al., 2016; Nixon, 2013;

Wong et al., 2004). Indeed, α-synuclein accumulation has been shown to affect lysosome hydrolase trafficking leading to endolysosome dysfunction and impair the localization of the small GTPase Rab1a, a key regulator of vesicular protein transport from ER to Golgi compartments (Mazzulli et al., 2016).

Impaired endolysosome function by α-synuclein has been implicated in the pathogenesis of PD. Although wild-type α-synuclein can be degraded efficiently once transferred to endolysosomes through chaperone-mediated autophagy (CMA), mutant forms of α-synuclein block lysosomal uptake and impair protein degradation by CMA (Cuervo et al., 2004). Further, variants of lysosomal genes observed in PD may increase the generation of oligomeric and fibrillar forms of α-synuclein (Klein and Mazzulli, 2018). Gene mutations involved in PD have been implicated in mitochondrial dysfunction and ROS production observed in PD which could further lead to lysosomal dysfunction and the formation of α-synuclein aggregates (Klein and Mazzulli, 2018). α-Synuclein aggregates can also block the trafficking of glucosylceramidase (GlcCerase), a lysosomal enzyme that hydrolyzes glucosylceramide into free ceramide and glucose (Mazzulli et al., 2011; Mazzulli et al., 2016). Moreover, in brain of PD patients a deficiency of GlcCerase has been reported (Murphy et al., 2014). Therefore, accumulation of α-synuclein and the subsequent impaired in lysosomal trafficking could play a role in PD pathogenesis (Klein and Mazzulli, 2018).

Leucine rich-repeat kinase 2 (LRRK2) is a kinase involved in cellular processes such as vesicular trafficking, mitochondrial dynamics, autophagy, oxidative stress, and neuronal

toxicity (Gomez-Suaga et al., 2012a; Heo et al., 2010; Ho et al., 2018; Nguyen et al., 2011; Shin et al., 2008; Wang et al., 2012). LRRK2 has also been linked to mitochondrial dysfunction in PD; decreases in mitochondrial membrane potential and ATP levels were observed in skin biopsies from PD patients possessing LRRK2 ^{G2019S} mutations (Liu et al., 2008; Mortiboys et al., 2010). LRRK2 ^{G2019S} mutations cause mitochondrial elongation and increased fusion between mitochondria (Mortiboys et al., 2010). Further evidence of the deleterious effects of mutant LRRK2 comes from findings that LRRK2 G2019S-induced mtDNA damage is LRRK2 kinase activity dependent, that mtDNA damage was blocked with a LRRK2 kinase inhibitor, and that this mtDNA damage was not observed in neurons expressing LRRK2 wild type or LRRK2 ^{D1994A} mutant (kinase dead). Interestingly, patient-derived lymphoblastoid cell lines harboring the G2019S mutation showed increased mtDNA damage that was blocked by a LRRK2 kinase inhibitor (Howlett et al., 2017).

Similar evidence comes from in vivo studies. Significant mitochondrial abnormalities consistent with mitochondrial fission arrest were found in the striatum of knock-in mice harboring the G2019S LRRK2 mutation (Yue et al., 2015). Further, interactions between mutant LRRK2 ^{G2019S} and fission dynamin-related protein 1 (Drp1) protein promoted mitochondrial fragmentation while inhibiting Drp1 or expressing the mutant form of Drp1, corrected excessive autophagy, and reduced mitochondrial fragmentation, lysosomal hyperactivity and neurite shortening (Su and Qi, 2013; Wang et al., 2012). Underlying mechanisms by which mutant LRRK2 are involved include calcium dysregulation, increased formation of autophagosomes through the activation of the calcium-

dependent protein kinase kinase-b (CaMKK-b)/adenosine monophosphate-activated protein kinase (AMPK), as well as decreased numbers of acidic lysosomes and activation of nicotinic acid adenine dinucleotide phosphate (NAADP)-sensitive two-pore channels (TPCs) located on acidic stores (Gomez-Suaga et al., 2012b).

Although the mechanisms involved in impaired inter-organellar crosstalk observed in PD are not clear, evidence suggests that damaged ER–mitochondria signaling may represent a new insight into PD pathogenesis and new drugs may target these pathways to prevent or cure PD.

Endolysosomes in cancer: Metastatic cancer cells show higher expression levels of lysosomal proteins (Saitoh et al., 1992), which could suggest a higher level of lysosomal activity. Glioblastoma multiforme (GBM) is the most common, life-threatening malignant brain tumor in adults; 16% of all primary brain tumors (Michael et al., 2018; Shea et al., 2016). GBM is typically characterized by high tumor heterogenicity, rapid development of primary tumors, high levels of angiogenesis, presence of hyperplastic blood vessels, and areas of necrotic tissue (Halcrow et al., 2019; Irtenkauf et al., 2017; Lee et al., 2018; Veeravagu et al., 2008). Acidic extracellular pH near GBM tumors is involved in tumorigenesis through increases in apoptosis resistance, autophagy and angiogenesis, and promotion of tumor invasion (Halcrow et al., 2019). v-ATPase upregulation has been identified to be involved in the pathogenesis of GBM while v-ATPase inhibition was protective against the disease. In GBM there is a significant upregulation of the ATP6V1G1 subunit of v-ATPase and knockdown of ATP6V1G1 subunits as well as v-

ATPase inhibition with bafilomycin A1 resulted in increased levels of tumor cell death. Bafilomycin A1 reversed lysosome acidification in cancer stem cell enriched in neurospheres isolated from GBM patients (Di Cristofori et al., 2015). Thus, lysosome de-acidification and the use of v-ATPase inhibitors might help halt GBM progression. Considering that lysosomal acidification is observed in cancer and that lysosomal de-acidification causes apoptosis (Di Cristofori et al., 2015; Nilsson et al., 2004), lysosomal de-acidification could be a potential therapeutic strategy against cancer.

Inter-organellar signaling in cancer: Dysregulation of Inter-organellar signaling may be a potential factor involved in the pathogenesis of GBM (Halcrow et al., 2019). Moreover, it has been reported that inducing apoptosis using sphingosine leads to the release of lysosomal proteolytic enzymes in cytosol and activation of apoptotic cascades suggesting proteases such as CatD act upstream of changes in mitochondrial membrane potential and the caspase cascade (Kågedal et al., 2001). Therefore, proteolytic enzymes could be involved in apoptosis either directly through the activation of pro-caspases or indirectly by the effect of proteases on mitochondrial membranes and release of pro-apoptotic factors such as cytochrome c (Guicciardi et al., 2000; Ishisaka et al., 1999; Kågedal et al., 2001; Roberg et al., 1999). More studies are required to clarify how impaired inter-organellar cross talk could be involved in the pathogenesis of cancer and such findings could lead to the development of new drugs against cancer.

Drug development involving endolysosomes: Drug delivery approaches now take advantage of the process of endocytosis and the targeting of receptors and ligands. Indeed, nanoscale drug carriers targeting endolysosomes show promising potential for the treatment of cancer, Alzheimer's disease, Parkinson's disease, and lysosomal storage diseases (Bareford and Swaan, 2007; Kilpatrick et al., 2015; Rappaport et al., 2016). Because of the upregulation of cell-surface receptors in some diseases, there is greater specificity of action to endolysosomes (Bareford and Swaan, 2007). For example, pharmacological activation of transcription factor EB (TFEB), a master regulator of the autophagy lysosomal pathway, using the endocytosed drug 2-hydroxypropyl-β-cyclodextrin (HPβCD) promoted autophagic clearance of α-synuclein (Kilpatrick et al., 2015). However, the use of at least some nanoparticles may be problematic because some have been found to cause endolysosome deacidification and increased amyloidogenesis (Ye et al., 2019).

Future perspective: Extracellular vesicles (EVs) are cell-derived membrane-bound vesicles released from cells into extracellular spaces (Shi et al., 2019). These vesicles, comprising exosomes originating from the endosomal system, and microvesicles formed by budding from plasma membranes, contain nucleic acid and proteins (Shi et al., 2019; van Niel et al., 2018). It has been suggested recently that EVs are capable of transiting from the CNS to the peripheral circulation (Shi et al., 2019). Although more studies are required to clarify the exact mechanisms, EVs originating from multivesicular bodies can cross the blood-brain barrier and enter other cells by endocytosis (Matsumoto et al., 2017; Record et al., 2011; Shi et al., 2014; Shi et al., 2019).

Therefore, EVs may afford diagnostic opportunities because they carry accessible biomarkers and endolysosome signaling pathways regulate EVs secretion. Of relevance, neurally-derived blood exosomes can predict the development of AD up to 10 years before the onset of clinical signs; the levels of P-S396-tau, P-T181-tau and Aβ1-42 were higher in AD patients compared to people at preclinical stages (Fiandaca et al., 2015).

Summary: Endolysosome dysfunction continues to be observed in AD, HAND, PD, cancer, and lysosome storage diseases. This dysfunction appears to be upstream of mechanistic events including impaired calcium homeostasis in other organelles. Considering the massive health care cost for neurodegenerative diseases and cancer, studies focusing on mechanisms involved in the pathogenesis of these diseases could have a substantial impact economically, socially, and clinically. While a complete understanding of the pathogenesis of AD, HAND, PD and different forms of cancer such as GBM remains elusive, current studies provide strong evidence supporting the role of endolysosomes dysfunction and impaired inter-organellar signaling in the development of these diseasess. Future studies in these areas may lead to the development of new therapeutic strategies targeting endolysosomes.

Figure 1. Insult-induced endolysosome deacidification by, for example, HIV-1 Tat and low density lipoprotein (LDL) cholesterol leads to the release of Ca^{2+} from endolysosomes. Ca^{2+} released from endolysosomes can increase influx of calcium from N-type calcium channels (NTCC) channels. Ca^{2+} overload in cytoplasm can activate calpains and calcineurin (CaN) enzymes leading to inhibition of long-term potentiation, induction of long-term depression, neuritic atrophy, modification of neuronal cytoskeleton, and disturbed levels of synaptic plasticity. Cytosolic Ca^{2+} can trigger Ca^{2+} release form endoplasmic reticulum (ER) via inositol 1,4,5-trisphosphate receptors (IP_3R), ryanodine receptors (RyR), sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and presenilin receptors (PSEN). Excessive calcium taken up by mitochondria through various channels including voltage-dependent anion channels (VDAC) followed by calcium overload can lead to mitochondrial dysfunction. Ca^{2+} movement can also occur through mitochondria-associated membrane (MAM) attachments between ER and mitochondria. Therefore, endolysosome de-acidification and dysfunction may be upstream of signaling dysregulation observed in various disease states.

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Disease relevance	Endolysosome morphological changes	Endolysosome functional changes	Impaired Inter-organellar signaling	Reference
AD	+	+	ND	Cataldo et al., 2004; Cataldo et al., 2008; Chen et al., 2010; Hui et al., 2012a; Kim et al., 2016; Hui et al., 2019a
	ND	+	ND	Lee et al., 2010; Avrahami et al., 2013; Wolfe et al., 2013; Piras et al., 2016
	ND	ND	+	Area-Gomez and Schon, 2017
	+	ND	ND	Nakamura et al.,1991; Ii et al., 1993
HAND	ND	+	ND	Achim et al., 2009
	+	+	ND	Hui et al., 2012b
	+	+	ND	Chen et al., 2013; El-Hage et al., 2015
	ND	ND	+	Huang et al., 2012; Nooka and Ghorpade, 2017
	ND	+	ND	Gelman et al., 2005; Soliman et al., 2017
PD	ND	+	ND	Cuervo et al., 2004
	+	+	ND	Dehay et al., 2012

	+	+	ND	Bae et al., 2015
	ND	+	ND	Rivero-Rios et al., 2019
	+	+	+	Garcia-Sanz et al., 2017
Brain cancer	ND	+	ND	Di Cristofori et al., 2015
	+	+	+	Halcrow et al., 2019

Table 1. Endolysosomal morpholigical and functional changes and impaired inter-organellar communications in Alzheimer's disease (AD), HIV associated neurodegenerative disease (HAND), Parkinson's disease (PD), and brain cancer. ND: not discussed.

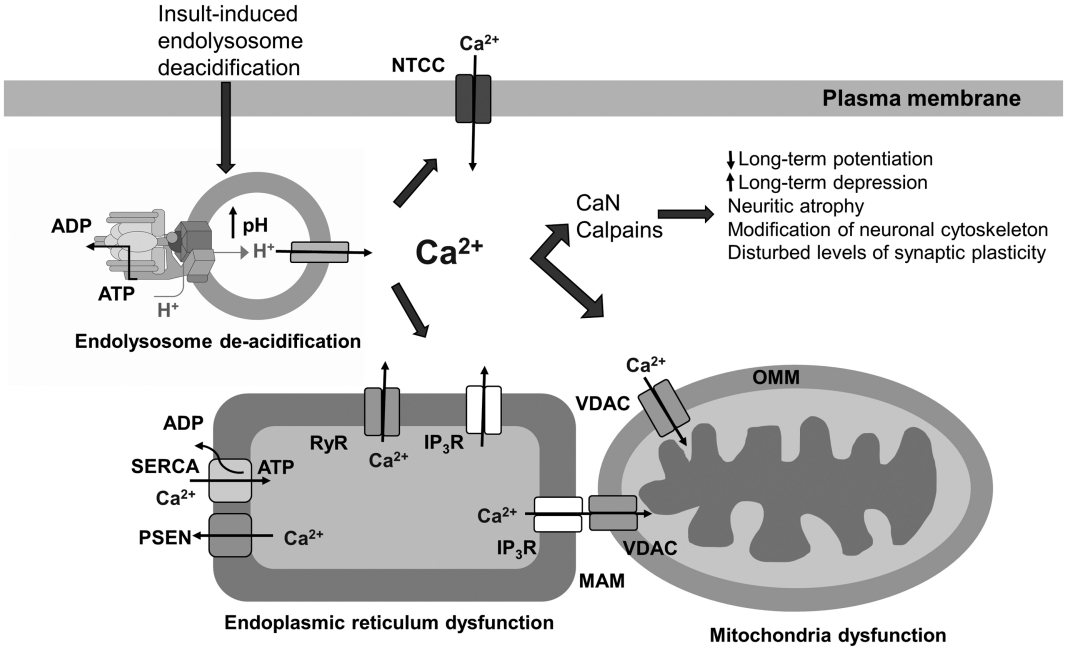
Insult-induced
endolysosome
deacidification
NTCC
Ca2+
Plasma membrane
ADP
pH
H+
ATP
H+
Endolysosome de-acidification
Ca2+
CaN
Calpains
↓Long-term potentiation
↑Long-term depression
Neuritic atrophy
Modification of neuronal cytoskeleton
Disturbed levels of synaptic plasticity
ADP
SERCA
ATP
Ca2+
PSEN
Ca2+
RyR
Ca2+
IP3R
Endoplasmic reticulum dysfunction
Ca2+
VDAC
OMM
Ca2+
IP3R
VDAC
MAM
Mitochondria dysfunction

Figure 1