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Graphical Review

Regulation of neuronal excitability by reactive oxygen species and calcium signaling: Insights into brain aging

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ABSTRACT:

Altered cognition and inefficient learning and memory are hallmarks of brain aging resulting from many small changes in the structure and function of neurons. One such change is a decrease in excitatory synaptic transmission mediated by glutamate and its binding to the AMPA and NMDA subtypes of glutamate receptors. Why there is decreased glutamatergic transmission in aging is not well understood. Interestingly, in aged excitatory neurons, abnormal calcium homeostasis and energy production are reliably observed. These processes have also been shown to modulate the transport and delivery of glutamate receptors to synapses. Most of these channels are translated in the cell body and must be transported to synapses by molecular motors and then transferred to the synaptic surface for proper function. Despite there being little to no research on how aging impacts these transport processes, a detailed understanding of the mechanisms regulating long-distance and local transport of these channels is coming together. Here, we review recent research on how synaptic content, specifically of glutamate receptors and voltage-gated calcium channels, is normally regulated by calcium and energy production. In addition, we discuss how that regulation may change in the aged nervous system. These advances begin to detail a mechanistic explanation in which an interplay between calcium signaling and metabolism are impacted by and, in-turn, regulate the strength of excitatory synapses.

1. Introduction

Physiological aging of the brain results in diminished cognitive abilities including poorer memory formation and motor coordination. Interestingly, little is known about the underlying mechanisms of physiological aging that cause altered neuronal function. This may be due to research on aging being complicated by large variations in cellular and molecular changes between neuronal types, brain regions, and individuals arising from environmental differences (Mattson and Arumugam, 2018; Müller et al., 2018). However, it is clear that altered activity of the brain's excitatory neurocircuitry, namely those controlled by glutamate, are heavily correlated with age-associated impairments in cognition, learning and memory (Nikoletopoulou and Tavernarakis, 2012). Here, we will highlight recent findings that support a central role for reactive oxygen species (ROS), normal byproducts of cellular respiration, and calcium signaling in the regulation of glutamatergic transmission and provide insight on how these roles may be altered in the aged brain. Given the focused scope of this review we will not discuss the molecular details of the reduction-oxidation (redox) mechanisms, but the cited references contain information on how redox modifications alter protein function.

2. Normal regulation of excitatory synaptic transmission by calcium

Calcium coordinates and regulates many processes important for neuronal excitation as well as synaptic plasticity. Thus, tight regulation of cytoplasmic resting calcium concentration is critical for neuronal function. Upon influx, calcium is buffered by uptake into mitochondria and the endoplasmic reticulum (Fig. 1). Remaining calcium is readily pumped into extracellular space by the plasma membrane calcium-ATPase (PMCA) to lower cytoplasmic calcium back to basal levels (~100 nM; Fig. 1). Neuronal activity brings cytoplasmic calcium to 100 times this concentration which initiates signaling pathways that regulate function, localization and expression of proteins that contribute to neuronal excitation (Nikoletopoulou and Tavernarakis, 2012).

In the presynaptic terminal, calcium initiates release of neurotransmitter-filled vesicles via the SNARE complex (reviewed in Nikoletopoulou and Tavernarakis, 2012). However, new findings describe additional roles for presynaptic calcium signaling. For example,

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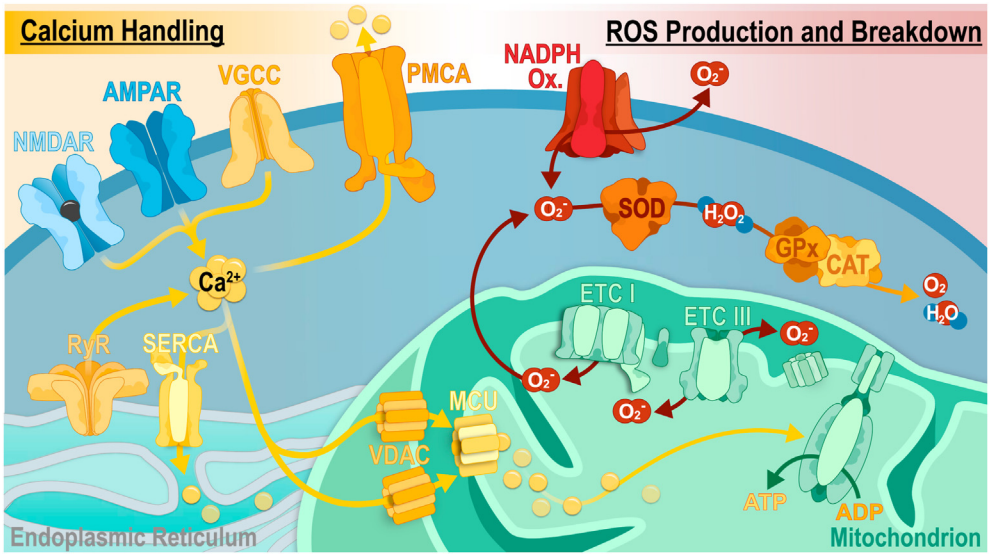

Fig. 1. Calcium and ROS homeostasis at glutamatergic synapses.
Left. Calcium enters the cytoplasm by activity-dependent opening of voltage-gated calcium channels (VGCCs), AMPA and NMDA receptors which can induce release of calcium stored in the endoplasmic reticulum (ER) via ryanodine receptors (RyR). Calcium is removed from the cytoplasm by efflux through plasma membrane calcium-ATPases (PMCA), uptake into ER via the sarcoendoplasmic reticulum calcium-ATPase (SERCA) and buffering by mitochondria (green compartment) via voltage-dependent anion channels (VDAC). Calcium shuttling into the mitochondrial matrix by the mitochondrial calcium uniporter (MCU) positively regulates the production of adenosine triphosphate (ATP).
Right. Most ATP is produced by the electron transport chain (ETC), but reactive oxygen species (ROS), specifically superoxide (O_2^-), are also produced. ROS is also produced by NADPH oxidase (NADPH Ox.). The ROS produced by these sources is rapidly broken down by antioxidant enzymes including superoxide dismutase (SOD), catalases (CAT) and glutathione peroxidase (GPx).

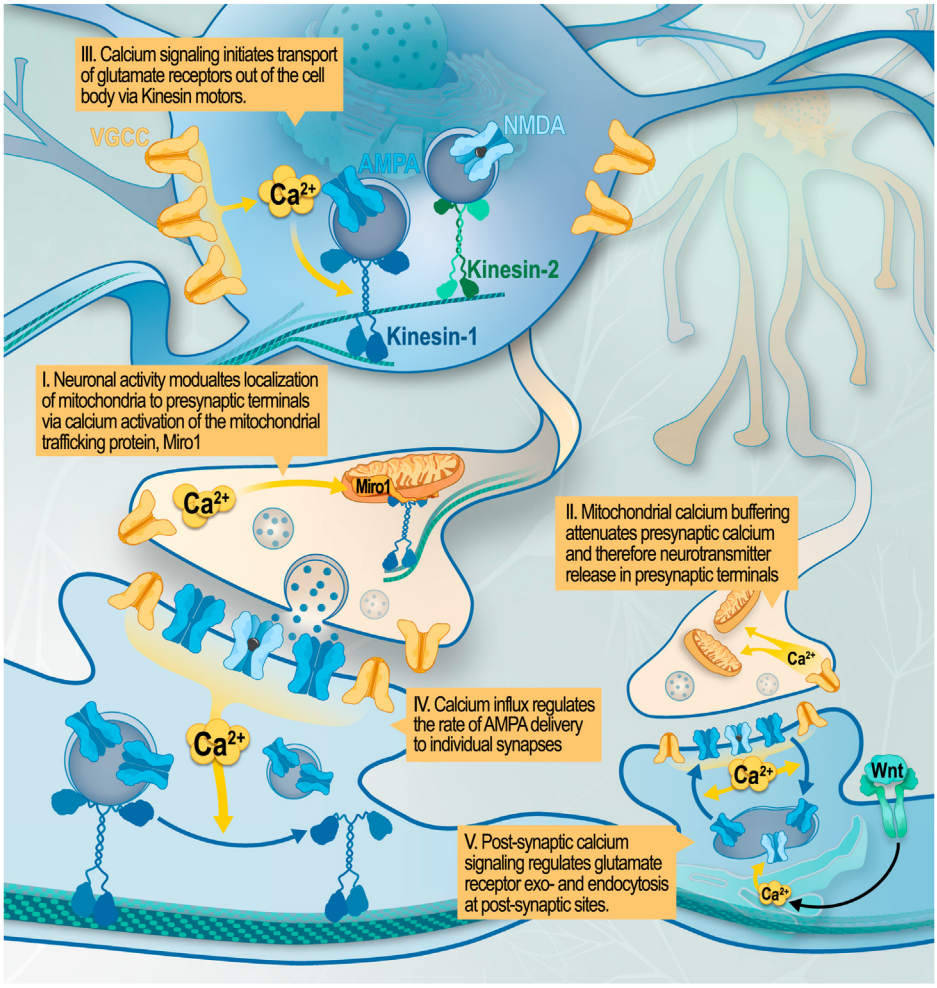

Fig. 2. Calcium signaling modulates synaptic excitability by regulating glutamate receptor and mitochondrial localization.
I. Mitochondrial transport to presynaptic sites is regulated by calcium influx and the calcium-sensitive mitochondrial trafficking protein Miro-1. More specifically, Miro-1 tethers mitochondria to the Kinesin-1 complex. The calcium sensing EF hands of Miro-1 initiate stopping of mitochondrial transport when high calcium levels are encountered to cause depositing of mitochondria at activated presynaptic terminals (Vaccaro et al., 2017).
II. Presynaptic mitochondria buffer calcium and attenuate presynaptic calcium signaling (Vaccaro et al., 2017).
III. In the cell body, calcium influx from voltage-gated calcium channels (VGCCs) triggers a signaling cascade involving calcium/cal modulin-dependent protein kinase II (CaMKII) that initiates the loading of vesicles containing AMPA receptors onto the molecular motor Kinesin-1 for microtubule-based export out of the cell body (Hoerndli et al., 2015). Similarly, the transport of NMDA receptors via Kinesin-2 is dependent on CaMKII activation, but it remains unclear if it is due to calcium from VGCCs specifically (Hirokawa and Tanaka, 2015).
IV. AMPA receptor delivery to postsynaptic sites is positively regulated by calcium influx (Doser et al., 2020; Hangen et al., 2018; Hoerndli et al., 2015).
V. Calcium influx from VGCCs positively correlates with the rate of AMPA receptor exocytosis to the postsynaptic membrane (Doser et al., 2020). NMDA receptor exocytosis rates are also increased by calcium influx; however, the calcium signal specific to this mechanism arises from Wnt5a (Wnt; teal ligand in bottom right synapse) activation of tyrosine kinase-like orphan receptors (RoR2; green receptor at the plasma membrane of bottom right synapse) triggering calcium release from intracellular stores (McQuate et al., 2017).

mitochondria transport into presynaptic terminals was also found to be under calcium regulation via the calcium-sensing mitochondrial trafficking protein, Miro1 (Fig. 2 I; Vaccaro et al., 2017). Interestingly, the presence of mitochondria in presynaptic terminals can modulate calcium levels and resultant neurotransmitter release (Fig. 2 II; Vaccaro et al., 2017). Together, these findings reveal a novel mechanism in which presynaptic activation regulates mitochondrial localization to cause homeostatic changes in presynaptic calcium signaling and transmission.

Across the synaptic cleft, calcium also regulates postsynaptic proteins to modulate the strength of glutamatergic transmission (Rao and Finkbeiner, 2007). Recent advances on this topic involve how calcium signaling regulates the transport of the two major types of ionotropic glutamate receptors (iGluRs; Fig. 2 III-V; Doser et al., 2020; Hangen et al., 2018; Hoerndli et al., 2015; McQuate et al., 2017). iGluRs are primarily translated in the cell body and must undergo long-distance transport to postsynaptic sites. Although this process is vital for synaptic expression of iGluRs, and therefore synaptic strength, surprisingly little is known about what it requires or how it is regulated.

The first type of iGluRs is the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which is responsible for rapid depolarization of postsynaptic sites upon presynaptic release of glutamate. Until recently, factors required for AMPA receptor transport remained incomplete. Our research coinciding with other findings has revealed that transport via the molecular motor Kinesin-1 as well as synaptic delivery and exocytosis of AMPA receptors to synapses is regulated by calcium signaling initiated by voltage-gated calcium channel (VGCCs) activation (Fig. 2 III-V; Doser et al., 2020; Hangen et al., 2018; Hoerndli et al., 2015). The second type of iGluRs is the N-methyl-D-aspartate (NMDA) receptor whose activation requires glutamate binding and postsynaptic depolarization. Due to a greater calcium conductance than calcium-permeable AMPA receptors, NMDA receptors are thought to be responsible for initiating several calcium signaling cascades such as those underlying synaptic strengthening (Rao and Finkbeiner, 2007). Long-distance transport of NMDA receptors via Kinesin-2 also depends on calcium signaling, specifically involving activation of calcium/calmodulin-dependent protein kinase II (CaMKII) (Fig. 2 III; Hirokawa and Tanaka, 2015). More recently, local trafficking of NMDA receptors at synapses was shown to be regulated by activation of a specific glycoprotein-associated pathway that causes calcium release from intracellular stores (Fig. 2 V; McQuate et al., 2017). These findings demonstrate how localized calcium signaling can differentially regulate synaptic expression of the iGluR subtypes. More specifically, it shows that rapid calcium influx through VGCCs triggers exocytosis of AMPA receptors whereas elevated calcium due to Wnt5a/RoR2 activation occurs more slowly to specifically initiate exocytosis of NMDA receptors. Additionally, this research has aided our understanding of how excitatory neurotransmission is regulated normally, which is required to grasp the mechanisms underlying weakened synaptic strength and inefficient plasticity in aged neurons (Rizzo et al., 2015).

3. Abnormal regulation of excitatory synaptic transmission by calcium in aging

The cognitive decline and diminished memory capabilities that are a hallmark of normal aging is correlated with shrunken cell bodies, synapse loss and changes in synaptic content of neurotransmitter receptors with the magnitude of these changes differing depending on neuronal type and brain region (Rizzo et al., 2015). The physiological changes that accompany these structural changes are less characterized. However, age-related dysregulation of calcium homeostasis, especially in glutamatergic neurons, is well-documented (Nikoletopoulou and Tavernarakis, 2012). More specifically, in aged neurons, there are elevated resting calcium levels and prolonged calcium signaling. This may be due to decreased calcium uptake into intracellular stores and diminished activity of the PMCA, which are localized both pre- and postsynaptically (Nikoletopoulou and Tavernarakis, 2012). Another age-related change in presynaptic function is increased expression of vesicular glutamate transporters resulting in increased release of glutamate, the primary excitatory neurotransmitter (Ménard et al., 2015). This is thought to be a compensatory change for an age-related decrease in postsynaptic iGluRs (Kumar et al., 2019; Ménard et al., 2015). Currently, it is unclear why there are fewer iGluRs at aged synapses, but the integrated role of calcium in the regulation of iGluRs (Fig. 2) suggests that altered calcium signaling could be central to the change in iGluR content and function in aging.

Unfortunately, few recent advancements have been made that pertain to iGluR regulation in normal aging. However, it has been consistently observed over the last 20 years that aged glutamatergic synapses also have more VGCCs both pre- and postsynaptically (Nikoletopoulou and Tavernarakis, 2012). These changes in synaptic content of iGluRs and VGCCs are correlated with increased presynaptic calcium influx and excitatory postsynaptic potentials in response to presynaptic stimulation (Pereda et al., 2019). The impact of these changes on synaptic plasticity is less clear-cut. There are mixed findings on whether induction of long-term potentiation (LTP), a form of synaptic strengthening, is changed at aged synapses. However, critical analysis of the literature suggests that there are age-related LTP deficits when the induction protocol elicits perithreshold stimulation. Alternatively, when induction of LTP results from suprathreshold stimulation, age-related deficits are rarely observed (Cuestas Torres and Cardenas, 2020). Assessing these findings in relation to their stimulation protocol point toward an increased threshold for induction of LTP in aging which corroborates other studies that directly address LTP threshold (Barnes, 2003; Cuestas Torres and Cardenas, 2020; Pereda et al., 2019). This change in LTP threshold results from elevated calcium-induced calcium release from intracellular stores due to increased VGCC surface expression which activates a hyperpolarizing current that prevents the repeated depolarization necessary for NMDA receptor activation (Foster, 2007). Additionally, it is clear that there are often fewer NMDA receptors at aged synapses that can contribute to LTP induction (Foster, 2007). However, there has been little to no research directly assessing if the transport of iGluRs to synapses is diminished with normal aging. Research aimed at assessing why iGluR content and function at synapses is altered in aging will be pivotal for understanding why transmission and plasticity is inefficient at aged excitatory synapses.

Interestingly, the age-related increase in intracellular calcium is amplified by the impact of elevated calcium on mitochondrial function. Calcium uptake into mitochondria upregulates oxidative phosphorylation (OXPHOS; Fig. 1) resulting in increased production of reactive oxygen species (ROS) (Hidalgo and Arias-Cavieres, 2016). Accumulating evidence supports a physiological role for ROS signaling in the regulation of transmission and plasticity as discussed in the following section (Doser et al., 2020; Hidalgo and Arias-Cavieres, 2016). Understanding these physiological roles would shed light on the impacts of the abnormally high production and decreased scavenging of ROS found in the aged brain.

4. ROS signaling at excitatory synapses during physiological states and aging

Physiological ROS signaling is involved in the development, differentiation and axon formation of neurons. In mature neurons, the rate of ROS production is higher due to the metabolic demands of neuronal activation, intracellular signaling and homeostatic processes. The presence of many antioxidant enzymes maintains low, physiological ROS concentrations (Fig. 1). At these concentrations, numerous signaling roles for ROS in neurons have been recognized over the last couple decades. For instance, at excitatory synapses, LTP is hindered by abnormally low as well as high ROS levels further supporting specific, concentration-dependent signaling roles for ROS (Hidalgo and Arias-Cavieres, 2016). The ROS-dependent mechanisms underlying LTP remain largely unidentified. However, it was recently demonstrated that

the ROS signaling required for LTP is induced by activity-dependent mitochondrial ROS production (Fu et al., 2017).

Redox modifications of proteins central to synaptic function and plasticity, such as calmodulin and CaMKII (Bayer and Schulman, 2019; Robison et al., 2007), were thought to underly regulation of synaptic transmission by ROS. However, the downstream impacts of these redox modifications remained unidentified until recently. For instance, recent research has begun to outline mechanisms in which physiological ROS signaling regulates the transport of mitochondria (Debattisti et al., 2017) and AMPA receptors to synapses (Fig. 3; Doser et al., 2020). These findings add to our fundamental understanding of how mitochondria and iGluR localization is regulated, but they are also insightful for aging since many lines of evidence point toward increased ROS production, mostly by mitochondria, as a major cause of neuronal aging. The oxidative stress due to elevated ROS leads to a long list of impairments and dysregulation (Mattson and Arumugam, 2018; Stefanatos and Sanz, 2018). At the glutamatergic synapse, few age-associated changes in the regulation of synaptic transmission by ROS have been described. To our knowledge, the only recently research on this topic is that NMDA receptor hypofunction in the aged brain is due to an altered redox state of CaMKII (Guidi et al., 2015; Kumar et al., 2019).

5. Regulation of excitatory synaptic transmission by a calcium-ROS interplay

Most of what is known about ROS signaling in mature neurons relates to its bidirectional regulation of calcium handling including cytoplasmic influx, buffering and release from intracellular stores (Görlach et al., 2015; Hidalgo and Arias-Cavieres, 2016). An interplay between ROS and calcium initially gained attention due to its role in the progression of neurodegenerative disorders and inflammation. Then, interrelated hypotheses formed which postulated that neuronal dysfunction and degeneration were caused by disruption in calcium homeostasis due to increased mitochondrial ROS or vice versa (Nikoletopoulou and Tavernarakis, 2012; Stefanatos and Sanz, 2018).

Although a ROS-calcium interplay in aging has been theorized for over half a century, calcium's regulation of OXPHOS in normal, healthy neurons was recognized only 25 years ago (Nikoletopoulou and Tavernarakis, 2012). In the last decade, it was uncovered that small fluctuations in ROS could feedback to regulate calcium influx and efflux in a way that may aid the precise spatiotemporal control of calcium concentrations necessary for specific regulation of calcium-dependent processes (Görlach et al., 2015). The direction of calcium modulation by ROS is dependent upon the calcium source. For instance, oxidation of the T-type VGCC is known to inhibit channel opening but oxidation of ryanodine receptors increases their calcium-induced opening (Görlach et al., 2015; Todorovic and Jevtovic-Todorovic, 2014). Little research has addressed the regulation of calcium signaling by ROS possibly due to the lack of highly sensitive ROS sensors. However, we recently demonstrated that physiological increases in ROS decrease calcium-dependent AMPA receptor transport in a way that impacts neuronal activation (Fig. 3; Doser et al., 2020). It is important to note that this phenomenon has only been described thus far in the nematode *C. elegans* which lack voltage-gated sodium channels meaning that modulation of calcium levels may have a greater impact on neuromodulation in this system compared to vertebrates. Regardless, the identified roles for an interplay between calcium and ROS signaling provide means by which neuronal activity can regulate the rate of energy production (Fig. 1) while also preventing excitotoxicity from an overabundance of cytoplasmic calcium.

The increased calcium and ROS in aged neurons seem to be interrelated, however neither the origin of the dysregulation nor the identity of which molecule becomes elevated first is clear (Mattson and Arumugam, 2018). Regardless, an increase in either calcium or ROS promotes and perpetuates the other (Fig. 4 IA and IB). Abnormally high ROS can increase cytoplasmic calcium by initiating release from intracellular stores and decreasing efflux through the PMCA (Fig. 4 IA). Elevated ROS can also modulate calcium signaling pathways. For instance, increased ROS can alter activation of calcineurin and CaMKII, calcium-dependent proteins central to induction of synaptic plasticity (Fig. 4 II; Erickson et al., 2008; Hidalgo and Arias-Cavieres, 2016).

Although the reciprocal regulation (i.e. regulation of ROS levels by calcium; Fig. 4 IB) is known to occur normally, it remains unclear if calcium dysregulation is a major cause of increased ROS production in

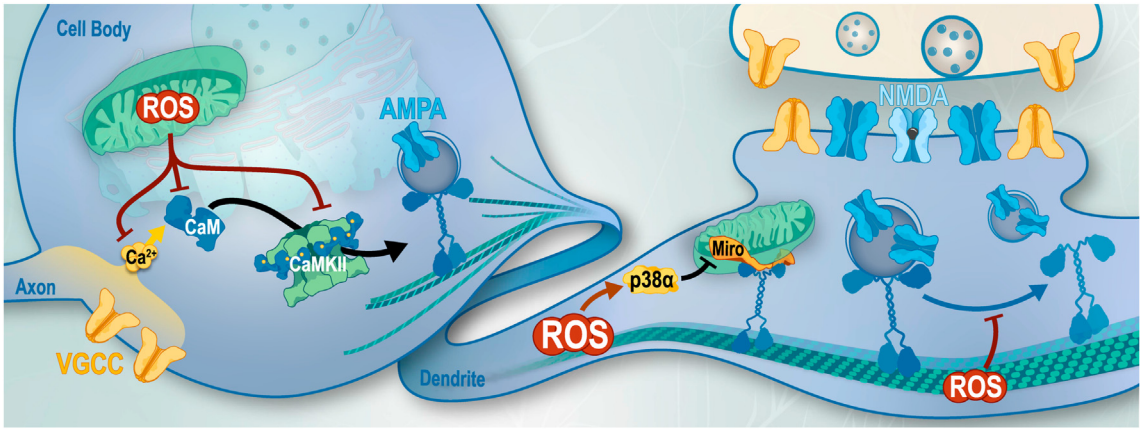

Fig. 3. Physiological ROS signaling regulates glutamate receptor and mitochondrial localization.
Cell Body. ROS signaling regulates of AMPA receptors export out of the neuronal cell body likely via modulation of calcium influx (Doser et al., 2020; Sies and Jones, 2020). Additionally, reversible oxidation of calmodulin (CaM) and CaMKII, regulators of AMPA transport, reduces their activation. Oxidation of CaM decreases its activation of CaMKII and PMCA which would hinder CaMKII-dependent changes in synaptic strength and slow calcium efflux through PMCAs to cause prolonged calcium signaling (Robison et al., 2007). The impact of oxidation on CaMKII activity is specific to which CaMKII residues is oxidized. Oxidation within CaMKII's regulatory domain is thought to cause sustained, calcium-independent activation of CaMKII. Alternatively, oxidation within the CaM-binding domain seems to decrease CaM trapping or the prolonged binding of CaM/CaMKII in the absence of calcium (Bayer and Schulman, 2019; Erickson et al., 2008). The differential susceptibility of various CaMKII residues to oxidation could allow for the degree and length of CaMKII activation to be modulated by local ROS levels.
Dendrite. ROS signaling reversibly inhibits mitochondrial transport by activation of the mitogen-activated protein kinase p38α likely due to inhibition of the mitochondrial protein Miro, but via a calcium-independent mechanism (Debattisti et al., 2017).
Synapse. Increases in synaptic ROS reduce the delivery of AMPA receptors to synapses (Doser et al., 2020).

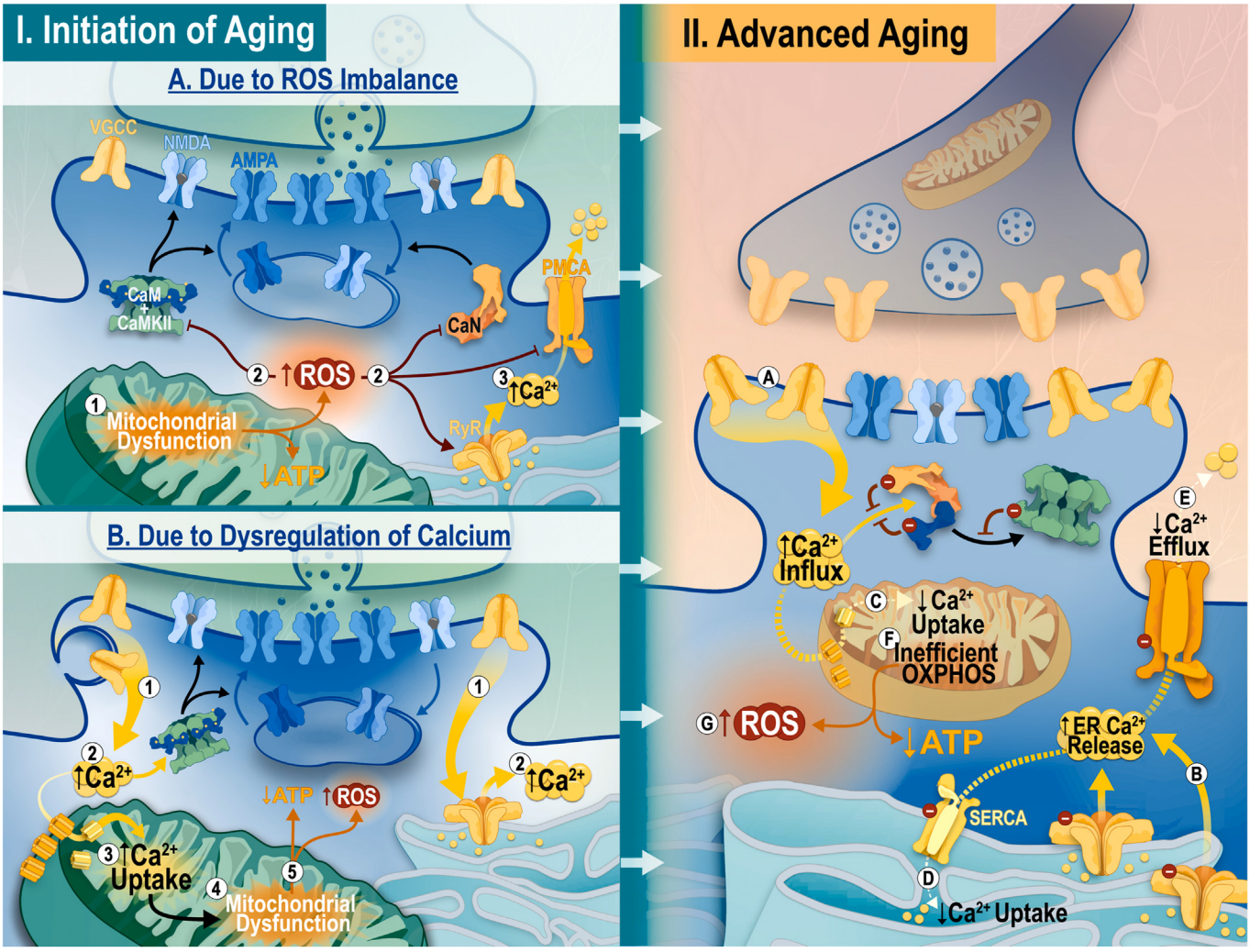

Fig. 4. How ROS imbalance or dysregulation of calcium could lead to the hallmarks of advanced aging.

IA. Although mitochondrial dysfunction has been recognized as central to cell aging, it is unclear what causes it or if it is causal to age-related neuronal dysregulation. Regardless, there are numerous downstream effects of mitochondrial dysfunction that could initiate aging: Inefficient OXPHOS within dysfunctional mitochondria results in decreased ATP and increased ROS production (Muller et al., 2018). ② Elevated ROS signaling alters neuronal function and excitability through redox regulation of various proteins, such as CaMKII and calcineurin (CaN; orange cytoplasmic molecule), that regulate AMPA and NMDA receptor function and localization (Erickson et al., 2008; Guidi et al., 2015; Hidalgo and Arias-Cavieres, 2016; Kumar et al., 2019). Additionally, direct oxidation of PMCA, or its main regulator calmodulin (CaM), decreases the rate of calcium efflux (Görlach et al., 2015). ③ Increased ROS can elevate cytoplasmic calcium by altering influx and buffering of calcium. For instance, increased ROS potentiates calcium-induced release of calcium from the endoplasmic reticulum (ER; teal compartment) via ryanodine receptors (RyR) and influx at the plasma membrane via VGCCs (Görlach et al., 2015).

IB. The altered synaptic expression of postsynaptic receptors, excess cytoplasmic calcium and increased ROS production typical of aged synapses could also be caused by an overabundance of cytoplasmic calcium (②), which would result from increased delivery of VGCCs to the synaptic membrane and calcium-induced calcium release from the ER (). This elevation in calcium would increase mitochondrial calcium buffering (③) potentially leading to mitochondrial dysfunction (④). This dysfunction would cause inefficient OXPHOS resulting in decreased ATP and increased ROS production (⑤; Müller et al., 2018). Despite these impacts of increased calcium, the age-related instigator(s) of altered calcium homeostasis remain unidentified.

II. In comparison to young excitatory synapses (see IA and IB), aged synapses have an increased pre- and postsynaptic VGCCs (yellow channel; Nikoletopoulou and Tavernarakis, 2012), but decreased NMDA (light blue) and AMPA (dark blue) receptors (Ménard et al., 2015). The causes of these expression changes are unknown, but we know that these changes cause weak postsynaptic responses to glutamate that are inadequate for initiating plasticity mechanisms. Aged synapses also have increased cytoplasmic calcium which results from the following: *A)* increased VGCC expression, *B)* increased calcium release from the ER, decreased uptake into *C)* dysfunctional mitochondria (represented by pale orange compartment) and *D)* the ER via the Sarcoendoplasmic Reticulum Calcium-ATPase (SERCA; Müller et al., 2018; Nikoletopoulou and Tavernarakis, 2012) as well as *E)* decreased calcium efflux by PMCAs.

As shown in IB, the impact of elevated calcium can be amplified due to the impact of calcium overload on mitochondria: *F)* inefficient mitochondrial OXPHOS and *G)* increased ROS production. ROS breakdown is also diminished in aged neurons (see Fig. 2; Mattson and Arumugam, 2018). Elevated ROS in aged cells exacerbates calcium dysregulation through its inhibition of PMCA and SERCA (Görlach et al., 2015; Robison et al., 2007) as well as potentiation of RyRs (Hidalgo and Arias-Cavieres, 2016). These functional changes are due to either direct oxidation of these proteins, or oxidation of their regulators. Additionally, direct oxidation of CaN, CaM (dark blue molecule), and CaMKII counteracts calcium-induced activation of these molecules (Erickson et al., 2008; Hidalgo and Arias-Cavieres, 2016; Robison et al., 2007).

aged neurons. Currently, it is clear that age-related ROS elevations are primarily due to increased mitochondrial ROS production and diminished antioxidant activity (Fig. 4 II; Müller et al., 2018; Olesen et al., 2020); however, it is unknown whether abnormal calcium handling causes this dysfunction. Interestingly, recent research identified synaptic mitochondria as especially susceptible to age-related dysfunction in comparison to their non-synaptic counterparts and that mitochondrial dysfunction can be triggered by calcium overload (Müller et al., 2018; Olesen et al., 2020). Dysfunction of synaptic mitochondria is characterized by inefficient OXPHOS leading to increased ROS production but decreased ATP synthesis and impaired calcium uptake (Fig. 4; Stefanatos and Sanz, 2018).

Altogether, physiological neuronal aging is characterized by increased cytoplasmic calcium and changes in synaptic bioenergetics which together are sufficient in perturbing the maintenance and plasticity of synapses likely due to the many targets of calcium and ROS signaling. These targets allow for a feedforward system in aged neurons where elevated ROS further increases cytoplasmic calcium.

6. Discussion

Clearly numerous signaling processes important for maintenance and plasticity of excitatory synapses are dependent on calcium, redox and metabolic homeostasis. At synapses where activity levels are diverse, energy production is regulated by synaptic calcium levels. However, because calcium regulates many neuronal mechanisms, especially at excitatory synapses, a negative feedback mechanism is required in order to prevent abnormally high and prolonged calcium signaling. The roles of ROS signaling thus far uncovered suggest that redox regulation by ROS is a major feedback mechanism that protects against unnecessary energy production and calcium overload. More specifically, physiological ROS signaling bidirectionally regulates cytoplasmic calcium levels and subsequent signaling pathways that are important for neuronal function. For instance, ROS decreases mitochondrial motility in a way that allows for depositing of mitochondria to overactive or metabolically taxed synapses where additional mitochondria are needed (Fig. 3). Similarly, our new understanding of how calcium influx and signaling proteins are regulated by oxidation (see Fig. 3) sheds light on how ROS may regulate downstream mechanisms, such as iGluR transport and delivery to the synaptic membrane.

When you consider these mechanisms and the regulatory changes that would hypothetically occur in aged neurons where ROS and calcium are elevated, the predicted results align with what is observed in the aged brain. First, elevated ROS may increase delivery of mitochondria to synapses possibly explaining why there is an accumulation of mitochondria in aged neurons (Fig. 3; Stefanatos and Sanz, 2018). Secondly, increased oxidation of calcium signaling molecules (i.e. CaM and CaMKII) in aging is hypothesized to decrease iGluR transport to synapses (Fig. 3) and dysregulate their local trafficking (Fig. 4 IA; Doser et al., 2020; Hirokawa and Tanaka, 2015) which could account for decreased iGluRs at aged synapses (Kumar et al., 2019; Ménard et al., 2015). Lastly, due to the impact oxidation has on proteins necessary for calcium buffering and removal (Fig. 4 II), age-related ROS elevations could alone account for the increase in basal and activity-dependent fluctuations in cytoplasmic calcium that are characteristic of aged neurons (Nikoletopoulou and Tavernarakis, 2012; Pereda et al., 2019). The resulting prolonged calcium signaling would perturb numerous plasticity mechanisms, trigger apoptotic signaling cascades and result in unneeded ATP synthesis meaning additional ROS production (Hidalgo and Arias-Cavieres, 2016). However, until research accumulates to provide a comprehensive understanding of how neuronal activity is normally regulated by a mutual calcium-ROS interplay, we will be unable to understand the changes that occur at excitatory synapses during physiological aging or why these changes can lead to neurodegenerative diseases.

Credit Author Statement

Hoerndli FJ and Doser RL conceived the manuscript and figures. Doser RL wrote the manuscript and created the figures. Hoerndli FJ edited and commented on the manuscript and figures. Doser RL revised the manuscript and figures for the final submission.

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.

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Appendix A. Peer Review Overview and Supplementary data

A Peer Review Overview and (sometimes) Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.crneur.2021.100012.

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