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Calcium's Role as Nuanced Modulator of Cellular Physiology in the Brain

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Calcium's role as nuanced modulator of cellular physiology in the brain

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Abstract

Neuroscientists studying normal brain aging, spinal cord injury, Alzheimer's disease (AD) and other neurodegenerative diseases have focused considerable effort on carefully characterizing intracellular perturbations in calcium dynamics or levels. At the cellular level, calcium is known for controlling life and death and orchestrating most events in between. For many years, intracellular calcium has been recognized as an essential ion associated with nearly all cellular functions from cell growth to degeneration. Often the emphasis is on the negative impact of calcium dysregulation and the typical worse-case-scenario leading inevitably to cell death. However, even high amplitude calcium transients, when executed acutely can alter neuronal communication and synaptic strength in positive ways, without necessarily killing neurons. Here, we focus on the evidence that calcium has a subtle and distinctive role in shaping and controlling synaptic events that underpin neuronal communication and that these subtle changes in aging or AD may contribute to cognitive decline. We emphasize that calcium imaging in dendritic components is ultimately necessary to directly test for the presence of age- or disease-associated alterations during periods of synaptic activation.

Keywords

afterhyperpolarization; familial Alzheimer's disease; insulin; estrogen; vitamin D; aging

1. Introduction

The role of calcium in neurodegenerative disorders has evolved significantly since early experiments showing hippocampal cell death in areas CA3 and CA1 in response to sustained synaptic activation of the perforant path *in vivo* [1]. These, and similar early experiments identified mechanisms of neuronal death reminiscent of calcium-induced necrosis, accompanied with blebbing of dendrites, retraction of processes, swelling of the soma and, ultimately, cellular death [2; 3; 4]. Framed in the context of a lengthy exposure to

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glutamatergic neurotransmitters, these necrosis-associated events provided robust evidence that calcium could be a perpetuator of cell death. However, a combination of advanced reporter technologies and improved resolution in calcium imaging techniques have provided more recent evidence that calcium can be very subtle and localized to small cellular domains in response to subthreshold or suprathreshold transient synaptic depolarizations.

In the field of neuronal calcium dynamics, perhaps understandably, there appears to be a subjective preoccupation with the harmful effects of calcium dysregulation. However, a brief survey of the literature shows this is not well supported by the extent of the overall research in this area. Here we attempted to translate this idea in graphical form using data on published manuscripts across several fields. Examination of the literature between 1970 and 2015 (Fig. 1) shows the number of published manuscripts linking “brain” and “calcium” to a variety of other neurological changes in brain physiology, and pathology over the 45-year span. As a proportion of the total number of published manuscripts in all fields of science, the number of published work on brain calcium and physiology increased nearly 10-fold between the years 1975 and 2000 (Fig 1A). It is interesting to note that whether looking at aging (Fig. 1B) or AD reports (Fig. 1C), physiological associations between brain and calcium represent the largest proportion of the overall scientific published work, while cell death, and pathology associated processes encompass a smaller body of work. We then determined what proportion of the manuscripts in the following categories: “calcium and brain” or “calcium and brain aging” or “calcium and brain and AD“, focused on either physiology, cell death of pathology. The data obtained every 5 years were then averaged across the last 30 years (Fig.1D). While scientific output steadily increased over that period (e.g., calcium and brain return 826 manuscripts in 1985, and 2032 manuscripts in 2015), the proportion of physiologically-related manuscripts within each of the categories has remained greater (~23 % to 55%, Fig 1D) compared to papers associating calcium in the brain with pathology or cell death (~3% to 20%). A caveat should be added that we did not attempt to identify repeat manuscripts in the dataset (i.e., papers studying both physiology and pathology in relationship to calcium in the brain), thus, the numbers we report may be slightly inflated. Nevertheless, together, these data suggest that more studies have been published on associations between calcium and its physiological consequences rather than on how calcium influences cell death or pathophysiology.

Here we briefly review how age- and neurodegeneration-related changes in oxidation/inflammation and certain hormones influence calcium dysregulation and impact cellular physiology. We also discuss the importance of focusing on the more subtle and localized calcium microdomains in neurons to better elucidate the impact of changes in calcium signaling in aging or in disease.

2. Calcium dysregulation in Alzheimer’s disease (AD) and AD models

Early studies by several pioneering groups identified cellular calcium dysregulation as a major factor underlying functional alterations in aging tissues. These observations contributed to the formulation of the calcium hypothesis of brain aging and AD [5; 6]. This work was followed by studies in human cortical cells showing that the β-amyloid peptide increases calcium levels at rest and in response to excitatory neurotransmitter release,

resulting in compromised neuronal cell health [7]. Later studies in neurons harboring presenilin-1 (PS-1) mutations, a key player in Aβ formation, helped identify several endoplasmic reticulum (ER) calcium handling proteins as targets of the genetic mutation [8]. Even human fibroblast and lymphoblasts display robust evidence of calcium dysregulation in AD [9; 10; 11], suggesting the dysregulation may be “system-wide” rather than just CNS-centered. Whether calcium dysregulation is a crucial initiator of the neuronal pathology, or a downstream event has been an open-ended question. Some studies have placed abnormal Ca^{2+} elevations downstream of PS-1 mutations [12; 13; 14]. On the other hand, ryanodine receptors and IP3 receptors have been identified as perpetrators of calcium dysregulation [15; 16; 17; 18; 19; 20] and reducing IP3R expression in 3×Tg mice attenuates Ca^{2+} signaling, Aβ production and Tau hyperphosphorylation [20]. PS1 and PS2 mutations have also been found to directly target ER function, reducing ER calcium leaks, and overloading the ER with excess calcium [21; 22; 23]. Loss-of-function PS1 mutations are also associated with disturbed calcium-dependent lysosomal and autophagic pathways [24; 25]. Interestingly, recent studies in animal models of AD using multiphoton calcium imaging techniques demonstrate that calcium overload may not be generalized to all neurons and could be dependent on proximity to a Aβ plaque [26; 27]; however, another study finds no association between distance from a plaque and neuronal calcium dysregulation [28]. In addition, neurofibrillary tangles do not appear to alter calcium levels or cellular excitability in the visual and somatosensory cortex [29], nor do they appear to alter calcium homeostasis in the cortex of animals displaying significant synapse loss [30].

Our understanding of the relationship between calcium dysregulation and AD in the brain still lacks clarity, and calcium dysregulation may also act upstream of AD pathology, whereby elevations in Ca^{2+} can increase production of oligomeric Aβ peptides [31]. As such, stabilizing ER calcium with dantrolene, a ryanodine receptor antagonist, restores normal synaptic function and plasticity and reduces amyloid load in the brains of 3×Tg AD mice [32] and knock-in FAD mice [33].

3. Oxidative stress, inflammation, and calcium

Calcium dysregulation tied to oxidative stress or inflammation in neuronal cells can have deleterious and long-lasting consequences resulting in calcium overload which may increase neuronal vulnerability under pathological conditions including AD [13; 19; 34; 35; 36]. Indeed, sustained NMDA receptor activation or even reduced NMDA receptor inactivation can increase calcium elevations (immediate or delayed) which in turn, can produce reactive oxygen species (ROS) as a result of increased mitochondrial energy demands [37]. Still, it is not clear that the increase in ROS seen around the time of neuronal cell death with calcium overload is actually the cause of death or the consequence of the depolarized mitochondria [37].

ROS production in response to Aβ peptides or other challenges in the brain [38; 39] is well known to alter protein function [40; 41], and recently has also been shown to directly alter calcium channels [42; 43]. Still, the threshold (if there is one) to induce these devastating signaling pathways and the relationship to Ca^{2+} levels *in vivo* has been as difficult to identify as the targets of the oxidative stressors in the brain [44]. The poor clinical

therapeutic translation seen in AD patients taking anti-oxidative therapies may be due to the fact that the precise targets are still unknown [45].

Brain inflammation, mediated by numerous cytokines (TNF-alpha, AIF, JNK) is common across brain aging and AD studies [46; 47; 48; 49] and has been linked to calcium dysregulation. This calcium dysregulation, in turn has been shown to have consequences for synaptic plasticity [50; 51]. Calcium dysregulation alters the balance between LTP and LTD presumably through changes in the activation of select phosphatases and kinases [52; 53; 54; 55; 56]. However, this relationship has never been tested *in vivo* or with sufficient spatial or temporal resolution to address calcium dynamics in microdomains near postsynaptic densities at the exact sites of synaptic communication. Given the complex structure of postsynaptic densities in dendritic spines which includes ion channels, anchoring proteins, kinases and phosphatases [57; 58; 59; 60; 61], this is a particularly important challenge that can only be surmounted with higher resolution microscopy that allows for measures of very controlled calcium rises during synaptic activation. Studies using tissue homogenates may be missing the impact of inflammation on calcium microdomains and the resulting synaptic processes.

At least one aspect of the association between oxidant/ inflammatory stressors and calcium dysregulation that has not received enough attention is whether different thresholds of dysregulation result in select activation of downstream pathways and/or different outcomes [7; 62; 63]. For example, it is not clear whether several repeated calcium events of smaller amplitudes (i.e., ministrokes) are as impactful as a single, large amplitude event (i.e., TBI, stroke). Also unclear, is whether the sensitivity of millisecond calcium cellular events to oxidant/inflammatory stressors changes across the lifespan.

4. The impact of disappearing hormones in the brain of aged animals may alter calcium homeostasis

While oxidative stress and inflammatory processes appear able to hasten calcium dysregulation with age, several endogenous steroid hormones including vitamin D, estrogen and insulin seem capable of redressing this dysregulation. We have shown that both vitamin D and estrogen alter L-VGCC activity and calcium-dependent processes. Vitamin D (1,25 dihydroxvitamin D3) reduces L-VGCC currents probably due to reductions in both $Ca_V1.2$ and $Ca_V1.3$ expression in primary hippocampal cultures [64]. This reduction in current activity was also found in CA1 hippocampal neurons and was correlated with an age-related reduction in the slow afterhyperpolarization (sAHP) which would affect neuronal excitability [65]. Further, long-term treatment (6 months) of rats beginning at mid-age (12 months) with high vitamin D (10,000 IU cholecalciferol/ Kg rodent diet) showed improved spatial memory performance on the Morris water maze challenge. Thus, it appears that interfering with calcium homeostasis through pathways that are capable of increasing vitamin D receptor activation in the brain, may be a therapeutically meaningful strategy to preserve cognitive function in age and perhaps AD.

Another hormone, estradiol, has also been shown to modulate L-VGCC expression and activity in hippocampal neurons and in GnRH related cells [66; 67]. Interestingly, in both of

these cell types estradiol decreased $Ca_v1.3$ expression but not $Ca_v1.2$. In addition to affecting the expression of the L-VGCC subunit estradiol also modulates L-VGCC activity via a rapid mechanism that results in an increase in calcium influx through L-VGCCs in neurons and other cell lines [68; 69; 70]. This rapid pathway was proposed to be part of a neuroprotective pathway; whether it also functions to regulate physiological processes such as the sAHP is unknown. Nevertheless, the genomic mechanism appears to reduce L-VGCC activity but the rapid mechanism increases L-VGCC activity. This suggests the possibility that L-VGCC channel expression and calcium influx are dynamically regulated by estradiol, and as we and others have previously shown, can be altered in aging [66; 71].

Another recently identified hormone modulator of L-VGCC function in the brain is insulin. While investigating new mechanisms by which certain antidiabetic compounds can reduce calcium channel function and the AHP in hippocampal cells [72; 73], we also recently uncovered the acute and significant actions of insulin on the sAHP [74; 75]. By causing a significant reduction in the AHP, we predict insulin may be able to enhance cellular excitability in aging and offset cognitive decline. Indeed, several clinical studies have provided robust evidence that increasing brain insulin availability through intranasal delivery of the hormone is able to enhance recall in young subjects [76; 77] or MCI patients [78; 79; 80]. Similarly, we have shown beneficial effects of intranasal insulin on memory recall in aged animals in the Morris water maze [74]. Surprisingly, both young healthy subjects and AD patients appear to benefit equally from intranasal insulin. At least in the case of AD, the intranasal administration is presumed to compensate for the reduced insulin signaling. Collectively, these results also suggest insulin signaling may be working differently in young *vs* aged brains. Irrespective, this work lends further support to continue therapeutic efforts attempting to maintain insulin signaling in the brain of the elderly population in order to offset cognitive decline with age or with AD.

In light of these studies, it is tempting to speculate that perhaps vitamin D, estrogen or insulin signaling are all compromised in the aged brain which may contribute to the development of dementia, and that increasing the availability of receptors for these hormones, or the levels of these hormones in the brain could combat cognitive decline in aging. Further, while it would seem that redressing calcium dyshomeostasis may be a pivotal approach to facilitate successful brain aging. However, more direct tests of this hypothesis are required, and investigating how these hormones regulate Ca^{2+} pathways will provide a framework on which to build new pharmacological approaches to combat cognitive decline in aging.

5. Cellular calcium transients have a dendritic origin

Nearly 20 years ago, imaging and electrophysiological approaches were used to derive new information on the complexity of dendritic actions and how neuronal output could be modified by key ion channels along the dendritic tree [81; 82; 83]. These findings culminated in the identification of different calcium sources along dendrites, main apical arbors, spines and shafts [84; 85; 86; 87; 88; 89]. The dendrite is the site for synaptic inputs where integration of signals from different areas of the brain occurs. As a result of action potential firing and the subsequent neurotransmitter release, small, albeit significant calcium

changes are seen in the dendrite and more specifically, the spines of neurons. There, the more subtle role of calcium in controlling encoding and dendritic excitability through local calcium transients is now becoming clear, and includes measures in behaving animals [90; 91; 92; 93; 94; 95; 96]. In field CA1, primary hippocampal neurons are able to integrate signals coming from distal inputs from the entorhinal cortex, and more proximal inputs emitting from area CA3. At least part of this integration is mediated by newly identified dendritic calcium plateau potentials *in vivo* [97]. These short-lived dendritic calcium transients can help drive complex spike output in the main pyramidal neurons of the hippocampus by inactivating sodium channels, enhancing LTP [98] and thereby enhancing firing from coincident inputs in different areas of the brain. This complexity is only beginning to be elucidated in the dendrites of young or adult animals and this level of spatial and temporal resolution has not yet been achieved in animal models of aging or AD.

With the exception of a few additional studies, very little is known about dendritic calcium transients, their spatial and temporal integration, or about the presence and role of back propagating action potentials in apical dendrites in models of aging [99; 100]. Furthermore, these studies did not address changes in cellular cytoarchitecture/ morphology with age, its potential impact on physiology, nor did they study the impact of age-related changes in calcium sources on synaptic plasticity or activation. However, more progress along these lines has been made in animal models of AD. Using genetically-encoded calcium indicators to monitor calcium in spines of cultured neurons from mutant presenilin mice (M146V), recent evidence shows the presence of alterations in stromal interaction molecule 2 function (STIM2; a key regulator of store-operated calcium entry) [101; 102]. In these studies, the authors suggest that the loss of mushroom spines is mediated by the loss of the stabilizing effect of STIM2 on spines, and perhaps occurs in response to elevations in ER calcium levels during aging or in AD [14; 54; 103]. Such studies are helping to identify new pharmaceutical targets and are highlighting new areas of focus in neuroscience.

Work using calcium imaging tools to focus on downstream consequences of calcium overload in AD models has helped shift the attention away from calcium-mediated cell death, and instead emphasize calcium-mediated changes in dendritic morphology, cellular excitability, network activity and plasticity. The first direct *in vivo* evidence showing that elevated Ca^{2+} in cortical dendrites is dependent on the presence of Aβ plaque deposition was recently identified in an AD animal model. Somewhat surprisingly, it was not the presenilin mutation, but rather, the APP mutation which was found to be associated with calcium dysregulation in aged mice [27]. Further, in these APP mutants (17–20 months old), proximity to the plaque was shown to heighten Ca^{2+} dysregulation. In another *in vivo* study using double transgenic mice, imaging from hippocampal CA1 neuronal somata also provided evidence of Ca^{2+} overload, but at much earlier ages (1–2 months) and prior to plaque deposition. However, a role for soluble amyloid still exists as calcium transients and hippocampal excitability were elevated upon application of Aβ dimmers [26]. In both studies, thus it appears that some form of amyloid β may be responsible for inducing neuronal calcium dysregulation.

Greater spatial and temporal resolutions are currently being implemented in the study of neuroscience following the discovery of genetically-encoded calcium indicators [104; 105;

106]. These indicators have the advantage of being fast reporters which can be targeted to specific cellular compartments like the ER and the mitochondria [107; 108]. Studies investigating changes in calcium homeostasis using large arrays of cells are also now providing new *in vivo* results, but only in a limited number of studies in AD models [27; 29; 109]. High resolution *in vivo* calcium imaging using pulsed lasers capable of generating longer wavelengths will provide important information along these lines.

6. New (and old) intricacies of calcium dysregulation with aging

Calcium is not always increased in aging and or in AD. Our lab has published evidence of reduced L-type Ca^{2+} currents in the aged APP/PS1 mouse [110]. Years ago, Lamour's lab showed that calcium dysregulation did not translate well across different strains of rats [111]. Similarly, the Griffith lab also has reported that depending on L-type calcium channel subunits present, increases in L-type currents are not always seen with aging in basal forebrain neurons [112], and are often met with significant increases in calcium buffering capacity [113; 114; 115]. Recently, it was also shown that while more calcium enters the plasma membrane of an aged CA1 pyramidal neuron [100; 116], a corresponding increase in buffering balances this influx up to a point where calcium overload occurs [100]. Of interest, in a study of normal brain aging, we have identified that aged CA1 pyramidal neurons which typically display larger Ca^{2+}-dependent afterhyperpolarizations when triggered postsynaptically, show significantly reduced hyperpolarization (e.g., enhanced hyperexcitability) compared to young animals, when stimulated *synaptically* across physiologically relevant frequencies (3–50 Hz) [117]. It is not yet clear that this form of hyperpolarization in the hippocampus with age during synaptic activity is dependent on calcium. It would be surprising if it were not, as stimulation at 7 Hz produces greater calcium in the soma [118] and dendrites [99; 100] in the aged animal. Given the importance of synaptic communication, stimulation protocols that approximate physiological patterns of activity may need to be studied further with aging and in AD-related neurodegeneration.

7. Overall

That changes in intracellular calcium levels occur with age and in Alzheimer's type dementia or in other neurodegenerative conditions is not new. As we have known for some time, calcium can be a sophisticated orchestrator of fine moment-by-moment events, or a deadly hammer that can overload mitochondria and other calcium buffering systems. Currently, there is greater appreciation for how calcium is able to shape synaptic events that underpin neuronal communication. However, in aging and AD, it is unclear the extent to which dendritic Ca^{2+} sources are modified. Clearly, associations between an animal's behavioral phenotype, electrophysiological characterization across multiple hippocampal subfields and regions (i.e., dorsal *vs.* ventral), network activity and sensitivity to hormones, all need further investigation to understand how calcium sensitive targets are modified in the context of aging. Perhaps insights from these types of studies will allow us to view calcium dysregulation in aging and AD as more than just a destructive force, but instead, allow us to pave the way for novel therapeutic approaches that focus on these more nuanced changes and their effects on neuronal physiology.

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- Dysregulated calcium is not only associated with cell death in aging or AD
- Improved resolution and reporter strategies need implementation in aging research
- Dendritic calcium imaging will provide insights into mechanisms of brain aging
- Hormonal influence over calcium regulation may be a promising therapeutic approach

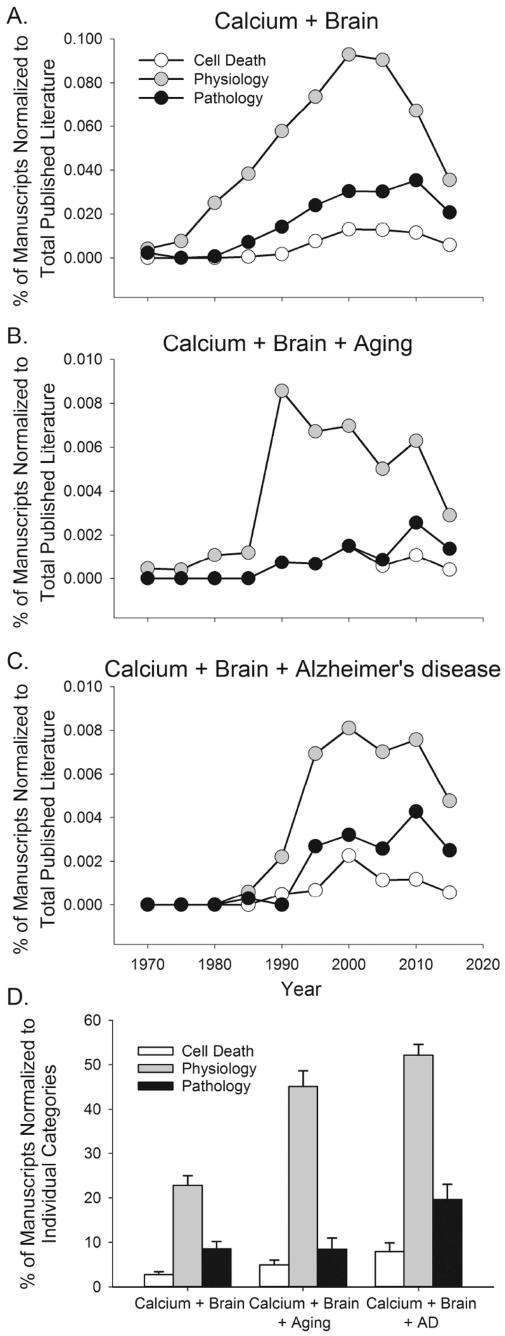

Figure 1.

Survey of the literature relating to calcium dysregulation in the brain. A PubMed search was performed with EndNote using the terms “calcium” and “brain” (**A**) or “calcium” and “brain” and “aging” (**B**), or “calcium” and “brain” and “Alzheimer’s disease” (**C**). The number of papers containing the combined keywords and an association with “cell death”, “physiology”, or “pathology” was obtained once every five years between the years 1970 and 2015 and was normalized to the total number of scientific publications that year. We then restricted the search to the past 30 years and collapsed the data across years and used

the same search strategy. This time, we normalized the number of papers in cell death, physiology or pathology to the total number of papers within “calcium” and “brain” or “calcium” and “brain” and “aging”, or “calcium” and “brain” and “Alzheimer’s disease” is shown in (**D**). It is clear that a greater proportion of the literature focusing on calcium in the brain contains a majority of the work centered on physiological outcomes.