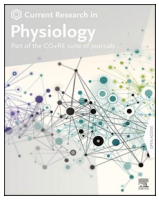
Current Research in Physiology 8 (2025) 100166

Contents lists available at ScienceDirect

Current Research in Physiology

journal homepage: www.sciencedirect.com/journal/current-research-in-physiology



The senescent synapse: A look at autophagy, calcium handling, and mitochondrial bioenergetics at the synapse in ageing and Parkinson's disease

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A B S T R A C T

The synapse is a vitally important physiological structure fundamental to electrochemical communication between neurones, and is required for basic and important functions we perform daily. Underpinning the normal physiological function of the synapse are crucial processes such as autophagy, calcium homeostasis, and mitochondrial bioenergetics, all of which are modified during ageing. It is necessary to understand how ageing affects these processes at the synapse, from a fundamental need to understand natural ageing, and in order to identify how these processes may become aberrant and indeed, pathological, in the context of ageing-related disorders, such as Parkinson's. This review addresses the importance of the aforementioned processes, autophagy, calcium homeostasis, and mitochondrial bioenergetics at the synapse in normal physiology, and discusses how they are altered during ageing, and in Parkinson's, an example of accelerated ageing.

1. Introduction: the synapse

1.1. Synapses as a conduit for physiological function

In contrast to normal ageing, neurodegenerative diseases represent a group of disorders characterised by progressive loss of neurones and synapses, leading to severe cognitive impairments and functional decline. There is evidence to suggest that neurodegenerative diseases are, in fact, an issue of accelerated ageing (Hou et al., 2019; Azam et al., 2021; Kesidou et al., 2023) and synaptic dysfunction has been identified as a key pathological process within them (Henstridge et al., 2016).

Using neurodegenerative disorders as exemplars of extreme ageing allows us to better understand both the role of synapses in normal brain function and how they are affected by ageing. In doing so, it also provides crucial insight into the pathological mechanisms underlying neurodegenerative processes and assists with development of effective therapeutic strategies. PD represents an exemplar neurodegenerative disorder where synaptic dysfunction is reported as an early and progressive part of the disease process (Schirinzi et al., 2016).

PD is one of the most common neurodegenerative diseases (Su et al., 2025). A multisystem disorder, it is characterised by neuronal loss throughout the brain, with particular vulnerability shown by the dopaminergic neurones of the substantia nigra pars compacta (SNpc) (Mancini et al., 2020). Critically, synapse loss is considered a major factor in PD with the "dying back" hypothesis suggesting that synaptic dysfunction and demise precedes neuronal death (Mancini et al., 2020; Burke and O'Malley, 2013; Beccano-Kelly et al., 2014; Parisiadou et al., 2014; Volta et al., 2017; Matikainen-Ankney et al., 2018).

Several genes have been implicated in familial PD, including SNCA (α-synuclein), LRRK2 (leucine-rich repeat kinase 2) and GBA1 (Glucocerebrosidase) (Deng et al., 2018), which contribute to the ~5–10 % of familial PD cases (Deng et al., 2018). Research into these genetic forms of PD have provided valuable insights into the molecular mechanisms underlying PD pathogenesis. Specifically, aberrant synaptic protein aggregation, impaired autophagy, calcium dyshomeostasis, and mitochondrial dysfunction, all processes linked with synaptic function, have been highlighted (Plowey and Chu, 2011).

Thus, a key field that has emerged is the study of synaptic dysfunction in PD. Many labs have identified aberrant synaptic function (Beccano-Kelly et al., 2014) and associated cognitive deficits within genetic models of PD (Hussein et al., 2022). PD mutation dependent changes in synapse formation (Parisiadou et al., 2014), structure, function (Matikainen-Ankney et al., 2016), plasticity (Matikainen-Ankney et al., 2018), neurotransmitter release (Volta et al.,

This article is part of a special issue entitled: Physiology of Ageing published in Current Research in Physiology.

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https://doi.org/10.1016/j.crphys.2025.100166
Received 19 September 2024; Received in revised form 27 August 2025; Accepted 23 September 2025
Available online 9 October 2025

2017), synaptic vesicle trafficking (Cirnaru et al., 2014; Carrion et al., 2017) and monoamine transporters (Cataldi et al., 2018) have been observed. This substantial evidence points to the importance of the synapse within PD pathology and offers it as a valuable model for studying the ageing brain. The pathways, mechanisms, and targets affected in both ageing and PD: autophagy, calcium handling, and mitochondrial bioenergetics, are the subject of the remainder of the review.

1.2. Plasticity at the synapse

Seminal works within the neuroscience field have shown that synapses are incredibly plastic, with response to chemical signals capable of being strengthened or weakened in an activity-dependent manner. This innate ability allows for a variety of functions ranging from memory formation and learning to cognitive flexibility. (Kandel and Tauc, 1965; Bliss and Lomo, 1973; Bear et al., 1987; Tsien et al., 1996; Bi and Poo, 1998).

At excitatory synapses, glutamate activates both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs), but their roles in synaptic plasticity differ. AMPARs mediate rapid membrane depolarisation via sodium influx (Kauer et al., 1988), with strong depolarisation alleviating magnesium block of NMDARs (Gustafsson et al., 1987; Citri and Malenka, 2008). This enables NMDAR-mediated calcium influx (Collingridge et al., 1983), with the calcium level determining plasticity direction: modest influx activates phosphatases like calcineurin and protein phosphatase 1 (PP1), triggering AMPAR internalisation and long-term depression (LTD) (Mulkey et al., 1993; Beattie et al., 2000) whilst higher calcium influx triggers kinases including CaMKII, PKC, and MAPK, enhancing AMPAR conductance, and promoting their insertion into the post-synaptic membrane, thereby promoting long-term potentiation (LTP) (Malenka, 1994; Roche et al., 1996; Hayashi et al., 2000). Thus, NMDARs function as "coincidence detectors", converting synaptic input strength into long-lasting synaptic weakening or strengthening via AMPAR regulation (Citri and Malenka, 2008).

As we age, LTP and LTD decline, compromising cognitive processes such as memory and skill formation (Watson et al., 2002; Takeuchi et al., 2014; Shetty et al., 2017). There have, however, been reports to the contrary, highlighting heterogeneity in ageing (Kumar et al., 2007; Sagheddu et al., 2024). A large body of evidence exists to support that these changes are a result of NMDAR alteration during ageing. Glutamate binding to NMDARs declines with age across various model systems (C57Bl/6, BALB/c mice, dogs, monkeys, Long-Evans rats) in a region and strain-specific manner (Hof et al., 2002; Magnusson, 1995; Magnusson et al., 2000; Nicolle and Baxter, 2003). While the GluN2A subunit shows little change, age-related reductions in GluN1 and GluN2B mRNA and protein, have been observed in several models (C57Bl/6 mice, Fischer 344 and F344XBN rats, macaque monkeys), likely contributing to decreased binding (Gazzaley et al., 1996; Eckles-Smith et al., 2000; Magnusson, 2000; Magnusson et al., 2002; Magnusson et al., 2002, 2002; Bai et al., 2004; Mesches et al., 2004; Ontl et al., 2004; Barria and Malinow, 2005; Shi et al., 2007; Zhao et al., 2009). Reductions in receptor expression, changes in subunit composition, and reductions in NMDAR-dependent plasticity have been reviewed extensively by Kumar (2015) and Magnusson et al. (2010), and highlight how critical NDMAR expression and function are to synapses, both physiologically, and during age-related decline (Magnusson et al., 2010; Kumar, 2015).

As another example of important receptor alterations with age, it has also been seen that adenosine A1 receptor (A1R) signalling plays a role in age-related synaptic plasticity changes. A1Rs can be found on glutamatergic neurones, where they regulate neurotransmitter release, and have been associated with development and consolidation of LTP (Giménez-Llort et al., 2005). In middle-aged rats (7–10 months), LTP is impaired in the basal but not apical dendrites of hippocampal pyramidal neurones compared to young adults (1–2 month-old) (Rex et al., 2005). This is due to persistent A1R activation, likely from reduced adenosine clearance, rather than receptor number changes, and was rescued by A1R antagonism and AMPAR agonism (Rex et al., 2005).

2. Autophagy

2.1. Autophagy at the synapse

Autophagy maintains synaptic integrity through three primary pathways; macroautophagy (autophagosome-mediated degradation), microautophagy (direct lysosomal engulfment) and chaperone-mediated autophagy (CMA) (LAMP2A dependent selective degradation of proteins bearing a KFERQ-like motif) (Fred Dice, 1990; Lynch--Day et al., 2012; He et al., 2013; Feng et al., 2014; Kaushik and Cuervo, 2018; Hollenstein and Kraft, 2020; Liénard et al., 2024).

Post-mitotic neurones are dependent on autophagic quality control due to their inability to dilute dysfunctional cellular components through cell division, and the extreme protein turnover demands of repetitive neurotransmitter release (Deng et al., 2021; Südhof, 2013). Furthermore, the highly polarised structure of neuronal architecture demands precise spatiotemporally regulated autophagy to maintain the thousands of synaptic proteins essential for transmission, with autophagic failure leading to synaptic dysfunction and neurodegeneration (Cai and Ganesan, 2022; Hoffmann et al., 2019; Maday and Holzbaur, 2016).

A number of activity-based autophagy initiation systems have been identified in recent years, whereby high metabolic demands and synaptic activity are matched by upregulation of the autophagy pathway. These include, but are not limited to, increases in autophagic activity upon NDMA treatment (Shehata et al., 2012), and induction of targeted autophagy to selectively clear damaged synaptic proteins (Hoffmann et al., 2019). Furthermore, high frequency stimulation in the *Drosophila* neuromuscular junction results in Atg8 (LC3)-positive autophagic puncta formation in presynaptic terminals (Bademosi et al., 2023; Decet and Soukup, 2024), and Atg9, a core member of the autophagy pathway, has been shown to cycle between the plasma membrane and intracellular vesicles in response to synaptic activity (Yang et al., 2022).

Independent of activity-based regulation, synaptic protein based mechanisms of autophagy modulation also exist. Bassoon, a synaptic protein, prevents excess synaptic vesicle degradation via interaction with Atg5, a protein required for autophagosome formation. Loss of Bassoon results in increased autophagosome number and reduction in synaptic vesicle pools (Okerlund et al., 2017). Interestingly, Epidermal Growth Factor Receptor (EGFR) activity also suppresses autophagy to maintain synaptic stability, with EGFR inactivity resulting in autophagy upregulation and degradation of active zone proteins such as Bruchpilot (Brp) (Dutta et al., 2023).

Conversely, research has shown autophagy impairment, induction, and loss of key autophagic pathway proteins also regulate synaptic function and plasticity. Impaired autophagy causes growth of dendritic spines (Tang et al., 2014). Loss of Atg7 in dopaminergic neurones of mice, via selective deletion of the Atg7 gene in the substantia nigra by dopamine transporter-controlled Cre expression, results in increased dopamine release (Hernandez et al., 2012). Similarly, loss of Atg5 in glutamatergic neurones of $Atg5^{flox/flox}$ mice, via stereotactic injection of CamKII-eGFP-Cre adeno-associated virus, alters AMPAR trafficking, causing increased excitatory transmission and seizures (Overhoff et al., 2022). Autophagic induction also facilitates degradation of endocytosed AMPA receptors, causing memory destabilisation (Shehata et al., 2018), and autophagy suppression via brain-derived neurotrophic factor (BDNF) signalling is key for synaptic plasticity and memory (Nikoletopoulou et al., 2017; Tavernarakis, 2020).

Overall, synaptic autophagy is an extremely intricate, fine-tuned process. It ensures the proper maintenance of synaptic machinery and, through this, the appropriate function of the synapse. It is clear that

autophagy and synaptic activity influence each other and share a regulatory relationship which is vital within this environment.

2.2. Autophagy at the synapse in physiological ageing

Autophagic activity has been found to have crucial roles in various aspects of health, disease and, indeed, ageing (Valencia et al., 2021). Both the activity of this degradative pathway and its relevant proteins have been found to decline over time. In fact, the build-up of abnormal proteins within the cytoplasm has been identified as a representative feature of senescence (He et al., 2013).

Further evidencing this change, a 70 % drop in autophagosome biogenesis has been identified within synapses of 24-month-old aged primary dorsal root ganglion (DRG) cultures compared to cultures from 1-month-old young mice (Tsong et al., 2023). Further research from the same lab also identified an increase in abnormal autophagic structures, with only 34 % in aged mice exhibiting double membrane morphology, compared to 80 % in young mice (Stavoe and Holzbaur, 2019). It was determined that WD Repeat Domain, Phosphoinositide Interacting Protein 2 (WIPI2), another protein required for autophagosome creation, becomes less functional during ageing due to a change in phosphorylation states. With age, failure to dephosphorylate WIPI2, and thus initiate productive autophagosome creation, accounts for loss of autophagosomes seen in aged neurones. Furthermore, this inability to dephosphorylate, which could be due to mislocalisation of the relevant phosphatase, could also account for the abnormal autophagosome morphology observed in these neurones (Stavoe and Holzbaur, 2019).

In addition to this, autophagy related proteins such as Atg5, Atg7 and Atg8, and those which form crucial molecular complexes with these core aspects of the autophagy pathway, for example, Sirtuin 1, have been identified as regulators of longevity. Phenotypes in both *Atg5*$^{-/-}$ and *Sirt1*$^{-/-}$ mice, where the autophagy pathway is inhibited, both display accumulation of damaged organelles, and early perinatal mortality (Lee et al., 2008). It has also been found that various activators of autophagy, such as caloric restriction, resveratrol (an indirect activator of Sirtuin-1), spermidine, rapamycin, and down-regulation of p53, promote extension of lifespan in various models ranging from yeast and cells to multicellular organisms such as worms and flies (He et al., 2013).

Research has also found that autophagy enhancers such as spermidine could be used to slow cognitive impairment, and potentially even neurodegeneration. Treatment of aged mice with mild cognitive impairment is possible using autophagy enhancers such as spermidine and TAT-Beclin1. They were able to restore post-translational modifications on AMPA receptor subunit GluR1 (GluA1) which are crucial for processing high memory loads, and rescue memory capacity deficits in aged mice (De Risi et al., 2020; Lee et al., 2010).

Similar results have also been found in mouse hippocampal neurones. During ageing, autophagic activity within the hippocampus decreases (Glatigny et al., 2019). Induction of autophagy within this region in aged mice was able to reverse memory deficits caused by ageing. Although this study did not observe synaptic autophagy, specifically, this autophagic upregulation resulted in enhancements to a number of synapse-related processes, including dendritic spine formation, neuronal facilitation and LTP (Glatigny et al., 2019). In combination with other research detailed in this review, it is likely that this autophagy induction affects a number of synaptic processes, such as GluA1 post-translational modification restoration seen above.

Work has also demonstrated that plant extracts can protect against age-related synaptic decline through activity on the autophagy lysosomal pathway. Application of American ginseng *(P. quinquefolius)* extract and exercise-mimetic compound β-guanidinopropionic acid (β-GPA), a creatine analogue, to long term 3D brain explants improved levels the active isoform of Cathepsin B (CatB), a lysosomal protease. Alongside increased levels of active CatB, enhanced autophagic flux and improved synaptic markers were seen, which indicated better synaptic health. Use of these compounds on Chloroquine treated explants, which simulated age-related compromise of lysosomal protein clearance, displayed protection of pre and postsynaptic proteins (Fernandes de Almeida et al., 2022).

CatB is a crucial lysosomal enzyme involved in regulating long-term plasticity of dendritic spines, as shown by work in rat hippocampal neurones. Back propagating action potentials can elicit lysosomal Ca^{2+} release, which triggers lysosomal exocytosis. This releases lysosomal contents into the extracellular space, where CatB cleaves matrix metalloproteinase-9, thereby enhancing its extracellular matrix remodelling capabilities (Padamsey et al., 2017). This is an important paradigm which shows how integrated autophagy and calcium handling are as fundamental, interconnected processes involved in synaptic health. It is highly likely that this mechanism plays a part in protection against the synaptic compromise seen in the research above.

Other aspects of autophagy are also changed during ageing. Wdfy3 (WD Repeat and FYVE Domain Containing 3) is a macroautophagic scaffold protein which regulates autophagy, specifically the degradation of certain cellular components such as mitochondria and glycogen. Dysfunctions in this protein can cause accumulation of these components, which can exacerbate age-related cognitive deficits, through reduced synaptic density and altered synaptic plasticity (Napoli et al., 2021). Mitochondria can also become damaged with age, and drive changes to synaptic morphology (Rybka et al., 2019). Indeed, Wdfy3 haploinsufficiency in mice results in decreased mitophagy and accumulation of damaged mitochondria with altered morphology, further exacerbating problems that may be seen in ageing (Napoli et al., 2021). This once again underlines how key autophagy is to maintaining a healthy synaptic environment, especially during ageing.

Contrary to much of the evidence provided above, formalin-fixed, paraffin-embedded human brain tissue from the prefrontal cortex, corpus striatum, and hippocampus in elderly individuals show increased autophagic and mitochondrial activity compared to young individuals. There was, however, significant neurone loss identified in these regions, implying these are compensatory mechanisms to cope with the degenerative changes. Unfortunately, it cannot be ascertained whether this is the case specifically within synapses, as that was not a direct focus of this study (Sukhorukov et al., 2022).

Research has also found that endolysosome deacidification may also be an important mechanism involved in age-dependent synapse loss. Aged neurites contained fewer terminal lysosomes, implying ageing results in compromised lysosomal function at the synapse. Endolysosomal activity at the synapse was reduced due to insufficient acidification of the vesicle, associated with a reduction in v-ATPase subunit V0a1, the proton pump which acidifies lysosomes. This decreases with ageing. Acidification of this vesicle was able to rescue degradative function and reverse synaptic decline (Burrinha et al., 2023). This suggests once again that this aspect of the autophagy pathway is crucial for both lysosomal and synaptic health. It also identifies this as another key mechanism involved in age-dependent synapse loss in neurones.

It has now become clear that autophagic perturbance is common during ageing, and often leads to accumulation of damaged proteins and synaptic compromise. Increased autophagic activity seen in human brain samples can be considered compensatory mechanisms to account for neuronal loss, yet this often fails to fully prevent synaptic decline. Research collated here also demonstrates the effectiveness of autophagic agonists and natural products. These compounds can rescue synaptic function and, thus, higher-level cognitive processes through restoration of autophagic flux and pathogenic protein degradation. Furthermore, it is evident that various aspects of the autophagy lysosomal pathway, including proteins and vesicles, at every step from initiation to degradation, play some vital roles which support synaptic integrity.

2.3. Autophagy at the synapse in PD

Dysfunctional autophagy has regularly been shown as a robust phenotype of PD (Alegre-Abarrategui et al., 2009; Orenstein et al., 2013;

P et al., 1997; Sidransky and Lopez, 2012). This dysfunction is thought to be at the heart of toxic protein aggregation seen in the disorder, resulting in the formation of Lewy bodies (LBs), a hallmark feature of PD. α-synuclein, a protein localised within the synapse, is one of the main components found within LBs (Spillantini et al., 1997). Wild type α-synuclein is primarily degraded through CMA (see Fig. 1). Pathogenic mutations in the *SNCA* gene, which encodes α-synuclein, such as A53T and A50P, however, cause binding to LAMP2A. The LAMP2A receptor facilitates the CMA process, and this binding blocks both α-synuclein uptake and degradation, as well as that of other proteins (Cuervo et al., 2004). Thus, blocked autophagy facilitates further α-synuclein aggregation, and aggregation circuitously blocks autophagy. It has also been discovered that overexpression of α-synuclein impairs macroautophagy via inhibition of Rab1a, another protein involved in autophagosome formation (Winslow et al., 2010). This also leads to mislocalisation of Atg9, which has been shown to be involved in activity-dependent autophagosome biogenesis in *C. elegans* (Yang et al., 2022).

This provides multiple pathways through which autophagy is inhibited, via prevention of autophagosome formation at the synapse, or through an uptake blockade of proteins directly into the lysosome. This clearly implies that synaptic activity would be affected through accumulation of damaged proteins within the synapse. Furthermore, enhanced deposition of α-synuclein in LBs and in presynaptic terminals has been observed when there are deficits in autophagy and in *Atg7*$^{-/-}$ mice, respectively (Friedman et al., 2012; Sato et al., 2018).

In addition to this, work in human induced pluripotent stem cell (hiPSC) derived dopaminergic neurones (DaNs) on another endocytic protein, auxilin, showed how a PD LRRK2 mutant can affect synaptic autophagy. Impairment of auxilin function resulted in build-up of oxidised dopamine, which is toxic to the cell. This in turn contributed to decreased activity of a lysosomal protease called GCase (encoded by the *GBA1* gene) (Nguyen and Krainc, 2018). It also increased levels of α-synuclein. Loss of GCase activity impairs autophagy, leading to further α-synuclein build up, which further reduces GCase activity, creating a feedback loop that worsens protein accumulation. In addition to this, there is an increase in release of α-synuclein fibrils which can spread α-synuclein pathology to healthy neurones (Gegg et al., 2020).

These pieces of evidence implicate the synapse as a core pathological target within PD, and paints autophagy as a key player which is dysregulated in this complicated environment. As aforementioned, PD is reviewed here as a condition that exhibits accelerated ageing, and LB pathology, of which α-synuclein is a key component, is also seen in healthy individuals, albeit at later ages than in PD patients (Lewis et al., 2025; Reeve et al., 2014). It is therefore likely that the pathological mechanisms seen in PD are conserved in the later stages of physiological ageing.

Heterozygous mutations in the *GBA1* gene are the biggest genetic risk factor for PD. There are wide ranging consequences to loss of GCase activity. This includes loss of activity of other proteases within the lysosome, as well as disruption of lysosomal pH and stability, as well as a build-up of sphingolipids and cholesterol within the lysosome (Navarro-Romero et al., 2022). All of these alterations have an impact on autophagy. There is also seemingly an impact on synaptic function. Dysregulation of calcium signalling within heterozygous *GBA1* hiPSC derived DaNs, particularly within the mitochondria, leads to reduced mitochondrial membrane potential, and a lower oxygen consumption rate. In turn, there is decreased synaptic activity as these neurones are unable to meet the energy demand required for electrophysiological activity (Beccano-Kelly et al., 2023).

α-synuclein is not the only protein involved in autophagy and autophagy related proteins at the synapse. Endophilin-A (EndoA), a protein involved in synaptic vesicle endocytosis, has been found to co-immunoprecipitate with Atg9-positive membranes, and has been functionally linked to three different PD associated proteins: leucine rich repeat kinase 2 (*LRRK2*), *PARK2*/Parkin and synaptojanin1 (*SYNJ1*) (Matta et al., 2012; Soukup et al., 2016; Soukup and Verstreken, 2017). Further to this, it has been found to induce membrane curvature, creating docking sites for autophagic proteins such as Atg3, and subsequently Atg8, crucial for autophagosome formation (Soukup and Verstreken, 2017).

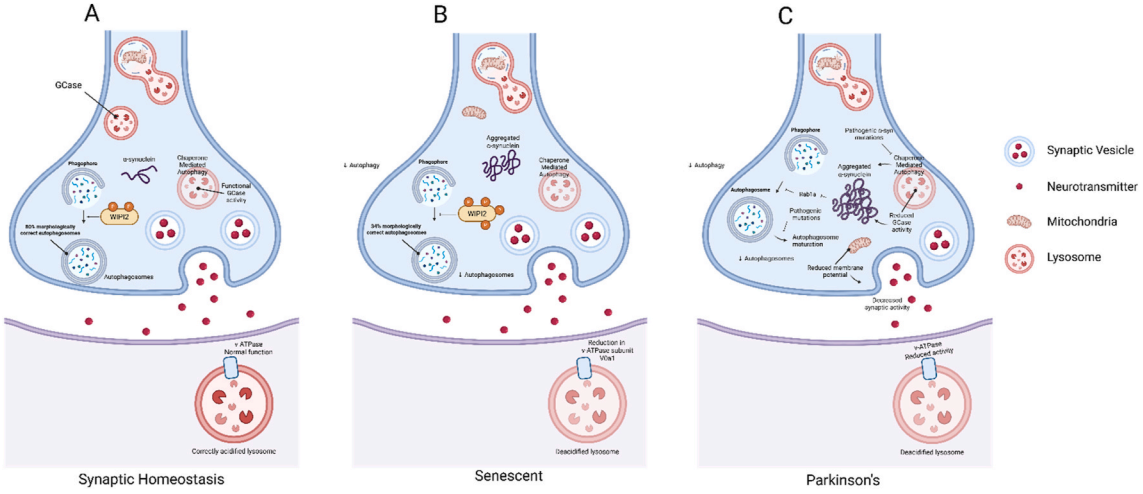

Fig. 1. Synaptic autophagy in (A) Physiological synaptic homeostasis, (B) Senescent synapses, and (C) Parkinson's Synapses. Created with BioRender.com. (A) Represents optimal synaptic homeostasis and normal neurotransmitter release. WIPI2 maintains proper dephosphorylation status, critical for generation of LC3-II autophagosomes. 80 % of autophagosomes display characteristic double-membrane structure. There is a presence of healthy mitochondria and efficient mitophagy. Properly acidified lysosomes are present in the pre and postsynaptic terminals, characterised by active v-ATPase and normal GCase and Cathepsin B activity. (B) In senescent synapses, there is a reduction in autophagy, resulting in abnormal protein build-up. There is also a reduction in Wdfy3-mediated mitophagy. Autophagosome morphology is altered, with only 34 % maintaining the normal double-membrane structure. Failure to dephosphorylate WIPI2 in ageing neurones accounts for loss of autophagosomes. Lysosomes demonstrate reduced acidification due to reduction in v-ATPase subunit V0a1. Reduced Cathepsin B activity. (C) In Parkinson's, there is reduced synaptic autophagy. Mitochondria display reduced membrane potential, and lower oxygen consumption rate, which in turn causes reduced synaptic activity due to an inability to meet the required energetic demands. Overexpression of α-synuclein impairs macroautophagy via Rab1a inhibition. Pathogenic mutations in α-synuclein block chaperone mediated autophagy (CMA), prevent uptake and degradation of α-synuclein and other proteins. Blocked autophagy facilitates α-synuclein aggregation. Other pathogenic mutations, such as in synaptojanin-1 (*SYNJ-1*) prevent autophagosome maturation, and further disrupt autophagy. Reduced GCase is also seen which impairs autophagy, leading to further α-synuclein build-up, and impairs lysosomal pH and lysosomal stability.

Work from the same lab has also identified novel PD risk variants within EndoA which impair a form of synaptic activity dependent regulation of autophagy. EndoA is able to mobilise from the plasma membrane upon calcium influx and promote Atg8-containing autophagosome formation (Decet and Soukup, 2024). Identified PD risk variants nullify EndoA calcium sensing ability (G267V), or make EndoA more rigid or flexible, (D265A and D265R), changing mobilisation ability and thereby blocking autophagosome formation, or mimicking calcium responsiveness, and over-activating autophagy (Bademosi et al., 2023).

In *C. elegans*, Atg9 dependent linking of the synaptic vesicle cycle to autophagy through exoendocytosis at the presynapse is another form of activity dependent autophagy regulation. PD associated mutations in *SYNJ1* also result in defective synaptic autophagy, and an accumulation of Atg9 at the synapse (Yang et al., 2022). The R258Q PD associated *SYNJ1* mutation also disrupts its role in autophagy, but not synaptic vesicle endocytosis, which remained normal in *Drosophila*. The affected SAC1 domain dephosphorylates phosphatidylinositol 3-phosphate (PI3P) and phosphatidylinositol 3,5-bisphosphate PI(3,5)P2, lipids required for autophagosome maturation. The R258Q mutant leads to abnormal accumulation of Atg18a, which binds PI(3)P/PI(3,5)P2), and an arrest of Atg18a mobility between being membrane bound and soluble (Vanhauwaert et al., 2017). This effectively traps Atg18a on nascent autophagosomes, preventing their maturation and disrupting autophagy.

Synaptic autophagosome biogenesis was seen to be reduced in aged primary DRG cultures due to phosphorylation status of WIPI2 (Tsong et al., 2023), and the PD risk variants detailed above also converge onto this autophagosome biogenesis and maturation pathway. While two of the EndoA risk variants cause a reduction in biogenesis, and α-synuclein overexpression can inhibit autophagosome formation via Rab1a inhibition (Winslow et al., 2010), the others presented here increase biogenesis or halt autophagosome maturation, and are still associated with PD pathogenesis. It seems that while aberrant increases in autophagosome biogenesis can also be pathogenic, inhibition of the autophagic pathway at this stage is a shared mechanism of aberrance in both ageing and PD.

These studies highlight the variety of ways in which autophagy is blocked in PD, and general ageing. There are a number of activity-dependent regulatory processes for autophagy within the synapse, many of which are impacted by PD associated mutations in multiple genes. These genes highlight many critical steps in the autophagy pathway, and their impact is similar to that seen in ageing. This illustrates that the autophagy pathway is a critical process necessary for synaptic function.

When considering how synaptic autophagy plays a role in synaptic health, calcium handling has emerged as a key process which is involved in both autophagic and synaptic activity (Luebke et al., 1993; Tian et al., 2015). We will discuss the role of calcium handling in the synapse next.

3. Calcium handling

3.1. Calcium handling at the synapse

Calcium (Ca^{2+}) dynamics are central to neurotransmitter release and plasticity, with cytosolic levels rising from baseline 200 nM to low micromolar concentrations following action potential-induced voltage-gated calcium channel (VGCC) activation and ER Ca^{2+} release (Bahar et al., 2016; Kawamoto et al., 2012). These Ca^{2+} transients drive receptor trafficking and vesicle dynamics that underlie synaptic transmission, with homeostatic regulation maintained through Ca^{2+} binding proteins and active uptake in to organelles (Catterall et al., 2005; Xu et al., 2022; Zamponi et al., 2015; see also Fig. 2).

3.1.1. Calcium handling via Voltage-Gated Calcium Channels (VGCCs)

VGCCs are key players in neuronal calcium signalling. In response to action potentials increasing membrane voltage, VGCCs at the presynapse undergo a conformational change to open and allow an influx of Ca^{2+} ions into cells. One of the responses to this is the fusion of synaptic vesicles with the plasma membrane, and subsequent neurotransmitter release from presynaptic terminals. VGCCs are subdivided into families (Ca_V1, Ca_V2, and Ca_V3) based on the current types they elicit, their physiological properties, and the pharmacological inhibitors that affect

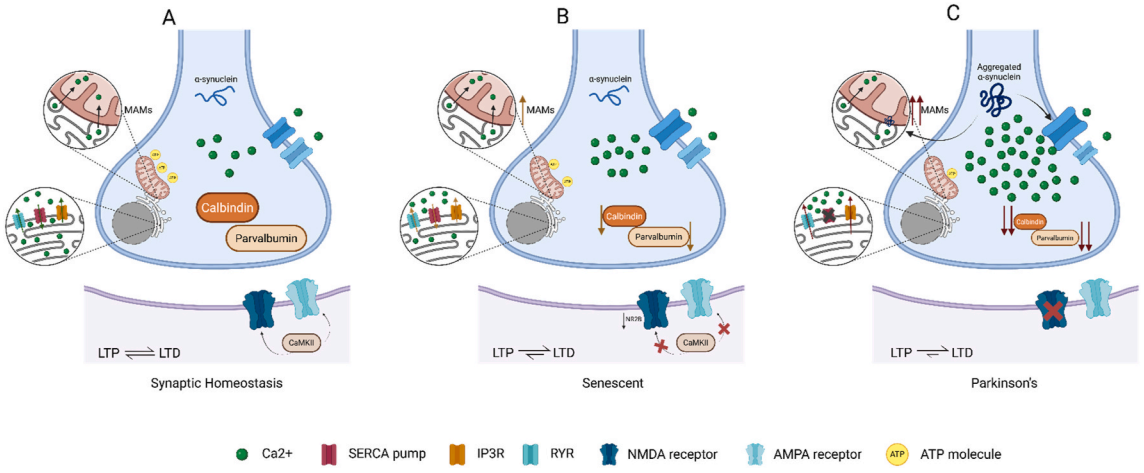

Fig. 2. Synaptic calcium signalling and molecular changes in (A) Physiological synaptic homeostasis, (B) Senescent synapses, and (C) Parkinson's synapses. Created with BioRender.com. (A) Depicts a healthy synaptic state with balanced calcium dynamics. The presynaptic terminal displays a uniform distribution of Ca_V1 and Ca_V2 type VGCCs. The ER expresses balanced RyRs, IP3Rs and efficient SERCA pumps maintaining calcium homeostasis, supported by appropriate levels of the Ca^{2+} binding proteins calbindin and parvalbumin. Mitochondria exhibit healthy morphology with optimal endoplasmic reticulum-mitochondria contact sites. Non-aggregated α-synuclein maintains normal protein functionality. At the post-synaptic terminal, LTP and LTD are in equilibrium and there is efficient translocation of CaMKII to post-synaptic receptors. (B) The presynaptic terminal displays heightened Ca^{2+} levels due to increased Ca_V1 channel activity, more permeable RYRs and IP3Rs, reduced SERCA pump efficiency and reduced Ca^{2+} binding proteins. Increased MAM sites increase Ca^{2+} transfer to mitochondria, and reduced ATP production. NMDARs at the post-synapse shift in receptor subunit composition, with decreased NR2B subunits. There is reduced CaMKII translocation and a transition towards LTD dominant signalling. (C) Parkinson's synapses exhibit pronounced $Ca_V1.3$ channel activity and downregulated $Ca_V2.3$ channels. Hypersensitive Ca^{2+} release channels, critically dysfunctional SERCA pumps and reduced Ca^{2+} binding proteins compromise calcium buffering. Aggregated α-synuclein directly interacts with, and disrupts, ion channels. α-synuclein also localises to MAMs and disrupts Ca^{2+} transfer between organelles. Post-synaptic NMDARs become compromised and there is a significant transition towards LTD signalling.

them, aspects which has been extensively reviewed in literature (Catterall et al., 2005; Zamponi et al., 2015). The distribution and expression of each VGCC varies across neuronal subtypes and subcellular compartments. This contributes to the unique synaptic transmission properties that different neuronal subtypes possess (Vierra and Trimmer, 2022). For instance, in dopaminergic neurones, neurotransmitter release from presynaptic terminals is primarily modulated by Ca^{2+} influx from the N-type and P/Q-type VGCCs (Rusakov, 2006). This facilitates the execution of the unique functions required by these neurones.

3.1.2. Calcium handling and the endoplasmic reticulum

The endoplasmic reticulum (ER) plays an essential role in calcium handling at the synapse, serving as a major Ca^{2+} store and a key regulator of local Ca^{2+} dynamics. ER calcium release at the synapse is mediated by two channels, inositol 1,4,5-trisphosphate receptors (IP3Rs) and ryanodine receptors (RyRs) (Stutzmann and Mattson, 2011). In response to Ca^{2+} influx via VGCCs, IP3Rs and RyRs facilitate calcium-induced calcium release (Sandler and Barbara, 1999), amplifying calcium signals at the synapse to facilitate neurotransmitter release from presynaptic terminals, thereby facilitating synaptic plasticity. The ER also aids in the termination of Ca^{2+} signals and maintenance of resting Ca^{2+} levels by sequestering Ca^{2+} through the action of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pumps (Wan et al., 2012).

Other cellular organelles can take advantage of ER Ca^{2+} stores. Mitochondria use specialised contact sites known as mitochondria-associated-membranes (MAMs) to draw Ca^{2+} from the ER to generate ATP. At the synapse, ATP is essential for the mobilisation, exocytosis and recycling of synaptic vesicles, which are very energy dense processes (Verstreken et al., 2005; Pathak et al., 2015).

3.1.3. Calcium handling and plasticity

Calcium signalling is involved in synaptic plasticity, with calcium serving as a key signalling molecule in mediating short-term and long-term changes in synaptic strength. At the presynaptic terminal, the magnitude and duration of Ca^{2+} flux directly influences neurotransmitter release, contributing to short-term plasticity mechanisms such as facilitation and depression (Catterall et al., 2013). Postsynaptically, however, NMDA receptor activation results in Ca^{2+} influx, which triggers events critical for the induction of LTP and LTD (Lüscher and Malenka, 2012), as mentioned earlier. For instance, increased intracellular Ca^{2+} activates calcium/calmodulin-dependent protein kinase II (CaMKII), a key mediator of LTP, which increases AMPA receptor conductance and insertion into the postsynaptic membrane (Lisman et al., 2012).

Ca^{2+}-binding proteins (e.g., parvalbumin, calbindin, and calreticulin) shape the spatial and temporal aspects of calcium signalling, influencing the specificity of plasticity induction. Parvalbumin modulates the decay of Ca^{2+} signals and influences short-term plasticity (Caillard et al., 2000). Calbindin and Calreticulin are involved in modulating the amplitude and duration of Ca^{2+} signals at presynaptic terminals (Schwaller, 2020). Calcium signalling also interfaces with other secondary messenger systems, such as cyclic adenosine monophosphate (cAMP) and endocannabinoid signalling, to fine-tune synaptic plasticity. For instance, coincident activation of calcium and cAMP signalling can lead to more robust and longer-lasting forms of LTP (Alberini, 2009).

3.2. Calcium handling at the synapse in physiological ageing

Ca^{2+} signalling alters with age and has been implicated in neurodegenerative diseases, making it crucial to understand the intricacies in Ca^{2+} dynamics and dysregulation in the brain.

One of the most prominent age-related changes of Ca^{2+} signalling is dysregulation of intracellular Ca^{2+} homeostasis (Nikoletopoulou and Tavernarakis, 2012) ($^{p2)}$. Key factors like mitochondrial dysfunction, dysregulation of Ca^{2+} channels by posttranslational modifications and oxidative stress, as well as impaired Ca^{2+} buffering, culminate in disruption of neuronal Ca^{2+} homeostasis during ageing (Gleichmann and Mattson, 2011).

3.2.1. Calcium handling and VGCCs in physiological ageing

The function and expression of VGCCs change with age. Specifically, alterations are observed in Ca_V1 L-type calcium channels, contributing to Ca^{2+} overload and altered firing patterns (Moore and Murphy, 2020). Immunoblotting studies in rats suggest that expression of L-type VGCCs is upregulated during ageing, correlating with impairments in memory (Veng et al., 2003; Veng and Browning, 2002). In ageing neurones from rabbit hippocampal slices, increased Ca_V1 currents have been shown to alter the afterhyperpolarization (AHP) phase of action potentials, resulting in longer lasting and larger AHPs. This reduces neuronal excitability and firing rates (Power et al., 2002). Intriguingly, this effect varies across Ca_v1 channels, with $Ca_v1.3$ more affected by these kinetic alterations than the $Ca_v1.2$ subtype (Cataldi, 2013; Qian et al., 2017). This increase in activity has been attributed to age-related changes in signalling, affecting channel phosphorylation states (Li et al., 2022a). Rat models of ageing have displayed a 2-fold increase in cAMP dependent protein kinase A (PKA)-dependent phosphorylation and activation of Ca_v1 channels (Davare and Hell, 2003).

3.2.2. Calcium handling and the endoplasmic reticulum in physiological ageing

At the synapse, Ca^{2+} release from intracellular stores becomes less tightly regulated in ageing neurones. There is increased Ca^{2+} release from IP3Rs, age-related oxidative stress modifies RyRs making them more prone to calcium leakage, and changes in the interaction between RyRs and their regulatory proteins can lead to increased Ca^{2+} channel opening (Andersson et al., 2011; Thibault et al., 2007). Furthermore, there are alterations in ER Ca^{2+} buffering. SERCA pumps show decreased efficiency with age, and there are alterations in the expression of functional Ca^{2+} binding proteins within the ER (e.g. Calreticulin), reducing Ca^{2+} storage capacity (Zarate et al., 2023). Age-related changes in Ca^{2+} binding proteins play a role in altered Ca^{2+} signalling. Calbindin and parvalbumin act as calcium buffers, and levels of these proteins are seen to decrease with age (Moreno et al., 2012; Wu et al., 1997; Riascos et al., 2011; Ueno et al., 2018). These factors lead to increased synaptic Ca^{2+} levels prolonging Ca^{2+} signalling, altered synaptic transmission and synaptic plasticity.

In ageing neurones, there is a general trend towards increased MAM formation, with a higher number of contact sites between the ER and mitochondria (Calvo-Rodríguez et al., 2016). Ca^{2+} overload causes mitochondrial dysfunction, reducing ATP production required for synaptic function.

3.2.3. Calcium handling and plasticity in physiological ageing

In healthy ageing, synaptic plasticity mechanisms undergo subtle but significant changes mentioned in the earlier plasticity section. This is largely influenced by alterations in calcium homeostasis by the ER affecting both LTP and LTD.

Due to age-related increases in Ca^{2+} levels at the synapse, the LTP induction threshold is heightened. Stronger or more repetitive stimulation is required to induce LTP in aged neurones and, when induced, LTPs show reduced magnitude and a shorter duration (Kumar, 2011). In fact, aged neurones have an enhanced propensity for LTD induction (Norris et al., 1996) and some forms of LTD are induced at stimulation frequencies that would typically induce LTPs in younger neurones (Hsu et al., 2002). The balance shift between LTP and LTD may be due to alterations in NMDA receptor subunit composition. Specifically, a decrease in the NR2B subunit incorporation affects receptor kinetics and Ca^{2+} permeability (Santucci and Raghavachari, 2008).

Furthermore, the Ca^{2+}-dependent activation of CaMKII and translocation to the postsynaptic density is impaired in ageing, affecting its

interaction with NMDARs required for LTP (Rumian et al., 2023). With age, the coupling between Ca^{2+} influx and cAMP production becomes less efficient, leading to a higher threshold for coincident activation of calcium and cAMP signalling, impacting LTP induction (Morrison and Baxter, 2012). Additionally, altered endocannabinoid synthesis and receptor expression modifies Ca^{2+} signalling, contributing to reduced synaptic plasticity (Bilkei-Gorzo, 2012).

Whilst these changes are part of normal ageing, they can set the stage for increased vulnerability to stress and neurodegenerative processes.

3.3. Calcium handling changes in PD

In PD, dysregulated intracellular Ca^{2+} levels and impaired calcium homeostasis are hallmark pathological features, and PD patients have been shown to exhibit higher average cytosolic Ca^{2+} levels compared to healthy individuals (Samavarchi Tehrani et al., 2020).

3.3.1. Calcium handling and VGCCs in PD

Dopaminergic neurones (DaNs) have unique calcium dynamics due to their pacemaking activity (Guzman et al., 2009). This is driven by L-type Ca_v1 channels, particularly the $Ca_v1.3$ subtype, making them particularly vulnerable to disturbances in Ca^{2+} homeostasis (Shin et al., 2022). The $Ca_v1.2$ and 1.3 channels allow oscillatory Ca^{2+} influx into DaNs. Therefore, the increased Ca_v1 function observed in PD leads to sustained postsynaptic Ca^{2+} entry (Verma and Ravindranath, 2019; Hurley et al., 2013), dysregulating synaptic transmission and plasticity. In adult mice, $Ca_v2.3$ channels have recently emerged as the most abundantly expressed VGCCs in dopaminergic neurones. Interestingly, there is no significant difference between $Ca_v1.2$, $Ca_v1.3$ and $Ca_v2.3$ channels in juvenile mice, illustrating an important temporal shift in functional expression of Ca^{2+} channels (Benkert et al., 2019). In models of PD $Ca_v2.3$ channels are downregulated, resulting in the reduction of action potential AHP amplitude. This alteration in action potential dynamics results in increased dopaminergic neurone vulnerability to degeneration (Benkert et al., 2019). Since Cav2.3 is more abundantly expressed at later ages, the effect of vulnerability is more pronounced in aged neurones. L-type Ca_V channels seem to be more important to DaN pacemaking activity at younger ages (Guzman et al., 2009), illustrating the importance of taking temporality into account in the assessment of synaptic function.

Mutant α-synuclein has also been shown to interact with ion channels to induce dopamine release (Subramaniam et al., 2014). When Ca_V2 channels are present on lipid-rich membranes, more energy is required for the channel's conformational change from closed to open (Levitan et al., 2010; Lundbaek et al., 1996). Mutant α-synuclein promotes relocalisation of Ca_V2 channels to low lipid environments, promoting Ca^{2+} influx into the presynapse, and inducing neurotransmitter release (Ronzitti et al., 2014). Furthermore, elevated Ca^{2+} levels have been shown to promote conformational changes and aggregation of α-synuclein, creating a positive feedback loop where α-synuclein dependent calcium dysregulation promotes further aggregation (Nath et al., 2011; Follett et al., 2013; Ramezani et al., 2023; Paillusson et al., 2017).

3.4. Calcium handling and the endoplasmic reticulum in PD

In PD, intracellular calcium stores in the ER exhibit significant dysregulation at the synapse. RyRs exhibit increased sensitivity to activation, leading to enhanced Ca^{2+}-induced calcium release. This dysregulation is exacerbated by oxidative modifications of RyRs, further increasing their open probability, resulting in uncontrolled Ca^{2+} release and dysregulation to action potential activation (Sun and Wei, 2021). IP3Rs exhibit altered function in PD synapses, with increased sensitivity to IP3. This hypersensitivity leads to excessive calcium release, disrupting local calcium signalling cascades crucial for synaptic plasticity (Yamamoto et al., 2019).

ER calcium homeostasis is severely disrupted in PD synapses. Genetic PD models show that the activity of SERCA pumps is diminished, impairing calcium sequestration into the ER (Solana-Manrique et al., 2021). The resultant cytoplasmic calcium elevations contribute to elevated neurotransmitter release resulting in excitotoxicity. Conversely, aggregated α-synuclein can activate SERCA pumps, promoting Ca^{2+} uptake into the ER, resulting in reduced cytosolic Ca^{2+} levels at the synapse (Betzer et al., 2018).

As observed in ageing, in PD there is an increase in ER-mitochondria contact sites, leading to enhanced calcium transfer between these organelles, ultimately contributing to mitochondrial calcium overload and dysfunction (Ramezani et al., 2023). The protein composition of MAMs is altered in PD, with increased localization of α-synuclein to these sites, disrupting Ca^{2+} transfer to the mitochondria, and dysregulating ATP production required for synaptic function (Paillusson et al., 2017).

3.5. Calcium handling and plasticity in PD

In PD, alterations in synaptic plasticity are heavily influenced by disrupted calcium dynamics. LTP induction in the striatum typically requires coordinated activation of D1 dopamine receptors and NMDA receptors, leading to calcium influx and subsequent activation of calcium-dependent signalling cascades (Meunier et al., 2015). The pathological loss of dopaminergic cells that occurs in PD disrupts this coordinated activation.

The balance between LTP and LTD is further skewed by altered calcium buffering in dendritic spines. In PD models, reduced expression of calcium-binding proteins like parvalbumin leads to prolonged calcium transients, potentially favouring LTD-like mechanisms over LTP. This shift can contribute to the weakening of specific synaptic connections important for motor control (Fernández-Suárez et al., 2012). There's a marked decrease in Calbindin in dopaminergic neurones, impairing their ability to buffer calcium influx, exacerbating excitotoxicity and oxidative stress (Ito et al., 1992; Iacopino and Christakos, 1990).Interestingly, Calbindin is preferentially expressed in dopaminergic neurones that are resistant to degeneration in models of PD (Inoue et al., 2019).

LTD, which normally relies on endocannabinoid signalling in the striatum, is also affected. The calcium-dependent synthesis of endocannabinoids is dysregulated due to abnormal cytosolic calcium levels. This disrupts retrograde signalling to presynaptic CB1 receptors, altering neurotransmitter release probability and affecting LTD induction (Stampanoni et al., 2017).

4. Energy and mitochondria

As covered previously, neuronal communication is a complex combination of processes which are finely balanced and require large amounts of energy. Thus, amongst the processes driving synaptic transmission, the function of intact mitochondria is also key. With age, the capacity of mitochondria to generate the required energy is diminished over time, affecting the efficiency of synaptic communication within the neuronal network (Chistiakov et al., 2014; Cicali and Tapia-Rojas, 2024). The energetic currency for transferring information between neurones is provided by ATP, generated mainly by glycolysis and oxidative phosphorylation (OXPHOS) (Li and Sheng, 2022). Bioenergetic failure is starting to be regarded as a common mechanism of early ageing and neurodegeneration, and evidence for this has been found in multiple neurodegenerative diseases, including AD, PD, and ALS (Błaszczyk, 2020; Strope et al., 2022).

4.1. Mitochondrial maintenance of synaptic functions

The release of a single synaptic neurotransmitter containing vesicle alone requires approximately 2×10^4 molecules of ATP (Cunnane et al., 2020; Rangaraju et al., 2014). This is a large amount of energy for a singular synaptic function, even before addressing other processes

within the neurone and the synapse, such as maintenance of the resting membrane potential, and neurotransmitter recycling at the synaptic cleft, which require even more ATP. Whilst changes in synaptic activity with enhanced energy requirements (e.g. prolonged synaptic stimuli) can be easily maintained in healthy conditions, during ageing and disease, this ability is compromised (Li and Sheng, 2022; Petralia et al., 2014; Devine and Kittler, 2018). As such, mitochondria are one of the central players in maintenance of proper neuronal performance. This, however, comes with the cost of production of reactive oxygen species, a major jeopardising factor of mitochondrial homeostasis (Li et al., 2020).

Synaptic mitochondria produce more ROS by default compared to soma mitochondria. This intrinsic difference is due to the decrease of their membrane potential, which is directly influenced by their distance from the nucleus (Baranov et al., 2021). Hence, distal neuronal compartments have a higher chance of accumulating dysfunctional mitochondria, which has a major impact on synaptic function. Synaptic mitochondrial dysfunction can range from structural alteration to electron transport chain defects, all of which lead to ATP decline and a drop in synaptic efficiency (Boveris and Navarro, 2008). A contra-effect of reduced synaptic mitochondria membrane potential is their reduced ability to support calcium handling, which is pivotal for both neurotransmitter release and uptake (Brown et al., 2006).

Physiologically, normal mitochondrial functions are maintained through tightly regulated mitochondrial turnover. This starts with biogenesis and culminates with mitophagy to eliminate defective organelles. With age, control over this mitochondrial turnover is lost (Bereiter-Hahn and Osiewacz, 2014).

Moreover, the deficits seen with age are observed in PD. Many PD related genes, such as E3-ubiquitin protein ligase Parkin, PTEN induced kinase 1 (*PINK1*), protein deglycase DJ1 (*DJ1*) and leucine-rich repeat kinase 2 (*LRRK2*), either directly or indirectly pathologically alter mitochondrial functions and life cycle (Henrich et al., 2023).

LRRK2 mutations can interfere with the main mitochondria turnover pathways via *DRP1* (fission) (Su and Qi, 2013), Miro (mitochondrial transport) (Hsieh et al., 2016, 2019), and *PINK*/Parkin (mitophagy) (Bonello et al., 2019). In healthy physiological conditions, *de novo* mitochondrial biogenesis, occurs primarily in the cell body. However, new mitochondria can be also generated distally through fission, the division of pre-existing mitochondria, a mechanism that is regulated by a member of the GTPase family, dynamin-related protein 1 (*DRP1*). In models with induced *DRP1* mutation, in DRP1 deficient samples, mitochondrial fission was suspended, which led to mitochondria depletion at synapses, and altered neurotransmission (Palikaras and Tavernarakis, 2020; Duarte et al., 2023). On the other hand, even uncontrolled fission can generate dysfunctional mitochondria which can alter synaptic activity. In a knock-in mouse model with the most prevalent *LRKK2* pathogenic mutation, *G2019S*, aberrant LRRK2 kinase function over-activates *DRP1,* altering the organelle dynamics and generating fragmented mitochondria (Ho et al., 2018). This pathological effect of *LRRK2* has been shown to potentially be inhibited *in vitro* by over-expressing a GTPase that regulates mitochondrial fusion, mitofusin 2 (*MFN2*), which counteracted the pathological occurrence of fission, promoting fusion between two mitochondria (Wang et al., 2012).

It is the well-balanced modulation of these two dynamic mechanisms that preserves intact mitochondrial function at the synapse, and has positioned these organelles as central hubs in synaptic modulation. However, when fusion/fission are not sufficient to maintain and provide enough functional mitochondria, Rho GTPase miro 1/2-driven mitochondrial transport and *PINK* and Parkin selective mitochondrial autophagy (mitophagy) are activated.

Miro 1 and 2, located on the outer mitochondrial membrane, anchor to microtubule motor proteins (kinesin and dynein), and orchestrate mitochondrial trafficking. Miro 1/2 have Ca^{2+} binding domains which can sense a reduction in calcium flux (Duarte et al., 2023). These binding sites activate the anchorage to kinesin (anterograde transport) and promote mitochondrial translocation at the synapse to fulfil synaptic metabolic demands. A detailed description of miro mitochondrial trafficking has been covered previously by Devine et al. (2016) (Devine et al., 2016). This highly conserved mechanism acts in concert with PINK and Parkin to remove defective mitochondria from synapses through mitophagy (via dynein retrograde transport). These mechanisms are dependent on the proper function of leucine-rich repeat kinase 2 (*LRRK2*). It has been shown that *LRRK2* forms a complex with Miro and microtubule proteins which appears to dictate mitochondrial trafficking dynamics (Singh et al., 2019). In *LRRK2 G2019S* PD mutant hiPSC derived neurones, pathogenic kinase function has been shown to arrest mitochondrial translocation, inhibiting mitophagic degradation of dysfunctional mitochondria through the *PINK1*/Parkin pathway (Hsieh et al., 2016, 2019).

The integrity of the mitochondrial degradation pathway is pivotal for synaptic maintenance. Dysfunctional mitochondria also produce more ROS, which can promote mitochondrial DNA (mtDNA) mutations. Accumulation of mtDNA mutations increase OXPHOS chain defects, which not only affect mitochondrial ability to produce ATP, but also alter calcium homeostasis, which culminates in synaptic failure (Palikaras and Tavernarakis, 2020).

Although mitochondrial dynamics represent core mechanisms for maintaining healthy neuronal communications, Friedlander has proposed a two-hit model of mitochondrial driven synapse loss in ageing and neurodegeneration (Baranov et al., 2021). The first hit is compartment specific, discriminating between synaptic viability and function. Non-synaptosomal mitochondria anterogradely transported to the synapse generally appear to be more functional than mitochondria that reside at synapses. Proximal mitochondria have intact functional capacity, not only due to lack of site-related free radical damage, but also because they can import functional proteins encoded by nuclear DNA (Mootha et al., 2003; Pfanner et al., 2019). Fusion and fission distally-generated mitochondria do not have adequate membrane potential to support the specialised protein import complexes needed for protein renewal (Malhotra et al., 2013). Furthermore, Baranov et al. (2019) suggest that dysfunctional distal mitochondria are more prone to cytochrome *c* release, which, instead of promoting normal synaptic remodelling, may negatively affect synaptic function (e.g. Ca^{2+} homeostasis) and neuronal viability (Baranov et al., 2019).

The second hit, according to Friedlander, is acquired cellular stress. Cellular stress can be either accumulated over time, such as ageing, or be innate, for example, disease causing mutant protein expression. It is this additional stressor which possibly drives synaptic vulnerability and cognitive decline as seen in several age-related neurodegenerative diseases (Baranov et al., 2021).

However the maintenance of healthy synaptic function is dependent on metabolic integrity as well, which will be discussed in the next section.

4.2. Synaptic metabolic support

Most of the brain's energy supply is used on synaptic transmission, therefore the amount of energy available to the synapse can make the difference in synaptic recovery i.e. deficits vs loss/degeneration. In the grand scheme of energy expenditure at the synapse, the main contributors are neurotransmitter release and reuptake, Ca^{2+} flux, and generation of synaptic currents (Harris et al., 2012).

In normal conditions neurones can adapt to bioenergetic challenges (e.g. changes in energy availability, energy source), either strengthening pre-existing synapses and neuronal circuitry, or reducing their firing rate. The preferential energy source for brain cells is glucose. However, depending on the circumstance, energy sources from other metabolic pathways can be used temporarily, for example, ketone bodies (Owen et al., 1967) and lactate (Camandola and Mattson, 2017). To be capable of "switching" between different energy sources, neurones are equipped with different carriers with a high affinity for these metabolites, and can also rely on astrocytic nutrient shuttles (Mächler et al., 2015). Glucose

transporter 3 (GLUT3), predominantly located in axon and dendrites, ensures a constant glucose supply even when glucose is scarce, to prevent a drop in synapse energetics. When the ATP supply from glucose is not sufficient, the monocarboxylic acid transporter 2 (MTC2), starts to pump lactate, pyruvate and ketone bodies at synaptic junctions to maintain and support synapse metabolism (Camandola and Mattson, 2017 see also Fig. 3).

Although these mechanisms run smoothly in a disease-free environment with intact antioxidant capacity, energetic performance steadily declines with age, and worsens with disease. Age-related glucose hypometabolism (de Leon et al., 1983) and poor utilisation (Gage et al., 1984), together with reduced nicotinamide adenine dinucleotide (NAD) bioavailability (Covarrubias et al., 2021; Lautrup et al., 2019; Verdin, 2015), reduced expression of glucose transporter proteins (Ding et al., 2013) and a reduction in key mitochondrial enzymes (Bowling et al., 1993) with increased oxidative stress, enhanced synaptic vulnerability and dysfunction, is observed.

In PD, besides the clear role of mitochondrial involvement in synaptic decline, studies have shown, at an early disease stage, a drop in the enzymatic efficiency of the pentose phosphate pathway (Dunn et al., 2014), as well as a pathological interaction between α-synuclein and glucose utilisation (Salah et al., 2022).

Although more studies are needed to elucidate the temporal evolution of energetic synaptic decline in ageing and disease, the current knowledge suggests that the interaction between these mechanisms, and subsequent loss of metabolic homeostasis, may drive aberrant synaptic function.

4.3. Strategies to restore/maintain or enhance neuronal bioenergetics

Metabolomics investigations of wild type mice brains at different time points (3 weeks, 16 weeks, 59 weeks and 92 weeks) show distinct metabolic signatures at each time point, with no overlap among the groups (Ding et al., 2021). The main metabolic shifts highlighted by this were around mitochondrial and synaptic metabolism, with glycolysis byproducts and neurotransmitter biosynthesis as the main hits (Ding et al., 2021). As confirmed by these results, the ageing brain goes through a metabolic crisis that may result in cognitive decline. While the mouse brain metabolome changes drastically when the animals are under calorie restriction, glucose levels tend to remain consistent despite the fasting, activating parallel metabolic pathways to maintain glucose homeostasis to preserve normal brain functions (Shao et al., 2023).

Although calorie restriction is one of the most effective non-pharmacological treatments to enhance neural functions (Fontán-Lozano et al., 2008), maintenance of an adequate energy homeostasis solely through a restricted diet in individuals with type 2 diabetes (T2D) has been shown to be challenging. At the core of T2D, there is an altered cellular metabolism driven by an inadequate insulin response which prevents the use of glucose as a source for energy production. Individuals affected by T2D have been shown to have a higher predisposition to developing neurodegenerative diseases, such as dementias, Alzheimer's and PD (Rotermund et al., 2018). Interestingly, in T2D patients treated with metformin, the incidence of developing neurodegenerative diseases has been found to be reduced, with positive influences on synaptic homeostasis in different neural networks. These effects appear to be related to metformin-mediated 5′-AMP-activated protein kinase (AMPK) activation. The AMPK mediated neuroprotective role has been reported to improve mitochondrial function (e.g. mitochondrial membrane potential, mitochondrial biogenesis) and the autophagic pathway, all mechanisms that affect neuronal function (Li et al., 2022b). Metformin has also been found to improve synaptic function, acting directly on the level of neurotransmitter release, or by modulating receptor expression on the postsynaptic membrane (Chen et al., 2020; Katila et al., 2017, 2020; Samuel et al., 2014).

With the same premise of boosting AMPK activity through metformin to improve neural function, activation of the serine/threonine kinase 1 (LKB1)-AMPK pathway has been shown to positively interfere with synaptic ageing. Samuel et al. (2014) illustrated that LBK1 and AMPK are involved in age-related synaptic remodelling (Samuel et al., 2014). Using the retina as an accessible model to study synaptic changes, they identified that a reduction in LBK1-AMPK levels or deletion of either LBK1 or AMPK led to age-related changes within retinal synapses of young mice (3–5 months) mirroring the one observed in old animals (24–30 months) (e.g. loss of synaptic connections within retinal layers

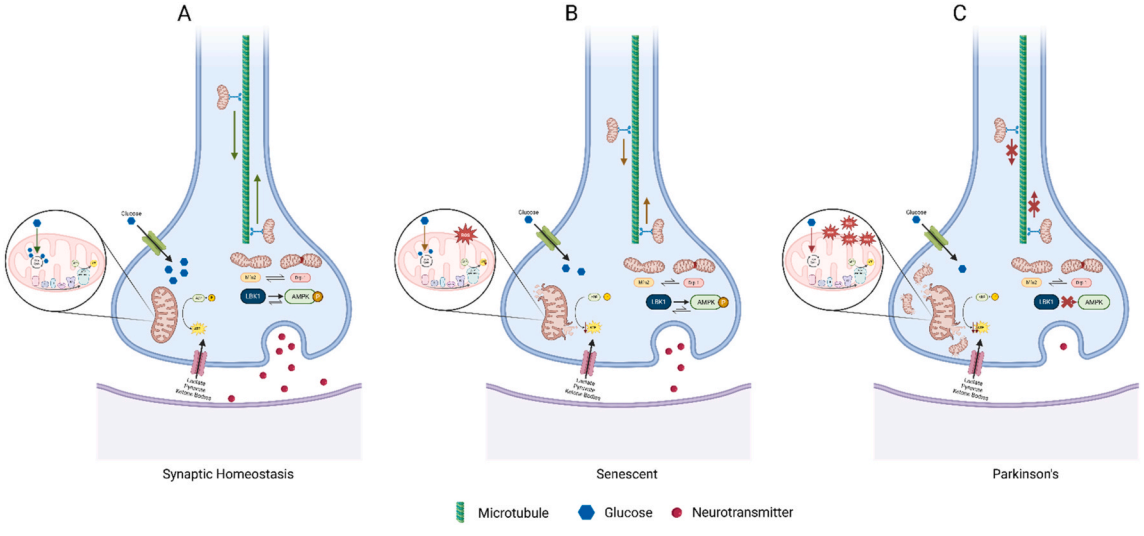

Fig. 3. Synaptic metabolism in (A) Physiological synaptic homeostasis, (B) Senescent synapses and (C) Parkinson's synapses. Created with BioRender.com. (A) Synaptic energy requirements are fulfilled by ATP production through mitochondrial OXPHOS. Constant substrate supply of glucose, pyruvate, lactate and ketone bodies through GLUT3 and MCT2 guarantee the energy homeostasis needed to support synaptic function. Equally, MIRO mediated mitochondrial transport at the synapse and an equilibrium between mitochondrial fusion and fission provide enough mitochondria to the synapse to match the functional demand. (B) During ageing, these processes are disrupted, with an increased number of dysfunctional mitochondria (with reduced ATP production capability and increased ROS production), due to reduced MIRO mediated mitochondrial transport and disrupted fusion-fission balance. Reduction of glucose metabolism affects the LBK1-AMPK pathway, which is dependent on ATP as well, which promotes synaptic pruning. (C) In Parkinson's Disease all these mechanisms are exacerbated to the extreme, leading to severe loss of synaptic function.

and synaptic pruning). Samuel et al. (2014) hypothesised that with age LKB1 protein levels decrease, reducing the ability to activate AMPK. Another hypothesis is that age-related metabolic decline, with consequent reduction in ATP levels, may limit the ability of AMPK to serve as a substrate for LBK1 (Samuel et al., 2014). To this end, experiments showed that caloric restriction led to a 50 % improvement in synaptic functions implying that other molecules might also be involved in the modulation of the LBK1-AMPK pathway. Thus, the literature suggests that both metformin and caloric restriction are able to interact with the LBK1-AMPK pathway, implying both hypotheses are true but not fully explaining the pathway. More work to further elucidate this pathway is required.

Studies carried out by Hang et al. (2019; 2021) found disruption in the AMPK pathway in different models of PD, suggesting that the AMPK pathway and its interaction with mitochondrial metabolism may be a key component of PD pathogenesis, but the mechanism can be partially reversed with pharmacological interventions targeting AMPK (e.g. metformin) (Hang et al., 2019, 2021).

Similarly to metformin, glucagon-like peptide 1 (GLP-1) receptor agonists, newly developed drugs for T2D, have been shown to be neuroprotective and to modulate synaptic transmission, affecting both excitatory and inhibitory pathways (Nowell et al., 2023; Zheng et al., 2024).

From these studies it can be concluded that energy homeostasis and neuronal functions are strictly related. However, a “one size fits all” approach with all the mechanisms that govern metabolite balance in the CNS will never be feasible. On the other hand, utilising a spatio-temporal approach looking at metabolic changes throughout time may help to identify pathway changes in a timely manner, before they lead to a pathological cascade.

5. Conclusion

Synapses are vitally important structures providing an interface via which neuronal communication can occur. This communication is electrochemical in nature, and neurotransmission and propagating electrical activity are fundamental to this process. However, to condense synapses to just ion channels and neurotransmitter containing vesicles is far too reductive. In this review we have covered key processes normally associated with wholesale cellular function, but which have specific and critical roles in the normal function of the synapse.

Despite these processes often being regarded as separate in nature to synaptic communication, here we have highlighted how autophagy, calcium homeostasis, and mitochondria directly impact synaptic function, and provide an important level of control to neuronal communication. As synapses hold such a complex and intricate role in animal physiology, it is of little wonder that multiple pathways exist to dictate the intricate control of their activity, plasticity, and signal integration.

These synaptic tasks drive key functions from movement to speech and cognition. Therefore, dysfunction of pathways such as autophagy, which contribute to synaptic function, will affect the ability to execute fundamental tasks. Our review has focused on the ageing synapse, and this review highlights direct evidence to show that the impact of age on processes at the synapse are the culprit.

Each of these processes can impact one another, perpetuating the decline of the synapse and accelerating the deterioration of processes like cognition. For instance, reduction of inhibitory transmission via loss of inhibitory synapses could result in knock-on overexcitation of neurones downstream of excitatory neurones. As excitatory neurones use more energy (Harris et al., 2012), this could further stress dysfunctional mitochondria present within synapses on these neurones. Furthermore, increased activity on downstream synapses could also impede plasticity of smaller synapses via aberrant pLIMK activity present in aged neurones and in smaller synapses. Thus, alterations to specific neuro-architecture can have an effect on mitochondrial function at the synapse, exacerbating the deficits caused by either alone. This is one potential example of the damaging ‘synergistic’ effect which could be possible with synaptic processes, although more have been described throughout the course of the review.

The exacerbation of synaptic dysfunction and the resultant clinical phenotypes have also been described here in the context of PD. PD represents a disorder intrinsically linked with age and which has been shown to have a profound and robust, early and persisting, synaptic dysfunction phenotype. Here we have described how PD affects pathways known to be impacted by age, and which are important for synaptic function. PD, and neurodegenerative disorders at large, are therefore assisted by an improved understanding of the processes which affect synaptic function, and which are perturbed in ageing. Here we have highlighted key targets and pathways which have either been, are being, or should be of interest to investigate moving forwards.

As a note, we do not claim that our work here has covered all functions which impact synaptic pathways. The formation of tripartite synapses with astrocytes, for instance, has not been covered. Those that have not been covered here have not been done so as they were either not internal processes within the neuronal synapse and thus deemed outside the scope of the current review, or research on the effects of ageing and/or ageing related diseases with regards to those topics was lacking, and thus information was sparse.

As a priority moving forwards, synaptic function must be researched in the context of all processes which affect its fundamental task of communication. Without such a holistic approach, we as a community risk missing critical pieces of information, and possible points of intervention for disorders related to age. As illustrated in our review, the impact of processes “outside the normal scope” of synaptic function are critical to assess, and represent a novel way to look at ageing in the synapse.

CRediT author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was funded by the UK Research Institute Future Leader Fellowship (UKRI FLF) (MR/T041129/1), Parkinson’s UK, and the Moondance Foundation, as part of the Moondance Dementia Research Laboratory. Shahzabe Mukhtar and Shikha Kataria were supported by Parkinson’s UK, and Gloria Cimaglia by the Moondance Foundation. All authors were supported by the UKRI FLF.

Data availability

No data was used for the research described in the article.

References

Alberini, C.M., 2009. Transcription factors in long-term memory and synaptic plasticity. Physiol. Rev. 89 (1), 121–145. https://doi.org/10.1152/physrev.00017.2008.

Alegre-Abarrategui, J., Christian, H., Lufino, M.M.P., et al., 2009. LRRK2 regulates autophagic activity and localizes to specific membrane microdomains in a novel human genomic reporter cellular model. Hum. Mol. Genet. 18 (21), 4022–4034. https://doi.org/10.1093/hmg/ddp346.

Andersson, D.C., Betzenhauser, M.J., Reiken, S., et al., 2011. Ryanodine receptor oxidation causes intracellular calcium leak and muscle weakness in aging. Cell Metab. 14 (2), 196–207. https://doi.org/10.1016/j.cmet.2011.05.014.

Azam, S., Haque, M.E., Balakrishnan, R., Kim, I.S., Choi, D.K., 2021. The ageing brain: molecular and cellular basis of neurodegeneration. Front. Cell Dev. Biol. 9, 683459. https://doi.org/10.3389/fcell.2021.683459.

Bademosi, A.T., Decet, M., Kuenen, S., et al., 2023. EndophilinA-dependent coupling between activity-induced calcium influx and synaptic autophagy is disrupted by a Parkinson-risk mutation. Neuron 111 (9), 1402–1422.e13. https://doi.org/10.1016/j.neuron.2023.02.001.

Bahar, E., Kim, H., Yoon, H., 2016. ER stress-mediated signaling: action potential and Ca (2+) as key players. Int. J. Mol. Sci. 17 (9), 1558. https://doi.org/10.3390/ijms17091558.

Bai, L., Hof, P.R., Standaert, D.G., et al., 2004. Changes in the expression of the NR2B subunit during aging in macaque monkeys. Neurobiol. Aging 25 (2), 201–208. https://doi.org/10.1016/S0197-4580(03)00091-5.

Baranov, S.V., Baranova, O.V., Yablonska, S., et al., 2019. Mitochondria modulate programmed neuritic retraction. Proc. Natl. Acad. Sci. USA 116 (2), 650–659. https://doi.org/10.1073/pnas.1811021116.

Baranov, S.V., Jauhari, A., Carlisle, D.L., Friedlander, R.M., 2021. Two hit mitochondrial-driven model of synapse loss in neurodegeneration. Neurobiol. Dis. 158, 105451. https://doi.org/10.1016/j.nbd.2021.105451.

Barria, A., Malinow, R., 2005. NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. Neuron 48 (2), 289–301. https://doi.org/10.1016/j.neuron.2005.08.034.

Bear, M.F., Cooper, L.N., Ebner, F.F., 1987. A physiological basis for a theory of synapse modification. Science 237 (4810), 42–48. https://doi.org/10.1126/science.3037696.

Beattie, E.C., Carroll, R.C., Yu, X., et al., 2000. Regulation of AMPA receptor endocytosis by a signaling mechanism shared with LTD. Nat. Neurosci. 3 (12), 1291–1300. https://doi.org/10.1038/81823.

Beccano-Kelly, D.A., Kuhlmann, N., Tatarnikov, I., et al., 2014. Synaptic function is modulated by LRRK2 and glutamate release is increased in cortical neurons of G2019S LRRK2 knock-in mice. Front. Cell. Neurosci. 8. https://www.frontiersin.org/articles/10.3389/fncel.2014.00301. (Accessed 8 January 2023).

Beccano-Kelly, D.A., Cherubini, M., Mousba, Y., et al., 2023. Calcium dysregulation combined with mitochondrial failure and electrophysiological maturity converge in Parkinson's iPSC-dopamine neurons. iScience 26 (7), 107044. https://doi.org/10.1016/j.isci.2023.107044.

Benkert, J., Hess, S., Roy, S., et al., 2019. Cav2.3 channels contribute to dopaminergic neuron loss in a model of Parkinson's disease. Nat. Commun. 10 (1), 5094. https://doi.org/10.1038/s41467-019-12834-x.

Bereiter-Hahn, J., 2014. Chapter four - mitochondrial dynamics in aging and disease. In: Osiewacz, H.D. (Ed.), Progress in Molecular Biology and Translational Science, 127. The Mitochondrion in Aging and Disease. Academic Press, pp. 93–131. https://doi.org/10.1016/B978-0-12-394625-6.00004-0.

Betzer, C., Lassen, L.B., Olsen, A., et al., 2018. Alpha-synuclein aggregates activate calcium pump SERCA leading to calcium dysregulation. EMBO Rep. 19 (5), e44617. https://doi.org/10.15252/embr.201744617.

Bi, G.Q., Poo, M.M., 1998. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. J. Neurosci. 18 (24), 10464–10472. https://doi.org/10.1523/JNEUROSCI.18-24-10464.1998.

Bilkei-Gorzo, A., 2012. The endocannabinoid system in normal and pathological brain ageing. Philos. Trans. R. Soc. Lond. B Biol. Sci. 367 (1607), 3326–3341. https://doi.org/10.1098/rstb.2011.0388.

Błaszczyk, J.W., 2020. Energy metabolism decline in the aging brain-pathogenesis of neurodegenerative disorders. Metabolites 10 (11), 450. https://doi.org/10.3390/metabo10110450.

Bliss, T.V., Lomo, T., 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J. Physiol. 232 (2), 331–356. https://doi.org/10.1113/jphysiol.1973.sp010273.

Bonello, F., Hassoun, S.M., Mouton-Liger, F., et al., 2019. LRRK2 impairs PINK1/Parkin-dependent mitophagy via its kinase activity: pathologic insights into Parkinson's disease. Hum. Mol. Genet. 28 (10), 1645–1660. https://doi.org/10.1093/hmg/ddz004.

Boveris, A., Navarro, A., 2008. Brain mitochondrial dysfunction in aging. IUBMB Life 60 (5), 308–314. https://doi.org/10.1002/iub.46.

Bowling, A.C., Mutisya, E.M., Walker, L.C., Price, D.L., Cork, L.C., Beal, M.F., 1993. Age-dependent impairment of mitochondrial function in primate brain. J. Neurochem. 60 (5), 1964–1967. https://doi.org/10.1111/j.1471-4159.1993.tb13430.x.

Brown, M.R., Sullivan, P.G., Geddes, J.W., 2006. Synaptic mitochondria are more susceptible to Ca2+Overload than nonsynaptic mitochondria. J. Biol. Chem. 281 (17), 11658–11668. https://doi.org/10.1074/jbc.M510303200.

Burke, R.E., O'Malley, K., 2013. Axon degeneration in parkinson's disease. Exp. Neurol. 246, 72–83. https://doi.org/10.1016/j.expneurol.2012.01.011.

Burrinha, T., Cunha, C., Hall, M.J., Lopes-da-Silva, M., Seabra, M.C., Guimas Almeida, C., 2023. Deacidification of endolysosomes by neuronal aging drives synapse loss. Traffic 24 (8), 334–354. https://doi.org/10.1111/tra.12889.

Cai, Q., Ganesan, D., 2022. Regulation of neuronal autophagy and the implications in neurodegenerative diseases. Neurobiol. Dis. 162, 105582. https://doi.org/10.1016/j.nbd.2021.105582.

Caillard, O., Moreno, H., Schwaller, B., Llano, I., Celio, M.R., Marty, A., 2000. Role of the calcium-binding protein parvalbumin in short-term synaptic plasticity. Proc. Natl. Acad. Sci. U. S. A. 97 (24), 13372–13377. https://doi.org/10.1073/pnas.230362997.

Calvo-Rodríguez, M., García-Durillo, M., Villalobos, C., Núñez, L., 2016. *In Vitro* aging promotes endoplasmic reticulum (ER)-Mitochondria Ca2 + cross talk and loss of store-operated Ca2 + entry (SOCE) in rat hippocampal neurons. Biochim. Biophys. Acta Mol. Cell Res. 1863 (11), 2637–2649. https://doi.org/10.1016/j.bbamcr.2016.08.001.

Camandola, S., Mattson, M.P., 2017. Brain metabolism in health, aging, and neurodegeneration. EMBO J. 36 (11), 1474–1492. https://doi.org/10.15252/embj.201695810.

Carrion, M.D.P., Marsicano, S., Daniele, F., et al., 2017. The LRRK2 G2385R variant is a partial loss-of-function mutation that affects synaptic vesicle trafficking through altered protein interactions. Sci. Rep. 7 (1), 5377. https://doi.org/10.1038/s41598-017-05760-9.

Cataldi, M., 2013. The changing landscape of voltage-gated calcium channels in neurovascular disorders and in neurodegenerative diseases. Curr. Neuropharmacol. 11 (3), 276–297. https://doi.org/10.2174/1570159X11311030004.

Cataldi, S., Follett, J., Fox, J.D., et al., 2018. Altered dopamine release and monoamine transporters in Vps35 p.D620N knock-in mice. npj Parkinson's Dis. 4 (1), 1–11. https://doi.org/10.1038/s41531-018-0063-3.

Catterall, W.A., Perez-Reyes, E., Snutch, T.P., Striessnig, J., 2005. International union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol. Rev. 57 (4), 411–425. https://doi.org/10.1124/pr.57.4.5.

Catterall, W.A., Leal, K., Nanou, E., 2013. Calcium channels and short-term synaptic plasticity. J. Biol. Chem. 288 (15), 10742–10749. https://doi.org/10.1074/jbc.R112.411645.

Chen, W.B., Chen, J., Liu, Z.Y., Luo, B., Zhou, T., Fei, E.K., 2020. Metformin enhances excitatory synaptic transmission onto hippocampal CA1 pyramidal neurons. Brain Sci. 10 (10), 706. https://doi.org/10.3390/brainsci10100706.

Chistiakov, D.A., Sobenin, I.A., Revin, V.V., Orekhov, A.N., Bobryshev, Y.V., 2014. Mitochondrial aging and age-related dysfunction of Mitochondria. BioMed Res. Int. 2014, 238463. https://doi.org/10.1155/2014/238463.

Cicali, K.A., Tapia-Rojas, C., 2024. Synaptic mitochondria: a crucial factor in the aged hippocampus. Ageing Res. Rev. 101, 102524. https://doi.org/10.1016/j.arr.2024.102524.

Cirnaru, M.D., Marte, A., Belluzzi, E., et al., 2014. LRRK2 kinase activity regulates synaptic vesicle trafficking and neurotransmitter release through modulation of LRRK2 macro-molecular complex. Front. Mol. Neurosci. 7. https://doi.org/10.3389/fnmol.2014.00049.

Citri, A., Malenka, R.C., 2008. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacol 33 (1), 18–41. https://doi.org/10.1038/sj.npp.1301559.

Collingridge, G.L., Kehl, S.J., McLennan, H., 1983. Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. J. Physiol. 334 (1), 33–46. https://doi.org/10.1113/jphysiol.1983.sp014478.

Covarrubias, A.J., Perrone, R., Grozio, A., Verdin, E., 2021. NAD+ metabolism and its roles in cellular processes during ageing. Nat. Rev. Mol. Cell Biol. 22 (2), 119–141. https://doi.org/10.1038/s41580-020-00313-x.

Cuervo, A.M., Stefanis, L., Fredenburg, R., Lansbury, P.T., Sulzer, D., 2004. Impaired degradation of mutant α-Synuclein by chaperone-mediated autophagy. Science 305 (5688), 1292–1295. https://doi.org/10.1126/science.1101738.

Cunnane, S.C., Trushina, E., Morland, C., et al., 2020. Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. Nat. Rev. Drug Discov. 19 (9), 609–633. https://doi.org/10.1038/s41573-020-0072-x.

Davare, M.A., Hell, J.W., 2003. Increased phosphorylation of the neuronal L-type Ca(2+) channel Ca(v)1.2 during aging. Proc. Natl. Acad. Sci. USA. 100 (26), 16018–16023. https://doi.org/10.1073/pnas.2236970100.

de Leon, M.J., Ferris, S.H., George, A.E., et al., 1983. Positron emission tomographic studies of aging and Alzheimer disease. AJNR Am. J. Neuroradiol. 4 (3), 568–571.

De Risi, M., Torromino, G., Tufano, M., et al., 2020. Mechanisms by which autophagy regulates memory capacity in ageing. Aging Cell 19 (9), e13189. https://doi.org/10.1111/acel.13189.

Decet, M., Soukup, S.F., 2024. Endophilin-A/SH3GL2 calcium switch for synaptic autophagy induction is impaired by a Parkinson's risk variant. Autophagy 20 (4), 925–927. https://doi.org/10.1080/15548627.2023.2200627.

Deng, H., Wang, P., Jankovic, J., 2018. The genetics of Parkinson disease. Ageing Res. Rev. 42, 72–85. https://doi.org/10.1016/j.arr.2017.12.007.

Deng, Z., Zhou, X., Lu, J.H., Yue, Z., 2021. Autophagy deficiency in neurodevelopmental disorders. Cell Biosci. 11 (1), 214. https://doi.org/10.1186/s13578-021-00726-x.

Devine, M.J., Kittler, J.T., 2018. Mitochondria at the neuronal presynapse in health and disease. Nat. Rev. Neurosci. 19 (2), 63–80. https://doi.org/10.1038/nrn.2017.170.

Devine, M.J., Birsa, N., Kittler, J.T., 2016. Miro sculpts mitochondrial dynamics in neuronal health and disease. Neurobiol. Dis. 90, 27–34. https://doi.org/10.1016/j.nbd.2015.12.008.

Ding, F., Yao, J., Rettberg, J.R., Chen, S., Brinton, R.D., 2013. Early decline in glucose transport and metabolism precedes shift to ketogenic system in female aging and Alzheimer's mouse brain: implication for bioenergetic intervention. PLoS One 8 (11), e79977. https://doi.org/10.1371/journal.pone.0079977.

Ding, J., Ji, J., Rabow, Z., et al., 2021. A metabolome atlas of the aging mouse brain. Nat. Commun. 12 (1), 6021. https://doi.org/10.1038/s41467-021-26310-y.

Duarte, F.V., Ciampi, D., Duarte, C.B., 2023. Mitochondria as central hubs in synaptic modulation. Cell. Mol. Life Sci. 80 (6), 173. https://doi.org/10.1007/s00018-023-04814-8.

Dunn, L., Allen, G.F.G., Mamais, A., et al., 2014. Dysregulation of glucose metabolism is an early event in sporadic Parkinson's disease. Neurobiol. Aging 35 (5), 1111–1115. https://doi.org/10.1016/j.neurobiolaging.2013.11.001.

Dutta, S.B., Linneweber, G.A., Andriatsilavo, M., Hiesinger, P.R., Hassan, B.A., 2023. EGFR-dependent suppression of synaptic autophagy is required for neuronal circuit development. Curr. Biol. 33 (3), 517–532.e5. https://doi.org/10.1016/j.cub.2022.12.039.

Eckles-Smith, K., Clayton, D., Bickford, P., Browning, M.D., 2000. Caloric restriction prevents age-related deficits in LTP and in NMDA receptor expression. Brain Res. Mol. Brain Res. 78 (1–2), 154–162. https://doi.org/10.1016/s0169-328x(00)00088-7.

Feng, Y., He, D., Yao, Z., Klionsky, D.J., 2014. The machinery of macroautophagy. Cell Res. 24 (1), 24–41. https://doi.org/10.1038/cr.2013.168.

Fernandes de Almeida, M., Kinsey, S., Bahr, B., 2022. Stimulation of autophagy and synaptic maintenance are commonalities induced by an exercise-mimetic and diet supplement to avoid initiators of age-related cognitive decline. FASEB J. 36. https://doi.org/10.1096/fasebj.2022.36.S1.R2596.

Fernández-Suárez, D., Celorrio, M., Lanciego, J.L., Franco, R., Aymerich, M.S., 2012. Loss of parvalbumin-positive neurons from the globus pallidus in animal models of Parkinson disease. J. Neuropathol. Exp. Neurol. 71 (11), 973–982. https://doi.org/10.1097/NEN.0b013e3182717cba.

Follett, J., Darlow, B., Wong, M.B., Goodwin, J., Pountney, D.L., 2013. Potassium depolarization and raised calcium induces α-synuclein aggregates. Neurotox. Res. 23 (4), 378–392. https://doi.org/10.1007/s12640-012-9366-z.

Fontán-Lozano, Á., López-Lluch, G., Delgado-García, J.M., Navas, P., Carrión, Á.M., 2008. Molecular bases of caloric restriction regulation of neuronal synaptic plasticity. Mol. Neurobiol. 38 (2), 167–177. https://doi.org/10.1007/s12035-008-8040-1.

Fred Dice, J., 1990. Peptide sequences that target cytosolic proteins for lysosomal proteolysis. Trends Biochem. Sci. 15 (8), 305–309. https://doi.org/10.1016/0968-0004(90)90019-8.

Friedman, L.G., Lachenmayer, M.L., Wang, J., et al., 2012. Disrupted autophagy leads to dopaminergic axon and dendrite degeneration and promotes presynaptic accumulation of α-synuclein and LRRK2 in the brain. J. Neurosci. 32 (22), 7585–7593. https://doi.org/10.1523/JNEUROSCI.5809-11.2012.

Gage, F.H., Kelly, P.A., Bjorklund, A., 1984. Regional changes in brain glucose metabolism reflect cognitive impairments in aged rats. J. Neurosci. 4 (11), 2856–2865. https://doi.org/10.1523/JNEUROSCI.04-11-02856.1984.

Gazzaley, A.H., Siegel, S.J., Kordower, J.H., Mufson, E.J., Morrison, J.H., 1996. Circuit-specific alterations of N-methyl-D-aspartate receptor subunit 1 in the dentate gyrus of aged monkeys. Proc. Natl. Acad. Sci. 93 (7), 3121–3125. https://doi.org/10.1073/pnas.93.7.3121.

Gegg, M.E., Verona, G., Schapira, A.H.V., 2020. Glucocerebrosidase deficiency promotes release of α-synuclein fibrils from cultured neurons. Hum. Mol. Genet. 29 (10), 1716–1728. https://doi.org/10.1093/hmg/ddaa085.

Giménez-Llort, L., Masino, S.A., Diao, L., et al., 2005. Mice lacking the adenosine A1 receptor have normal spatial learning and plasticity in the CA1 region of the hippocampus, but they habituate more slowly. Synapse 57 (1), 8–16. https://doi.org/10.1002/syn.20146.

Glatigny, M., Moriceau, S., Rivagorda, M., et al., 2019. Autophagy is required for memory formation and reverses age-related memory decline. Curr. Biol. 29 (3), 435–448.e8. https://doi.org/10.1016/j.cub.2018.12.021.

Gleichmann, M., Mattson, M.P., 2011. Neuronal calcium homeostasis and dysregulation. Antioxidants Redox Signal. 14 (7), 1261–1273. https://doi.org/10.1089/ars.2010.3386.

Gustafsson, B., Wigström, H., Abraham, W.C., Huang, Y.Y., 1987. Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials. J. Neurosci. 7 (3), 774–780. https://doi.org/10.1523/JNEUROSCI.07-03-00774.1987.

Guzman, J.N., Sánchez-Padilla, J., Chan, C.S., Surmeier, D.J., 2009. Robust pacemaking in substantia nigra dopaminergic neurons. J. Neurosci. 29 (35), 11011–11019. https://doi.org/10.1523/JNEUROSCI.2519-09.2009.

Hang, L., Thundyil, J., Goh, G.W.Y., Lim, K.L., 2019. AMP kinase activation is selectively disrupted in the ventral midbrain of mice deficient in parkin or PINK1 expression. Neuromol. Med. 21 (1), 25–32. https://doi.org/10.1007/s12017-018-8517-7.

Hang, L., Wang, Z., Foo, A.S.C., et al., 2021. Conditional disruption of AMP kinase in dopaminergic neurons promotes Parkinson's disease-associated phenotypes in vivo. Neurobiol. Dis. 161, 105560. https://doi.org/10.1016/j.nbd.2021.105560.

Harris, J.J., Jolivet, R., Attwell, D., 2012. Synaptic energy use and supply. Neuron 75 (5), 762–777. https://doi.org/10.1016/j.neuron.2012.08.019.

Hayashi, Y., Shi, S.H., Esteban, J.A., Piccini, A., Poncer, J.C., Malinow, R., 2000. Driving AMPA receptors into synapses by LTP and CaMKII: requirement for GluR1 and PDZ domain interaction. Science 287 (5461), 2262–2267. https://doi.org/10.1126/science.287.5461.2262.

He, LQ, Lu, JH, Yue, ZY, 2013. Autophagy in ageing and ageing-associated diseases. Acta Pharmacol. Sin. 34 (5), 605–611. https://doi.org/10.1038/aps.2012.188.

Henrich, M.T., Oertel, W.H., Surmeier, D.J., Geibl, F.F., 2023. Mitochondrial dysfunction in Parkinson's disease – a key disease hallmark with therapeutic potential. Mol. Neurodegener. 18 (1), 83. https://doi.org/10.1186/s13024-023-00676-7.

Henstridge, C.M., Pickett, E., Spires-Jones, T.L., 2016. Synaptic pathology: a shared mechanism in neurological disease. Ageing Res. Rev. 28, 72–84. https://doi.org/10.1016/j.arr.2016.04.005.

Hernandez, D., Torres, C.A., Setlik, W., et al., 2012. Regulation of presynaptic neurotransmission by macroautophagy. Neuron 74 (2), 277–284. https://doi.org/10.1016/j.neuron.2012.02.020.

Ho, D.H., Je, A.R., Lee, H., et al., 2018. LRRK2 kinase activity induces mitochondrial fission in microglia via Drp1 and modulates neuroinflammation. Experimental Neurobiol. 27 (3), 171–180. https://doi.org/10.5607/en.2018.27.3.171.

Hof, P.R., Duan, H., Page, T.L., et al., 2002. Age-related changes in GluR2 and NMDAR1 glutamate receptor subunit protein immunoreactivity in corticocortically projecting neurons in macaque and patas monkeys. Brain Res. 928 (1), 175–186. https://doi.org/10.1016/S0006-8993(01)03345-5.

Hoffmann, S., Orlando, M., Andrzejak, E., et al., 2019. Light-activated ROS production induces synaptic autophagy. J. Neurosci. 39 (12), 2163–2183. https://doi.org/10.1523/JNEUROSCI.1317-18.2019.

Hollenstein, D.M., Kraft, C., 2020. Autophagosomes are formed at a distinct cellular structure. Curr. Opin. Cell Biol. 65, 50–57. https://doi.org/10.1016/j.ceb.2020.02.012.

Hou, Y., Dan, X., Babbar, M., et al., 2019. Ageing as a risk factor for neurodegenerative disease. Nat. Rev. Neurol. 15 (10), 565–581. https://doi.org/10.1038/s41582-019-0244-7.

Hsieh, C.H., Shaltouki, A., Gonzalez, A.E., et al., 2016. Functional impairment in miro degradation and mitophagy is a shared feature in familial and sporadic parkinson's disease. Cell Stem Cell 19 (6), 709–724. https://doi.org/10.1016/j.stem.2016.08.002.

Hsieh, C.H., Li, L., Vanhauwaert, R., et al., 2019. Miro1 marks Parkinson's disease subset and Miro1 reducer rescues neuron loss in parkinson's models. Cell Metab. 30 (6), 1131–1140.e7. https://doi.org/10.1016/j.cmet.2019.08.023.

Hsu, K.S., Huang, C.C., Liang, Y.C., et al., 2002. Alterations in the balance of protein kinase and phosphatase activities and age-related impairments of synaptic transmission and long-term potentiation - PubMed. Hippocampus 12 (6), 787–802. https://doi.org/10.1002/hipo.10032.

Hurley, M.J., Brandon, B., Gentleman, S.M., Dexter, D.T., 2013. Parkinson's disease is associated with altered expression of CaV1 channels and calcium-binding proteins. Brain 136 (7), 2077–2097. https://doi.org/10.1093/brain/awt134.

Hussein, A., Tielemans, A., Baxter, M.G., Benson, D.L., Huntley, G.W., 2022. Cognitive deficits and altered cholinergic innervation in young adult male mice carrying a Parkinson's disease *Lrrk2*G2019S knockin mutation. Exp. Neurol. 355, 114145. https://doi.org/10.1016/j.expneurol.2022.114145.

Iacopino, A.M., Christakos, S., 1990. Specific reduction of calcium-binding protein (28-kilodalton calbindin-D) gene expression in aging and neurodegenerative diseases. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 87, p. 11. https://doi.org/10.1073/pnas.87.11.4078. United States.

Inoue, K.I., Miyachi, S., Nishi, K., et al., 2019. Recruitment of calbindin into nigral dopamine neurons protects against MPTP-induced parkinsonism. Mov. Disord. 34 (2), 200–209. https://doi.org/10.1002/mds.107.

Ito, H., Goto, S., Sakamoto, S., Hirano, A., 1992. Calbindin-D28K in the basal ganglia of patients with parkinsonism. Ann. Neurol. 32 (4), 543–550. https://doi.org/10.1002/ana.410320410.

Kandel, E.R., Tauc, L., 1965. Heterosynaptic facilitation in neurones of the abdominal ganglion of Aplysia depilans. J. Physiol. 181 (1), 1–27.

Katila, N., Bhurtel, S., Shadfar, S., et al., 2017. Metformin lowers α-synuclein phosphorylation and upregulates neurotrophic factor in the MPTP mouse model of Parkinson's disease. Neuropharmacology 125, 396–407. https://doi.org/10.1016/j.neuropharm.2017.08.015.

Katila, N., Bhurtel, S., Park, P.H., Hong, J.T., Choi, D.Y., 2020. Activation of AMPK/aPKCζ/CREB pathway by metformin is associated with upregulation of GDNF and dopamine. Biochem. Pharmacol. 180, 114193. https://doi.org/10.1016/j.bcp.2020.114193.

Kauer, J.A., Malenka, R.C., Nicoll, R.A., 1988. A persistent postsynaptic modification mediates long-term potentiation in the hippocampus. Neuron 1 (10), 911–917. https://doi.org/10.1016/0896-6273(88)90148-1.

Kaushik, S., Cuervo, A.M., 2018. The coming of age of chaperone-mediated autophagy. Nat. Rev. Mol. Cell Biol. 19 (6), 365–381. https://doi.org/10.1038/s41580-018-0001-6.

Kawamoto, E.M., Vivar, C., Camandola, S., 2012. Physiology and pathology of calcium signaling in the brain. Front. Pharmacol. 3, 61. https://doi.org/10.3389/fphar.2012.00061.

Kesidou, E., Theotokis, P., Damianidou, O., et al., 2023. CNS ageing in health and neurodegenerative disorders. J. Clin. Med. 12 (6), 2255. https://doi.org/10.3390/jcm12062255.

Kumar, A., 2011. Long-term potentiation at CA3-CA1 hippocampal synapses with special emphasis on aging, disease, and stress. Front. Aging Neurosci. 3, 7. https://doi.org/10.3389/fnagi.2011.00007.

Kumar, A., 2015. NMDA receptor function during senescence: implication on cognitive performance. Front. Neurosci. 9. https://doi.org/10.3389/fnins.2015.00473.

Kumar, A., Thinschmidt, J.S., Foster, T.C., King, M.A., 2007. Aging effects on the limits and stability of long-term synaptic potentiation and depression in rat hippocampal area CA1. J. Neurophysiol. 98 (2), 594–601. https://doi.org/10.1152/jn.00249.2007.

Lautrup, S., Sinclair, D.A., Mattson, M.P., Fang, E.F., 2019. NAD+ in brain aging and neurodegenerative disorders. Cell Metab. 30 (4), 630–655. https://doi.org/10.1016/j.cmet.2019.09.001.

Lee, I.H., Cao, L., Mostoslavsky, R., et al., 2008. A role for the NAD-Dependent deacetylase Sirt1 in the regulation of autophagy. Proc. Natl. Acad. Sci. U. S. A. 105 (9), 3374–3379. https://doi.org/10.1073/pnas.0712145105.

Lee, H.K., Takamiya, K., He, K., Song, L., Huganir, R.L., 2010. Specific roles of AMPA receptor subunit GluR1 (GluA1) phosphorylation sites in regulating synaptic plasticity in the CA1 region of Hippocampus. J. Neurophysiol. 103 (1), 479–489. https://doi.org/10.1152/jn.00835.2009.

Levitan, I., Fang, Y., Rosenhouse-Dantsker, A., Romanenko, V., 2010. Cholesterol and ion channels. Subcell. Biochem. 51, 509–549. https://doi.org/10.1007/978-90-481-8622-8_19.

Lewis, M.M., Mailman, R.B., Cheng, X.V., et al., 2025. Clinical progression of Parkinson's disease in the early 21st century: insights from the accelerating medicine partnership (AMP-PD) data. Park. Relat. Disord. 130, 107186. https://doi.org/10.1016/j.parkreldis.2024.107186.

Li, S., Sheng, Z.H., 2022. Energy matters: presynaptic metabolism and the maintenance of synaptic transmission. Nat. Rev. Neurosci. 23 (1), 4–22. https://doi.org/10.1038/s41583-021-00535-8.

Li, Y., Yu, H., Chen, C., et al., 2020. Proteomic profile of mouse brain aging contributions to mitochondrial dysfunction, DNA oxidative damage, loss of neurotrophic factor, and synaptic and ribosomal proteins. Oxid. Med. Cell. Longev. 2020, 5408452. https://doi.org/10.1155/2020/5408452.

Li, Y., Yang, H., He, T., Zhang, L., Liu, C., 2022a. Post-Translational modification of Cav1.2 and its role in neurodegenerative diseases. Front. Pharmacol. 12, 775087. https://doi.org/10.3389/fphar.2021.775087.

Li, N., Zhou, T., Fei, E., 2022b. Actions of metformin in the brain: a new perspective of metformin treatments in related neurological disorders. Int. J. Mol. Sci. 23 (15), 8281. https://doi.org/10.3390/ijms23158281.

Liénard, C., Pintart, A., Bomont, P., 2024. Neuronal autophagy: regulations and implications in health and disease. Cells 13 (1), 103. https://doi.org/10.3390/cells13010103.

Lisman, J., Yasuda, R., Raghavachari, S., 2012. Mechanisms of CaMKII action in long-term potentiation. Nat. Rev. Neurosci. 13 (3), 169–182. https://doi.org/10.1038/nrn3192.

Luebke, J.I., Dunlap, K., Turner, T.J., 1993. Multiple calcium channel types control glutamatergic synaptic transmission in the hippocampus. Neuron 11 (5), 895–902. https://doi.org/10.1016/0896-6273(93)90119-C.

Lundbaek, J.A., Birn, P., Girshman, J., Hansen, A.J., Andersen, O.S., 1996. Membrane stiffness and channel function. Biochemistry 35 (12), 3825–3830. https://doi.org/10.1021/bi952250b.

Lüscher, C., Malenka, R.C., 2012. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). Cold Spring Harbor Perspect. Biol. 4 (6), a005710. https://doi.org/10.1101/cshperspect.a005710.

Lynch-Day, M.A., Mao, K., Wang, K., Zhao, M., Klionsky, D.J., 2012. The role of autophagy in parkinson's disease. Cold Spring Harb. Perspect. Med. 2 (4), a009357. https://doi.org/10.1101/cshperspect.a009357.

Mächler, P., Wyss, M.T., Elsayed, M., et al., 2015. In vivo evidence for a lactate gradient from astrocytes to neurons. Cell Metab. 23 (1), 94–102. https://doi.org/10.1016/j.cmet.2015.10.010.

Maday, S., Holzbaur, E.L.F., 2016. Compartment-specific regulation of autophagy in primary neurons. J. Neurosci. 36 (22), 5933–5945. https://doi.org/10.1523/JNEUROSCI.4401-15.2016.

Magnusson, K.R., 1995. Differential effects of aging on binding sites of the activated NMDA receptor complex in mice. Mech. Ageing Dev. 84 (3), 227–243. https://doi.org/10.1016/0047-6374(95)01658-9.

Magnusson, K.R., 2000. Declines in mRNA expression of different subunits may account for differential effects of aging on agonist and antagonist binding to the NMDA receptor. J. Neurosci. 20 (5), 1666–1674. https://doi.org/10.1523/JNEUROSCI.20-05-01666.2000.

Magnusson, K.R., Scanga, C., Wagner, A.E., Dunlop, C., 2000. Changes in anesthetic sensitivity and glutamate receptors in the aging canine brain. J. Gerontol.: Series A 55 (9), B448–B454. https://doi.org/10.1093/gerona/55.9.B448.

Magnusson, K.R., Nelson, S.E., Young, A.B., 2002. Age-related changes in the protein expression of subunits of the NMDA receptor. Mol. Brain Res. 99 (1), 40–45. https://doi.org/10.1016/S0169-328X(01)00344-8.

Magnusson, K.R., Brim, B.L., Das, S.R., 2010. Selective vulnerabilities of N-methyl-D-aspartate (NMDA) receptors during brain aging. Front. Aging Neurosci. 2, 11. https://doi.org/10.3389/fnagi.2010.00011.

Malenka, R.C., 1994. Synaptic plasticity in the hippocampus: LTP and LTD. Cell 78 (4), 535–538. https://doi.org/10.1016/0092-8674(94)90517-7.

Malhotra, K., Sathappa, M., Landin, J.S., Johnson, A.E., Alder, N.N., 2013. Structural changes in the mitochondrial Tim23 channel are coupled to the proton-motive force. Nat. Struct. Mol. Biol. 20 (8), 965–972. https://doi.org/10.1038/nsmb.2613.

Mancini, A., Mazzocchetti, P., Sciaccaluga, M., et al., 2020. From synaptic dysfunction to neuroprotective strategies in genetic parkinson's disease: lessons from LRRK2. Front. Cell. Neurosci. 14, 158. https://doi.org/10.3389/fncel.2020.00158.

Matikainen-Ankney, B.A., Kezunovic, N., Mesias, R.E., et al., 2016. Altered development of synapse structure and function in striatum caused by Parkinson's disease-linked LRRK2–G2019S mutation. J. Neurosci. 36 (27), 7128–7141. https://doi.org/10.1523/JNEUROSCI.3314-15.2016.

Matikainen-Ankney, B.A., Kezunovic, N., Menard, C., et al., 2018. Parkinson's disease-linked LRRK2-G2019S mutation alters synaptic plasticity and promotes resilience to chronic social stress in young adulthood. J. Neurosci. 38 (45), 9700–9711.

Matta, S., Van Kolen, K., da, Cunha R., et al., 2012. LRRK2 controls an EndoA phosphorylation cycle in synaptic endocytosis. Neuron 75 (6), 1008–1021. https://doi.org/10.1016/j.neuron.2012.08.022.

Mesches, M.H., Gemma, C., Veng, L.M., et al., 2004. Sulindac improves memory and increases NMDA receptor subunits in aged fischer 344 rats. Neurobiol. Aging 25 (3), 315–324. https://doi.org/10.1016/S0197-4580(03)00116-7.

Meunier, C.N.J., Callebert, J., Cancela, J.M., Fossier, P., 2015. Effect of dopaminergic D1 receptors on plasticity is dependent of serotoninergic 5-HT1A receptors in L5-Pyramidal neurons of the prefrontal cortex. PLoS One 10 (3), e0120286. https://doi.org/10.1371/journal.pone.0120286.

Moore, S.J., Murphy, G.G., 2020. The role of L-Type calcium channels in neuronal excitability and aging. Neurobiol. Learn. Mem. 173, 107230. https://doi.org/10.1016/j.nlm.2020.107230.

Mootha, V.K., Bunkenborg, J., Olsen, J.V., et al., 2003. Integrated analysis of protein composition, tissue diversity, and gene regulation in mouse mitochondria. Cell 115 (5), 629–640. https://doi.org/10.1016/s0092-8674(03)00926-7.

Moreno, H., Burghardt, N.S., Vela-Duarte, D., et al., 2012. The absence of the calcium-buffering protein calbindin is associated with faster age-related decline in hippocampal metabolism. Hippocampus 22 (5), 1107–1120. https://doi.org/10.1002/hipo.20957.

Morrison, J.H., Baxter, M.G., 2012. The ageing cortical synapse: hallmarks and implications for cognitive decline. Nat. Rev. Neurosci. 13 (4), 240–250. https://doi.org/10.1038/nrn3200.

Mulkey, R.M., Herron, C.E., Malenka, R.C., 1993. An essential role for protein phosphatases in hippocampal long-term depression. Science 261 (5124), 1051–1055. https://doi.org/10.1126/science.8394601.

Napoli, E., Panoutsopoulos, A.A., Kysar, P., et al., 2021. Wdfy3 regulates glycophagy, mitophagy, and synaptic plasticity. J. Cerebr. Blood Flow Metabol. 41 (12), 3213–3231. https://doi.org/10.1177/0271678X211027384.

Nath, S., Goodwin, J., Engelborghs, Y., Pountney, D.L., 2011. Raised calcium promotes α-synuclein aggregate formation. Mol. Cell. Neurosci. 46 (2), 516–526. https://doi.org/10.1016/j.mcn.2010.12.004.

Navarro-Romero, A., Fernandez-Gonzalez, I., Riera, J., et al., 2022. Lysosomal lipid alterations caused by glucocerebrosidase deficiency promote lysosomal dysfunction, chaperone-mediated-autophagy deficiency, and alpha-synuclein pathology. npj Parkinson's Dis. 8 (1), 1–15. https://doi.org/10.1038/s41531-022-00397-6.

Nguyen, M., Krainc, D., 2018. LRRK2 phosphorylation of auxilin mediates synaptic defects in dopaminergic neurons from patients with Parkinson's disease. Proc. Natl. Acad. Sci. 115 (21), 5576–5581. https://doi.org/10.1073/pnas.1717590115.

Nicolle, M.M., Baxter, M.G., 2003. Glutamate receptor binding in the frontal cortex and dorsal striatum of aged rats with impaired attentional set-shifting. Eur. J. Neurosci. 18 (12), 3335–3342. https://doi.org/10.1111/j.1460-9568.2003.03077.x.

Nikoletopoulou, V., Tavernarakis, N., 2012. Calcium homeostasis in aging neurons. Front. Genet. 3, 200. https://doi.org/10.3389/fgene.2012.00200.

Nikoletopoulou, V., Sidiropoulou, K., Kallergi, E., Dalezios, Y., Tavernarakis, N., 2017. Modulation of autophagy by BDNF underlies synaptic plasticity. Cell Metab. 26 (1), 230–242.e5. https://doi.org/10.1016/j.cmet.2017.06.005.

Norris, C.M., Korol, D.L., Foster, T.C., 1996. Increased susceptibility to induction of long-term depression and long-term potentiation reversal during aging. J. Neurosci. 16 (17), 5382–5392. https://doi.org/10.1523/JNEUROSCI.16-17-05382.1996.

Nowell, J., Blunt, E., Gupta, D., Edison, P., 2023. Antidiabetic agents as a novel treatment for Alzheimer's and Parkinson's disease. Ageing Res. Rev. 89, 101979. https://doi.org/10.1016/j.arr.2023.101979.

Okerlund, N.D., Schneider, K., Leal-Ortiz, S., et al., 2017. Bassoon controls presynaptic autophagy through Atg5. Neuron 93 (4), 897–913.e7. https://doi.org/10.1016/j.neuron.2017.01.026.

Ontl, T., Xing, Y., Bai, L., et al., 2004. Development and aging of *n*-methyl-d-aspartate receptor expression in the prefrontal/frontal cortex of mice. Neuroscience 123 (2), 467–479. https://doi.org/10.1016/j.neuroscience.2003.09.006.

Orenstein, S.J., Kuo, S.H., Tasset, I., et al., 2013. Interplay of LRRK2 with chaperone-mediated autophagy. Nat. Neurosci. 16 (4). https://doi.org/10.1038/nn.3350.

Overhoff, M., Tellkamp, F., Hess, S., et al., 2022. Autophagy regulates neuronal excitability by controlling cAMP/protein kinase A signaling at the synapse. EMBO J. 41 (22), e110963. https://doi.org/10.15252/embj.2022110963.

Owen, O.E., Morgan, A.P., Kemp, H.G., Sullivan, J.M., Herrera, M.G., Cahill, G.F., 1967. Brain metabolism during fasting. J. Clin. Investig. 46 (10), 1589–1595. https://doi.org/10.1172/JCI105650.

P, A., S, V., F, J.A., et al., 1997. Apoptosis and autophagy in nigral neurons of patients with Parkinson's disease. Histol. Histopathol. 12 (1). https://pubmed.ncbi.nlm.nih.gov/9046040/. (Accessed 18 September 2024).

Padamsey, Z., McGuinness, L., Bardo, S.J., et al., 2017. Activity-dependent exocytosis of lysosomes regulates the structural plasticity of dendritic spines. Neuron 93 (1), 132–146. https://doi.org/10.1016/j.neuron.2016.11.013.

Paillusson, S., Gomez-Suaga, P., Stoica, R., et al., 2017. α-Synuclein binds to the ER-mitochondria tethering protein VAPB to disrupt Ca2+ homeostasis and mitochondrial ATP production. Acta Neuropathol. 134 (1), 129–149. https://doi.org/10.1007/s00401-017-1704-z.

Palikaras, K., Tavernarakis, N., 2020. Regulation and roles of mitophagy at synapses. Mech. Ageing Dev. 187, 111216. https://doi.org/10.1016/j.mad.2020.111216.

Parisiadou, L., Yu, J., Sgobio, C., et al., 2014. LRRK2 regulates synaptogenesis and dopamine receptor activation through modulation of PKA activity. Nat. Neurosci. 17 (3), 367–376.

Pathak, D., Shields, L.Y., Mendelsohn, B.A., et al., 2015. The role of mitochondrially derived ATP in synaptic vesicle recycling. J. Biol. Chem. 290 (37), 22325–22336. https://doi.org/10.1074/jbc.M115.656405.

Petralia, R.S., Mattson, M.P., Yao, P.J., 2014. Communication breakdown: the impact of ageing on synapse structure. Ageing Res. Rev. 14, 31–42. https://doi.org/10.1016/j.arr.2014.01.003.

Pfanner, N., Warscheid, B., Wiedemann, N., 2019. Mitochondrial proteins: from biogenesis to functional networks. Nat. Rev. Mol. Cell Biol. 20 (5), 267–284. https://doi.org/10.1038/s41580-018-0092-0.

Plowey, E.D., Chu, C.T., 2011. Synaptic dysfunction in genetic models of parkinson's disease: a role for autophagy? Neurobiol. Dis. 43 (1), 60–67. https://doi.org/10.1016/j.nbd.2010.10.011.

Power, J.M., Wu, W.W., Sametsky, E., Oh, M.M., Disterhoft, J.F., 2002. Age-related enhancement of the slow outward calcium-activated potassium current in

hippocampal CA1 pyramidal neurons in vitro. J. Neurosci. 22 (16), 7234–7243. https://doi.org/10.1523/JNEUROSCI.22-16-07234.2002.
Qian, H., Patriarchi, T., Price, J.L., et al., 2017. Phosphorylation of Ser1928 mediates the enhanced activity of the L-type Ca2+ channel Cav1.2 by the β2-adrenergic receptor in neurons. Sci. Signal. 10 (463), eaaf9659. https://doi.org/10.1126/scisignal.aaf9659.
Ramezani, M., Wagenknecht-Wiesner, A., Wang, T., Holowka, D.A., Eliezer, D., Baird, B. A., 2023. Alpha synuclein modulates mitochondrial Ca2+ uptake from ER during cell stimulation and under stress conditions. bioRxiv. https://doi.org/10.1101/2023.04.23.537965. Published online April 24, 2023.04.23.537965.
Rangaraju, V., Calloway, N., Ryan, T.A., 2014. Activity-driven local ATP synthesis is required for synaptic function. Cell 156 (4), 825–835. https://doi.org/10.1016/j.cell.2013.12.042.
Reeve, A., Simcox, E., Turnbull, D., 2014. Ageing and Parkinson's disease: why is advancing age the biggest risk factor? Ageing Res. Rev. 14 (100), 19–30. https://doi.org/10.1016/j.arr.2014.01.004.
Rex, C.S., Kramár, E.A., Colgin, L.L., Lin, B., Gall, C.M., Lynch, G., 2005. Long-term potentiation is impaired in middle-aged rats: regional specificity and reversal by adenosine receptor antagonists. J. Neurosci. 25 (25), 5956–5966. https://doi.org/10.1523/JNEUROSCI.0880-05.2005.
Riascos, D., de Leon, D., Baker-Nigh, A., et al., 2011. Age-related loss of calcium buffering and selective neuronal vulnerability in alzheimer's disease. Acta Neuropathol. 122 (5), 565–576. https://doi.org/10.1007/s00401-011-0865-4.
Roche, K.W., O'Brien, R.J., Mammen, A.L., Bernhardt, J., Huganir, R.L., 1996. Characterization of multiple phosphorylation sites on the AMPA receptor GluR1 subunit. Neuron 16 (6), 1179–1188. https://doi.org/10.1016/s0896-6273(00)80144-0.
Ronzitti, G., Bucci, G., Emanuele, M., et al., 2014. Exogenous alpha-Synuclein decreases raft partitioning of Cav2.2 channels inducing dopamine release. J. Neurosci. 34 (32), 10603–10615.
Rotermund, C., Machetanz, G., Fitzgerald, J.C., 2018. The therapeutic potential of metformin in neurodegenerative diseases. Front. Endocrinol. 9. https://doi.org/10.3389/fendo.2018.00400.
Rumian, N.L., Freund, R.K., Dell'Acqua, M.L., Coultrap, S.J., Bayer, K.U., 2023. Decreased nitrosylation of CaMKII causes aging-associated impairments in memory and synaptic plasticity in mice. Sci. Signal. 16 (795), eade5892. https://doi.org/10.1126/scisignal.ade5892.
Rusakov, D.A., 2006. Ca2+-Dependent mechanisms of presynaptic control at central synapses. Neuroscientist 12 (4), 317–326. https://doi.org/10.1177/1073858405284672.
Rybka, V., Suzuki, Y.J., Gavrish, A.S., Dibrova, V.A., Gychka, S.G., Shults, N.V., 2019. Transmission electron microscopy study of mitochondria in aging brain synapses. Antioxidants 8 (6), 171. https://doi.org/10.3390/antiox8060171.
Sagheddu, C., Stojanovic, T., Kouhnavardi, S., et al., 2024. Cognitive performance in aged rats is associated with differences in distinctive neuronal populations in the ventral tegmental area and altered synaptic plasticity in the hippocampus. Front. Aging Neurosci. 16. https://doi.org/10.3389/fnagi.2024.1357347.
Salah, N.Y., Taha, S.I., Hassan, S., Abdeen, M.S.E., Hashim, M.A., Mahmoud, R., 2022. Metabolism and memory: α-synuclein level in children with obesity and children with type 1 diabetes; relation to glucotoxicity, lipotoxicity and executive functions. Int. J. Obes. 46 (11), 2040–2049. https://doi.org/10.1038/s41366-022-01222-z.
Samavarchi Tehrani, S., Sarfi, M., Yousefi, T., et al., 2020. Comparison of the calcium-related factors in Parkinson's disease patients with healthy individuals. Caspian J. Intern. Med. 11 (1), 28–33. https://doi.org/10.22088/cjim.11.1.28.
Samuel, M.A., Voinescu, P.E., Lilley, B.N., et al., 2014. LKB1 and AMPK regulate synaptic remodeling in old age. Nat. Neurosci. 17 (9), 1190–1197. https://doi.org/10.1038/nn.3772.
Sandler, V.M., Barbara, J.G., 1999. Calcium-induced calcium release contributes to action potential-evoked calcium transients in hippocampal CA1 pyramidal neurons. J. Neurosci. 19 (11), 4325–4336. https://doi.org/10.1523/JNEUROSCI.19-11-04325.1999.
Santucci, D.M., Raghavachari, S., 2008. The effects of NR2 subunit-dependent NMDA receptor kinetics on synaptic transmission and CaMKII activation. PLoS Comput. Biol. 4 (10), e1000208. https://doi.org/10.1371/journal.pcbi.1000208.
Sato, S., Uchihara, T., Fukuda, T., et al., 2018. Loss of autophagy in dopaminergic neurons causes lewy pathology and motor dysfunction in aged mice. Sci. Rep. 8, 2813. https://doi.org/10.1038/s41598-018-21325-w.
Schirinzi, T., Madeo, G., Martella, G., et al., 2016. Early synaptic dysfunction in Parkinson's disease: insights from animal models. Mov. Disord. 31 (6), 802–813. https://doi.org/10.1002/mds.26620.
Schwaller, B., 2020. Cytosolic Ca2+ buffers are inherently Ca2+ signal modulators. Cold Spring Harbor Perspect. Biol. 12 (1), a035543. https://doi.org/10.1101/cshperspect.a035543.
Shao, Y., Fu, Z., Wang, Y., et al., 2023. A metabolome atlas of mouse brain on the global metabolic signature dynamics following short-term fasting. Signal Transduct. Targeted Ther. 8 (1), 1–12. https://doi.org/10.1038/s41392-023-01552-y.
Shehata, M., Matsumura, H., Okubo-Suzuki, R., Ohkawa, N., Inokuchi, K., 2012. Neuronal stimulation induces autophagy in hippocampal neurons that is involved in AMPA receptor degradation after chemical long-term depression. J. Neurosci. 32 (30), 10413–10422. https://doi.org/10.1523/JNEUROSCI.4533-11.2012.
Shehata, M., Abdou, K., Choko, K., Matsuo, M., Nishizono, H., Inokuchi, K., 2018. Autophagy enhances memory erasure through synaptic destabilization. J. Neurosci. 19. https://doi.org/10.1523/JNEUROSCI.3505-17.2018. Published online March.
Shetty, M.S., Sharma, M., Sajikumar, S., 2017. Chelation of hippocampal zinc enhances long-term potentiation and synaptic tagging/capture in CA1 pyramidal neurons of aged rats: implications to aging and memory. Aging Cell 16 (1), 136–148. https://doi.org/10.1111/acel.12537.
Shi, L., Adams, M.M., Linville, M.C., et al., 2007. Caloric restriction eliminates the aging-related decline in NMDA and AMPA receptor subunits in the rat hippocampus and induces homeostasis. Exp. Neurol. 206 (1), 70–79. https://doi.org/10.1016/j.expneurol.2007.03.026.
Shin, J., Kovacheva, L., Thomas, D., et al., 2022. Cav1.3 calcium channels are full-range linear amplifiers of firing frequencies in lateral DA SN neurons. Sci. Adv. 8 (23), eabm4560. https://doi.org/10.1126/sciadv.abm4560.
Sidransky, E., Lopez, G., 2012. The link between the GBA gene and parkinsonism. Lancet Neurol. 11 (11), 986–998. https://doi.org/10.1016/S1474-4422(12)70190-4.
Singh, A., Zhi, L., Zhang, H., 2019. LRRK2 and mitochondria: recent advances and current views. Brain Res. 1702, 96–104. https://doi.org/10.1016/j.brainres.2018.06.010.
Solana-Manrique, C., Muñoz-Soriano, V., Sanz, F.J., 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 (7), 166152. https://doi.org/10.1016/j.bbadis.2021.166152.
Soukup, S.F., Verstreken, P., 2017. EndoA/Endophilin-A creates docking stations for autophagic proteins at synapses. Autophagy 13 (5), 971–972. https://doi.org/10.1080/15548627.2017.1286440.
Soukup, S.F., Kuenen, S., Vanhauwaert, R., et al., 2016. A LRRK2-Dependent EndophilinA phosphoswitch is critical for macroautophagy at presynaptic terminals. Neuron 92 (4), 829–844. https://doi.org/10.1016/j.neuron.2016.09.037.
Spillantini, M.G., Schmidt, M.L., Lee, V.M.Y., Trojanowski, J.Q., Jakes, R., Goedert, M., 1997. α-Synuclein in lewy bodies. Nature 388 (6645), 839–840. https://doi.org/10.1038/42166.
Stampanoni, Bassi M., Sancesario, A., Morace, R., Centonze, D., Iezzi, E., 2017. Cannabinoids in parkinson's disease. Cannabis Cannabinoid Res. 2 (1), 21–29. https://doi.org/10.1089/can.2017.0002.
Stavoe, A.K.H., Holzbaur, E.L.F., 2019. Neuronal autophagy declines substantially with age and is rescued by overexpression of WIPI2. Autophagy 16 (2), 371–372. https://doi.org/10.1080/15548627.2019.1695401.
Strope, T.A., Birky, C.J., Wilkins, H.M., 2022. The role of bioenergetics in neurodegeneration. Int. J. Mol. Sci. 23 (16), 9212. https://doi.org/10.3390/ijms23169212.
Stutzmann, G.E., Mattson, M.P., 2011. Endoplasmic reticulum Ca2+ handling in excitable cells in health and disease. Pharmacol. Rev. 63 (3), 700–727. https://doi.org/10.1124/pr.110.003814.
Su, Y.C., Qi, X., 2013. Inhibition of excessive mitochondrial fission reduced aberrant autophagy and neuronal damage caused by LRRK2 G2019S mutation. Hum. Mol. Genet. 22 (22), 4545–4561. https://doi.org/10.1093/hmg/ddt301.
Su, D., Cui, Y., He, C., et al., 2025. Projections for prevalence of Parkinson's disease and its driving factors in 195 countries and territories to 2050: modelling study of Global burden of disease study 2021. Br. Med. J. 388, e080952. https://doi.org/10.1136/bmj-2024-080952.
Subramaniam, M., Althof, D., Gispert, S., et al., 2014. Mutant α-synuclein enhances firing frequencies in dopamine substantia nigra neurons by oxidative impairment of A-type potassium channels. J. Neurosci. 34 (41), 13586–13599. https://doi.org/10.1523/JNEUROSCI.5069-13.2014.
Südhof, T.C., 2013. Neurotransmitter release: the last millisecond in the life of a synaptic vesicle. Neuron 80 (3), 675–690. https://doi.org/10.1016/j.neuron.2013.10.022.
Sukhorukov, V., Magnaeva, A., Baranich, T., et al., 2022. Brain neurons during physiological aging: morphological features, autophagic and mitochondrial contribution. Int. J. Mol. Sci. 23 (18), 10695. https://doi.org/10.3390/ijms231810695.
Sun, L., Wei, H., 2021. Ryanodine receptors: a potential treatment target in various neurodegenerative disease. Cell. Mol. Neurobiol. 41 (8), 1613–1624. https://doi.org/10.1007/s10571-020-00936-w.
Takeuchi, T., Duszkiewicz, A.J., Morris, R.G.M., 2014. The synaptic plasticity and memory hypothesis: encoding, storage and persistence. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (1633), 20130288. https://doi.org/10.1098/rstb.2013.0288.
Tang, G., Gudsnuk, K., Kuo, S.H., et al., 2014. Loss of mTOR-Dependent macroautophagy causes autistic-like synaptic pruning deficits. Neuron 83 (5), 1131–1143. https://doi.org/10.1016/j.neuron.2014.07.040.
Tavernarakis, N., 2020. Regulation and roles of autophagy in the brain. Adv. Exp. Med. Biol. 1195, 33. https://doi.org/10.1007/978-3-030-32633-3_5.
Thibault, O., Gant, J.C., Landfield, P.W., 2007. Expansion of the calcium hypothesis of brain aging and Alzheimer's disease: minding the Store. Aging Cell 6 (3), 307–317. https://doi.org/10.1111/j.1474-9726.2007.00295.x.
Tian, X., Gala, U., Zhang, Y., et al., 2015. A voltage-gated calcium channel regulates lysosomal fusion with endosomes and autophagosomes and is required for neuronal homeostasis. PLoS Biol. 13 (3), e1002103. https://doi.org/10.1371/journal.pbio.1002103.
Tsien, J.Z., Huerta, P.T., Tonegawa, S., 1996. The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. Cell 87 (7), 1327–1338. https://doi.org/10.1016/s0092-8674(00)81827-9.
Tsong, H., Holzbaur, E.L., Stavoe, A.K., 2023. Aging differentially affects axonal autophagosome Formation and maturation. Autophagy 19 (12), 3079–3095. https://doi.org/10.1080/15548627.2023.2236485.
Ueno, H., Takao, K., Suemitsu, S., et al., 2018. Age-dependent and region-specific alteration of parvalbumin neurons and perineuronal nets in the mouse cerebral cortex. Neurochem. Int. 112, 59–70. https://doi.org/10.1016/j.neuint.2017.11.001.
Valencia, M., Kim, S.R., Jang, Y., Lee, S.H., 2021. Neuronal autophagy: characteristic features and roles in neuronal pathophysiology. Biomol Ther. (Seoul). 29 (6), 605–614. https://doi.org/10.4062/biomolther.2021.012.

Vanhauwaert, R., Kuenen, S., Masius, R., et al., 2017. The SAC1 domain in synaptojanin is required for autophagosome maturation at presynaptic terminals. EMBO J. 36 (10), 1392–1411. https://doi.org/10.15252/embj.201695773.

Veng, L.M., Browning, M.D., 2002. Regionally selective alterations in expression of the α1D subunit (Cav1.3) of L-type calcium channels in the hippocampus of aged rats. Mol. Brain Res. 107 (2), 120–127. https://doi.org/10.1016/S0169-328X(02)00453-9.

Veng, L.M., Mesches, M.H., Browning, M.D., 2003. Age-related working memory impairment is correlated with increases in the L-type calcium channel protein α1D (Cav1.3) in area CA1 of the hippocampus and both are ameliorated by chronic nimodipine treatment. Mol. Brain Res. 110 (2), 193–202. https://doi.org/10.1016/S0169-328X(02)00643-5.

Verdin, E., 2015. NAD+ in aging, metabolism, and neurodegeneration. Science 350 (6265), 1208–1213. https://doi.org/10.1126/science.aac4854.

Verma, A., Ravindranath, V., 2019. CaV1.3 L-Type calcium channels increase the vulnerability of substantia nigra dopaminergic neurons in MPTP mouse model of parkinson's disease. Front. Aging Neurosci. 11, 382. https://doi.org/10.3389/fnagi.2019.00382.

Verstreken, P., Ly, C.V., Venken, K.J.T., Koh, T.W., Zhou, Y., Bellen, H.J., 2005. Synaptic mitochondria are critical for mobilization of reserve pool vesicles at drosophila neuromuscular junctions. Neuron 47 (3), 365–378. https://doi.org/10.1016/j.neuron.2005.06.018.

Vierra, N.C., Trimmer, J.S., 2022. Ion channel partnerships: odd and not-so-odd couples controlling neuronal ion channel function. Int. J. Mol. Sci. 23 (4), 1953. https://doi.org/10.3390/ijms23041953.

Volta, M., Beccano-Kelly, D.A., Paschall, S.A., et al., 2017. Initial elevations in glutamate and dopamine neurotransmission decline with age, as does exploratory behavior, in LRRK2 G2019S knock-in mice. eLife 6, e28377. https://doi.org/10.7554/eLife.28377.

Wan, Q.F., Nixon, E., Heidelberger, R., 2012. Regulation of presynaptic calcium in a Mammalian synaptic terminal. J. Neurophysiol. 108 (11), 3059–3067. https://doi.org/10.1152/jn.00213.2012.

Wang, X., Yan, M.H., Fujioka, H., et al., 2012. LRRK2 regulates mitochondrial dynamics and function through direct interaction with DLP1. Hum. Mol. Genet. 21 (9), 1931–1944. https://doi.org/10.1093/hmg/dds003.

Watson, J.B., Khorasani, H., Persson, A., Huang, K.P., Huang, F.L., O'Dell, T.J., 2002. Age-related deficits in long-term potentiation are insensitive to hydrogen peroxide: coincidence with enhanced autophosphorylation of Ca2+/calmodulin-dependent protein kinase II. J. Neurosci. Res. 70 (3), 298–308. https://doi.org/10.1002/jnr.10427.

Winslow, A.R., Chen, C.W., Corrochano, S., et al., 2010. α-Synuclein impairs macroautophagy: implications for Parkinson's disease. J. Cell Biol. 190 (6), 1023–1037. https://doi.org/10.1083/jcb.201003122.

Wu, C.K., Mesulam, M.M., Geula, C., 1997. Age-related loss of calbindin from human basal forebrain cholinergic neurons. Neuroreport 8 (9–10), 2209–2213. https://doi.org/10.1097/00001756-199707070-00024.

Xu, J., Minobe, E., Kameyama, M., 2022. Ca2+ dyshomeostasis links risk factors to neurodegeneration in parkinson's disease. Front. Cell. Neurosci. 16. https://doi.org/10.3389/fncel.2022.867385.

Yamamoto, K., Izumi, Y., Arifuku, M., Kume, T., Sawada, H., 2019. α-Synuclein oligomers mediate the aberrant form of spike-induced calcium release from IP3 receptor. Sci. Rep. 9 (1), 15977. https://doi.org/10.1038/s41598-019-52135-3.

Yang, S., Park, D., Manning, L., et al., 2022. Presynaptic autophagy is coupled to the synaptic vesicle cycle via ATG-9. Neuron 110 (5), 824–840.e10. https://doi.org/10.1016/j.neuron.2021.12.031.

Zamponi, G.W., Striessnig, J., Koschak, A., Dolphin, A.C., 2015. The physiology, pathology, and pharmacology of voltage-gated calcium channels and their future therapeutic potential. Pharmacol. Rev. 67 (4), 821–870. https://doi.org/10.1124/pr.114.009654.

Zarate, S.M., Huntington, T.E., Bagher, P., Srinivasan, R., 2023. Aging reduces calreticulin expression and alters spontaneous calcium signals in astrocytic endfeet of the mouse dorsolateral striatum. npj Aging. 9 (1), 1–15. https://doi.org/10.1038/s41514-023-00102-8.

Zhao, X., Rosenke, R., Kronemann, D., et al., 2009. The effects of aging on *N*-methyl-d-aspartate receptor subunits in the synaptic membrane and relationships to long-term spatial memory. Neuroscience 162 (4), 933–945. https://doi.org/10.1016/j.neuroscience.2009.05.018.

Zheng, Z., Zong, Y., Ma, Y., et al., 2024. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduct. Targeted Ther. 9 (1), 1–29. https://doi.org/10.1038/s41392-024-01931-z.