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FORUM EDITORIAL

Redox Control of Brain Calcium in Health and Disease

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Abstract

Calcium ion is a highly versatile cellular messenger. Calcium signals—defined as transient increments in intracellular-free calcium concentration—elicit a multiplicity of responses that depend on cell type and signal properties such as their intensity, duration, cellular localization, and frequency. The vast literature available on the role of calcium signals in brain cells, chiefly centered on neuronal cells, indicates that calcium signals regulate essential neuronal functions, including synaptic transmission, gene expression, synaptic plasticity processes underlying learning and memory, and survival or death. The eight articles comprising this forum issue address different and novel aspects of calcium signaling in normal neuronal function, including how calcium signals interact with the generation of reactive species of oxygen/nitrogen with various functional consequences, and focus also on how abnormal calcium homeostasis and signaling, plus oxidative stress, affect overall brain physiology during aging and in neurodegenerative conditions such as Alzheimer's or Parkinson's disease. *Antioxid. Redox Signal.* 14, 1203–1207.

THE UNIVERSAL ROLE of Ca^{2+} as a versatile cellular messenger is well established (6). At rest, the intracellular-free Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) is at least 10,000-fold lower than free extracellular $[Ca^{2+}]$. This asymmetry plus the existence of a negative resting membrane potential provides a significant electrochemical driving force for cellular Ca^{2+} influx. Consequently, to maintain Ca^{2+} homeostasis, excitable cells such as neurons use different transport systems, including plasma membrane and sarcoplasmic/endoplasmic reticulum (ER) Ca^{2+}-ATPases, plasma membrane sodium/calcium exchangers, and the mitochondrial uniporter to terminate Ca^{2+} signals and also to counterbalance the basal Ca^{2+} influx and Ca^{2+} leakage from Ca^{2+}-rich intracellular stores that occur at rest (Fig. 1). As pointed out by Gleichmann and Mattson (11), the cost for extensive neuronal Ca^{2+} signaling is increased energy demand, as Ca^{2+} removal from the cytoplasm by ATP-dependent Ca^{2+} transporters entails significant ATP consumption.

Calcium signals, defined as transient increases in $[Ca^{2+}]_{cyt}$, trigger neuronal functions as diverse as neurotransmitter release into the synaptic space, axonal growth, and neuronal plasticity processes that entail gene transcription and that are the cellular basis of complex brain functions such as learning and memory (1). The negative aspect of Ca^{2+} signaling resides in the fact that uncontrolled increases in $[Ca^{2+}]_{cyt}$ damage neuronal cells and may even cause their death. To avoid this downside effect, cells activate different mechanisms to restrain the magnitude and duration of Ca^{2+} signals. Alongside with Ca^{2+} binding to intracellular buffers and activation of Ca^{2+}-dependent K^+ channels to reduce their excitability, neuronal cells also limit the duration of Ca^{2+} entry and release fluxes from intracellular stores and engage homeostatic mechanisms to lower $[Ca^{2+}]_{cyt}$ (4).

Stimulation of Ca^{2+} entry through different plasma membrane pathways or of release of Ca^{2+} from intracellular stores generates cellular Ca^{2+} signals that target different cellular compartments where they evoke different responses (Fig. 1). Calcium influx from the extracellular medium occurs through diverse plasma membrane Ca^{2+} channels, gated by voltage, agonists, or second messengers (7, 15), or by Ca^{2+} store emptying (20). Calcium entry also occurs after activation by diverse stimuli (G proteins, temperature, and mechanical stretch) of other channels, including transient receptor potential channels (17) [see also Zündorf and Reiser (29)]. Calcium release from the ER mediated by two intracellular Ca^{2+} channels—the inositol 1,4,5-trisphosphate ($InsP_3$) receptors ($InsP_3R$) and the ryanodine receptors (RyR)—also produces Ca^{2+} signals (Fig. 1); the importance of these signals for the function of brain cells is becoming increasingly apparent, as discussed in several articles of this forum issue. The brain possesses all three isoforms of these two Ca^{2+} release channels, distributed asymmetrically in different brain regions where they contribute to modulate neuronal function (2, 9, 10, 16).

Calcium signals vary in amplitude, duration, localization, and, in some cases, even in frequency. The presence of high affinity cytoplasmic Ca^{2+} buffers significantly restricts the diffusion of Ca^{2+} ions throughout the cytoplasm. Yet, *via* the

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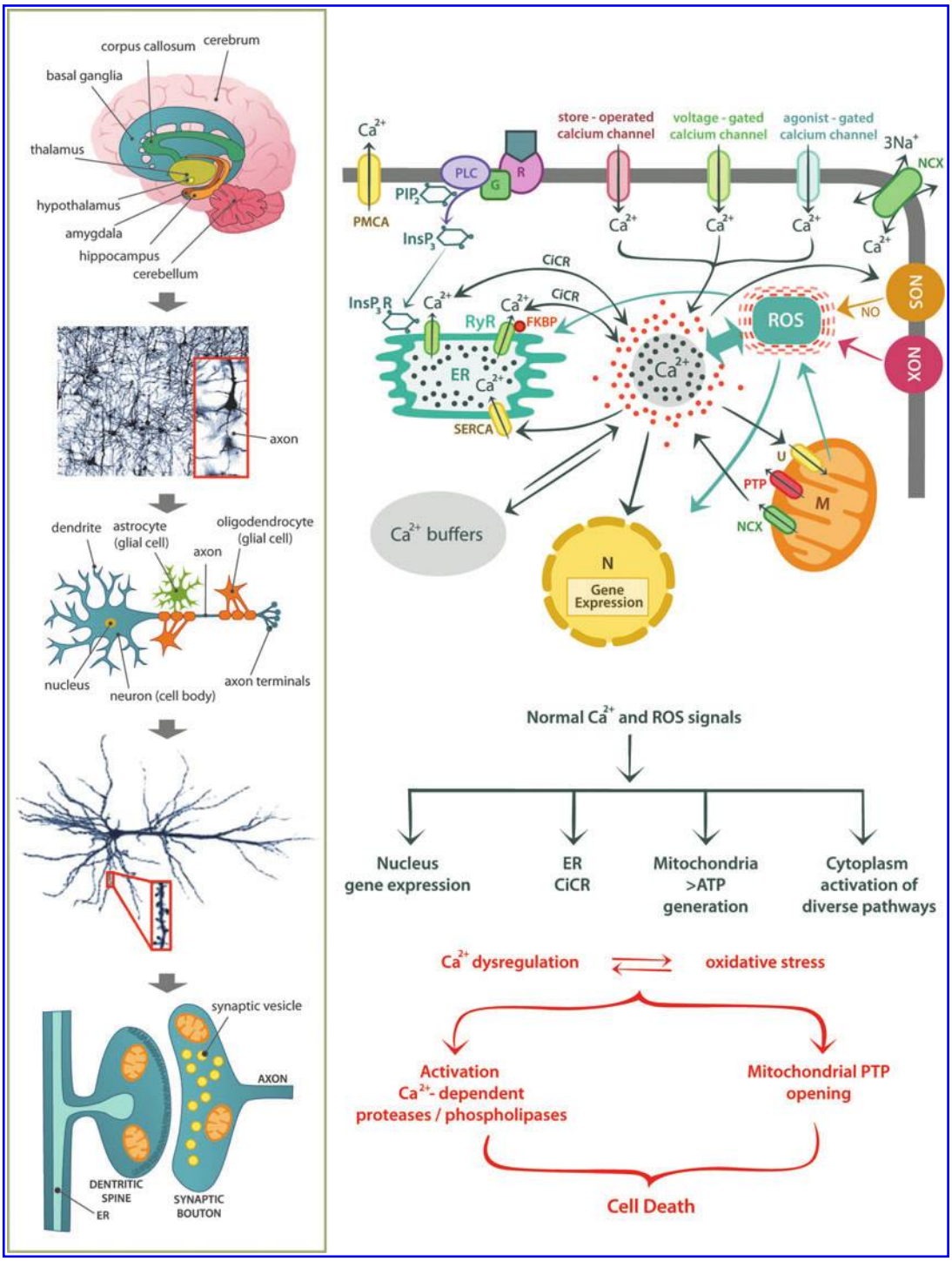

FIG. 1. A scheme showing the main sources of calcium and ROS in neuronal cells, and their possible targets under physiological and pathological conditions. The *left panel* illustrates the complexity of the brain, from its different regions and cellular components to a scheme of the sub-cellular structure of a synapse. At *right*, the figure presents the different molecular entities responsible for the generation of Ca^{2+} and ROS signals, plus the components that maintain Ca^{2+} homeostasis. Here, the term ROS is used in its widest connotation and includes reactive species of oxygen and nitrogen. The physiological targets of Ca^{2+} and ROS signals are exemplified in dark gray text at bottom right, whereas the deleterious consequences of excessive production of Ca^{2+} and ROS signals are indicated in red text. M, mitochondria; NOS, nitric oxide synthase; NOX, NADPH oxidase; N, nucleus; PTP, permeability transition pore of mitochondria; ROS, reactive oxygen species; U, uniporter. The molecular identities of the mitochondrial PTP and the Ca^{2+} uniporter remain unknown.

mechanism known as Ca^{2+}-induced Ca^{2+} release (CICR), Ca^{2+} signals are known to propagate in regenerative fashion to other cell regions, including the nucleus. As illustrated in Figure 1, a vital component of regenerative Ca^{2+} signal propagation *via* CICR is the activation by Ca^{2+} of both Ca^{2+} release channels, $InsP_3R$ and RyR (5, 8, 14). Additionally, it is becoming increasingly apparent that mitochondria play a significant role not only as Ca^{2+} buffers but also in their fused state as continuous elements that propagate Ca^{2+} signals through their interior from one cell region to another (23). Generation of local or propagated Ca^{2+} signals has important functional consequences (22), especially in neuronal cells that possess a complex morphology with different and highly specialized structural domains (Fig. 1) and where the correct spatiotemporal distribution of Ca^{2+} signals is essential. Thus, imaging studies (19) are highly valuable to elucidate the functions of Ca^{2+} and Ca^{2+}-associated signaling molecules. Local Ca^{2+} signals are particularly important for pre- and postsynaptic events, whereas Ca^{2+} signal propagation to the nucleus is a key event in the activation of Ca^{2+}-dependent gene transcription necessary for learning and memory processes.

The central topic on this ARS forum issue, which contains both review articles and original articles, is to analyze how brain cells generate Ca^{2+} signals and how changes in cellular redox sate affects these signals in health and disease. Although the brain is a highly complex organ that contains diverse regions and cells types (Fig. 1), most studies have focused on Ca^{2+} signaling in neuronal cells, producing a copious literature on this topic (a literature search with "calcium" and "neurons" as keywords yielded close to 1200 articles published so far in 2010). Consequently, this current forum issue presents for the most part the current knowledge and important new findings related to different aspects of Ca^{2+} and redox signaling in neuronal cells. The review articles by Zündorf and Reiser (29) and Gleichmann and Mattson (11) present a detailed description of Ca^{2+} homeostasis and signaling. In addition, Zündorf and Reiser (29) discuss the different stimuli that generate Ca^{2+} signals, the role of mitochondria in Ca^{2+} signaling in neuronal cells, as well as some features of Ca^{2+} signals in astrocytes, while the review article by Gleichmann and Mattson (11) addresses the issue of mitochondrial and ER Ca^{2+} homeostasis and how it is related to Ca^{2+} signaling processes, neuronal energy metabolism, aging, and neurodegeneration. Both review articles also deal with a new and emerging topic, cross talk between Ca^{2+} and reactive oxygen species (ROS) generation and signaling (13), and address how perturbations of Ca^{2+} homeostasis occur during aging and in some neurodegenerative conditions such as ischemia or brain inflammation, and in disease conditions such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, and multiple sclerosis.

The role of Ca^{2+} release from the ER in the generation and propagation of Ca^{2+} signals, although not widely acknowledged, is beginning to emerge as discussed in several articles of the present issue. The review article by Okubo *et al.* (19) analyzes how interactions between $InsP_3R$-mediated Ca^{2+} signaling, the excitatory neurotransmitter glutamate, and nitric oxide contribute to regulate cellular function in the cerebellum, and also addresses newly recognized neuronal and glial functions that are regulated by $InsP_3R$-mediated Ca^{2+} release under physiological and pathological conditions. Special emphasis is placed on the use of imaging studies, which allow analysis of spatiotemporal distribution of signaling molecules and identification of Ca^{2+}-regulated signaling pathways in the brain including synaptic maintenance and glial cell-dependent neurite growth.

Understanding the role of nuclear Ca^{2+} and oxidative species as regulators of gene transcription is essential to comprehend brain function. DREAM/KChIP3 is a multifunctional nuclear Ca^{2+} binding protein that acts in the nucleus as a Ca^{2+}-dependent transcriptional repressor. The original research article by Rivas *et al.* (25) describes Ca^{2+}- and redox-dependent activation of DREAM by peroxiredoxin 3, an antioxidant enzyme that uses the thioredoxin system as electron donor. These authors report that co-expression of peroxiredoxin 3 enhances DREAM repressor activity *in vivo* and identify two cysteine residues in the N-terminal domain of DREAM as responsible for its redox modulation, since double Cys to Ser substitution yields a mutant DREAM with stronger repressor activity. Moreover, they suggest that DREAM exerts a protective role against neuronal oxidative damage, since transient DREAM knockdown sensitizes PC12 cells to oxidative stress. Many studies have shown that neuronal electrical activity generates Ca^{2+} signals and increases ROS production. Activation of NFκB-dependent transcription in primary hippocampal neurons by high-frequency field stimulation is the central theme of the original article by Riquelme *et al.* (24). These authors describe how electrical stimulation induces reciprocal activation of RyR-mediated Ca^{2+} signals and ROS (hydrogen peroxide) generation, and how these signals stimulate jointly NFκB activity and increase *c-fos* mRNA and the protein content of the RyR2 isoform.

As illustrated in Figure 1, dysregulation of Ca^{2+} signaling and oxidative stress mutually enhance one another and pose a severe risk to normal neuronal function and survival. The three remaining articles of this forum issue, together with the review articles by Zündorf and Reiser (29) and Gleichmann and Mattson (11), address the role of Ca^{2+} signals and oxidative stress in Parkinson and Alzheimer diseases, two major universal neurodegenerative conditions that afflict the mental health of millions of the aged population. The review article by Surmeier *et al.* (28) tackles Parkinson disease, and focuses on a novel aspect—how dopamine-producing neurons of *substantia nigra pars compacta* are at greatest risk caused by sustained Ca^{2+} entry into the cytoplasm as a consequence of L-type Ca^{2+} channel opening during autonomous pacemaking activity. Sustained Ca^{2+} entry produces elevated mitochondrial oxidant stress, which presumably contributes to the significant damage to this particular neuronal type that occurs during the progression of the disease. This review article, which presents a novel perspective on a cell-specific stress produced by Ca^{2+} entry as a causative condition for Parkinson's disease, concludes by discussing how antagonists for L-type Ca^{2+} channels may provide a novel neuroprotective strategy at the early stages of this disease.

Defective Ca^{2+} homeostasis and signaling may contribute to the development of Alzheimer's disease (3). The original article by Muller *et al.* (18) discusses how presenilin mutations associated to familial Alzheimer's disease affect intracellular Ca^{2+} homeostasis by considerably enhancing $InsP_3R$ activity, and how the ensuing unregulated Ca^{2+} signaling increases ROS generation, presumably an important element in Alzheimer's disease pathogenesis. These authors show that mutant presenilins interact with $InsP_3R$ Ca^{2+} release channels and enhance their activation by low levels of $InsP_3$, such as those present in resting cells, leading to the generation of exaggerated Ca^{2+} signals. Yet, other authors (26) have presented results showing that many familial Alzheimer's disease mutations impair the

Ca^{2+}-leak-channel function of presenilin; the resulting excessive ER Ca^{2+} accumulation would enhance Ca^{2+} release through $InsP_3R$ or RyR channels. Interestingly, presenilin also interacts with the DREAM protein, although conflicting reports exist regarding the functional effects of this interaction on the inhibition or activation of presenilin-induced Ca^{2+} release (25).

The original article by Paula-Lima *et al.* (21) describes how sub-lethal concentrations of soluble amyloid beta peptide oligomers, which are increasingly recognized as causative agents of Alzheimer's disease, generate ROS-dependent prolonged Ca^{2+} signals in primary hippocampal neurons, which are due to RyR-mediated amplification of Ca^{2+} entry *via* N-methyl-D-aspartate receptors. Longer incubation with these oligomers decreases RyR2 protein content, promotes mitochondrial fragmentation, and prevents dendritic spine remodeling induced by brain-derived neurotrophic factor; RyR inhibition affords significant protection against these effects. The authors propose that these deleterious effects may contribute to impair synaptic plasticity processes during the progression of Alzheimer's disease. The reduction of RyR2 protein content produced by amyloid beta peptide oligomers is intriguing, however, since upregulation of RyR3 expression occurs in different transgenic mouse models of Alzheimer's disease. Thus, double or triple transgenic animals overexpressing both the amyloid precursor protein (APP) and presenilin 1 display neuronal RyR3 overexpression and aberrant Ca^{2+} signaling in overall neuronal compartments but primarily in dendritic spines (12). Surprisingly, however, reduction of RyR3 expression by small interfering RNA promoted neuronal death in a transgenic mice model that overexpresses APP but not presenilin 1, indicating a protective role for RyR3 (27). Yet, in agreement with the RyR2 reduction reported by Paula-Lima *et al.* (21), downregulation of RyR expression, particularly of the RyR2 isoform, occurs very early in AD brain human postmortem samples.

To conclude, the role of Ca^{2+} signals on the function of such a complex organ as the brain is an ever-expanding subject that is likely to generate significant progresses in the near future. Although many functions related to Ca^{2+} signaling in the brain have been described, it is likely that there are many others that remain unrecognized, as pointed out by Okubo *et al.* (19). Knowledge gained in this field will allow a better understanding of normal brain function, which should in turn provide useful insights on how alterations in brain Ca^{2+} and ROS signaling cause severe pathological conditions. The hope remains that new tools will be developed in the near future to combat the painful neurodegenerative diseases associated with aging and that affect a large number of the world population.

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Dedication

This forum is dedicated to the memory of Dr. M. Angélica Carrasco, who passed away in November 2010.

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Abbreviations Used

APP = amyloid precursor protein
CICR = Ca^{2+}-induced Ca^{2+} release
ER = endoplasmic reticulum
$InsP_3$ = inositol 1,4,5-trisphosphate
$InsP_3R$ = $InsP_3$ receptor
NOS = nitric oxide synthase
NOX = NADPH oxidase
PTP = permeability transition pore of mitochondria
ROS = reactive oxygen species
RyR = ryanodine receptors

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