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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.

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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 [2–4]. Framed in the context of a lengthy exposure to glutamatergic neurotransmitters, these necrosis-associated events provided robust evidence that calcium could be a perpetuator of

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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%–55%, Fig. 1D) compared to papers associating calcium in the brain with pathology or cell death (~3%–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 [9–11], suggesting the dysregulation may be "system-wide" rather than just CNS-centered. Whether

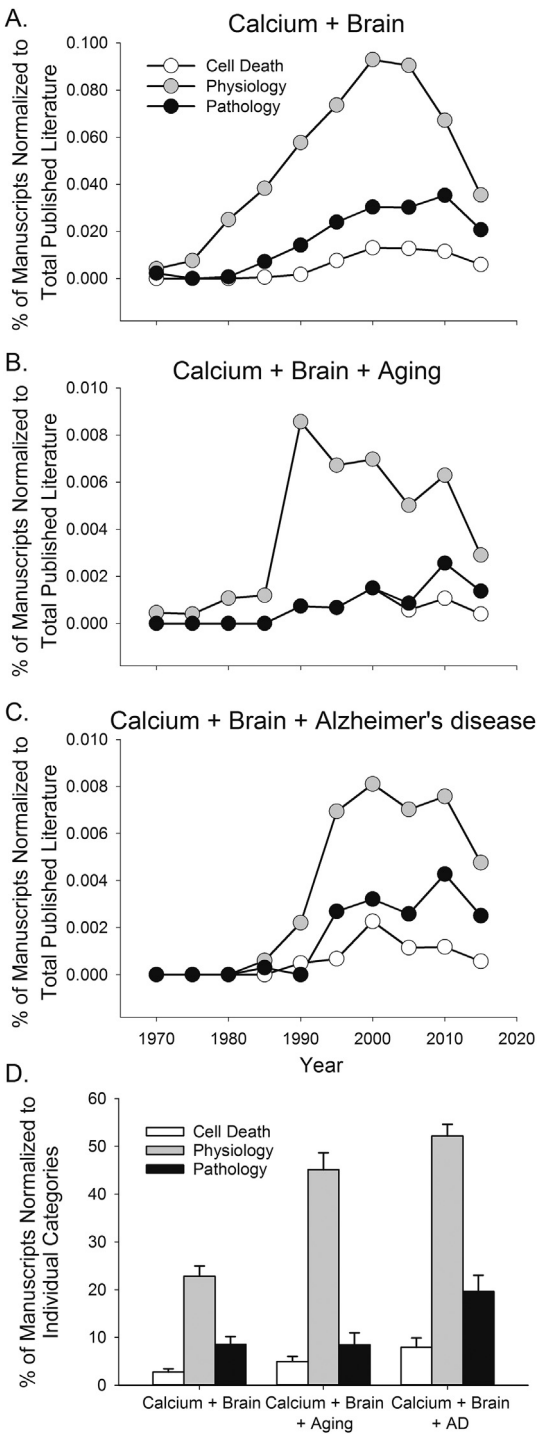

Fig. 1. Survey of the literature relating to calcium dysregulation in the brain. A PubMed search was performed with EndNote using the terms "calcium" and "brain" (**A**) or "calcium" and "brain" and "aging" (**B**), or "calcium" and "brain" and "Alzheimer's disease" (**C**). The number of papers containing 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 (**D**). 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". 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.

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