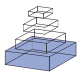
frontiers in
AGING NEUROSCIENCE

REVIEW ARTICLE
published: 27 November 2009
doi: 10.3389/neuro.24.002.2009



Susceptibility to calcium dysregulation during brain aging

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Calcium (Ca^{2+}) is a highly versatile intracellular signaling molecule that is essential for regulating a variety of cellular and physiological processes ranging from fertilization to programmed cell death. Research has provided ample evidence that brain aging is associated with altered Ca^{2+} homeostasis. Much of the work has focused on the hippocampus, a brain region critically involved in learning and memory, which is particularly susceptible to dysfunction during senescence. The current review takes a broader perspective, assessing age-related changes in Ca^{2+} sources, Ca^{2+} sequestration, and Ca^{2+} binding proteins throughout the nervous system. The nature of altered Ca^{2+} homeostasis is cell specific and may represent a deficit or a compensatory mechanism, producing complex patterns of impaired cellular function. Incorporating the knowledge of the complexity of age-related alterations in Ca^{2+} homeostasis will positively shape the development of highly effective therapeutics to treat brain disorders.

Keywords: calcium homeostasis, aging, brain, hippocampus, *N*-methyl-D-aspartate receptor, voltage-dependent calcium channels, intracellular calcium stores, cognitive impairments

INTRODUCTION

The Ca^{2+} ion is a central signaling molecule in numerous cellular functions including apoptosis, energy production, gene regulation, cell proliferation, membrane excitability, synaptic transmission and plasticity. Due to the ubiquitous nature of Ca^{2+} signaling, Ca^{2+} is one of the most highly regulated ions with the concentration inside the cell maintained at a level 10,000 times lower than the concentration in the extracellular space (Berridge et al., 2000; Rizzuto, 2001; Orrenius et al., 2003). Accordingly, any change in Ca^{2+} regulating mechanisms, unless compensated by another mechanism, will result in an alteration in cell function.

The Ca^{2+} 'dysregulation' hypothesis of brain aging and Alzheimer's disease formulated in the 1980s was based on discrete observations of alterations in processes that are regulated by Ca^{2+} (Landfield and Pitler, 1984; Gibson and Peterson, 1987; Khachaturian, 1989). Over 20 years of research has accumulated substantial evidence for alterations in Ca^{2+} homeostasis in contributing to cellular senescence. However, no single mechanism for Ca^{2+} dysregulation has been found. Rather the causes and consequences of Ca^{2+} dysregulation vary across the nervous system. As we increase our sophistication for identifying molecular and cellular processes, we are likely to find complex patterns of impaired/spared cellular function related to multiple Ca^{2+} regulating mechanisms. Several recent reviews have detailed how different mechanisms for Ca^{2+} dysregulation contribute to changes in cell excitability (Disterhoft and Oh, 2006) and synaptic plasticity (Foster, 2007) in the hippocampus. Conversely, in other regions of the nervous system, changes in Ca^{2+} regulation may represent compensation to delay physiological aging (Buchholz et al., 2007; Murchison and Griffith, 2007), suggesting that cell specific differences in the expression of Ca^{2+} regulating mechanisms may contribute to regional differences in the rate of brain aging. Similarly, cell specific differences in Ca^{2+} regulating mechanisms may interact with neurodegenerative disorders to determine the pattern of cell death within the brain (Morrison et al., 1998; LaFerla, 2002; Mattson, 2007; Chan et al., 2009; Naidoo, 2009). Thus, mutations for genes involved in one aspect of Ca^{2+} regulation may result is pathogenesis in regions which are more susceptible to other forms of Ca^{2+} dysregulation. In this review, we focus on cell specificity in the operation of a subset of Ca^{2+} regulatory mechanisms during aging and how this specificity might relate to the loss or preservation of cell function.

Ca^{2+}-signaling depends principally on a rapid and transient increase in intracellular Ca^{2+} concentration through influx of Ca^{2+} from several sources. In most cells, multiple mechanisms exist whereby elevation in intracellular Ca^{2+} concentrations may occur. The major sources of intracellular Ca^{2+} include Ca^{2+} influx through ligand-gated glutamate receptors, such as *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) or various voltage-dependent Ca^{2+} channels (VDCCs), as well as the release of Ca^{2+} from intracellular stores (Ghosh et al., 1994; Geiger et al., 1995; Berridge, 1998). The relative contribution of these sources will depend on the cell type: neuron, astrocyte, oligodendrocyte or microglia. In the case of neurons, Ca^{2+} sources will vary depending on their size, transmitter system, and location in neural circuits (i.e., excitatory or inhibitory). Finally, we discuss age-related changes to the other aspect of Ca^{2+} homeostasis, the Ca^{2+} buffering and extrusion mechanisms (**Figure 1**).

NMDA RECEPTORS

NMDARs are ionotropic non-selective cationic glutamate receptors, which play a central role in the rapid regulation of synaptic plasticity. NMDARs are hetero-tetrameric protein complexes composed of two classes of subunits, the ubiquitously expressed and essential subunit (NR1) and a modulatory subunit (NR2A-NR2D) (Moriyoshi et al., 1991; Kutsuwada et al., 1992; Meguro et al., 1992; Monyer et al., 1992; Cull-Candy et al., 2001). The activation of NMDAR requires binding of a ligand (glutamate), membrane depolarization (to remove the Mg^{2+} block of the channel), and binding of a co-agonist, glycine. Since NMDAR is a non-selective cation channel, its activation and opening leads to simultaneous

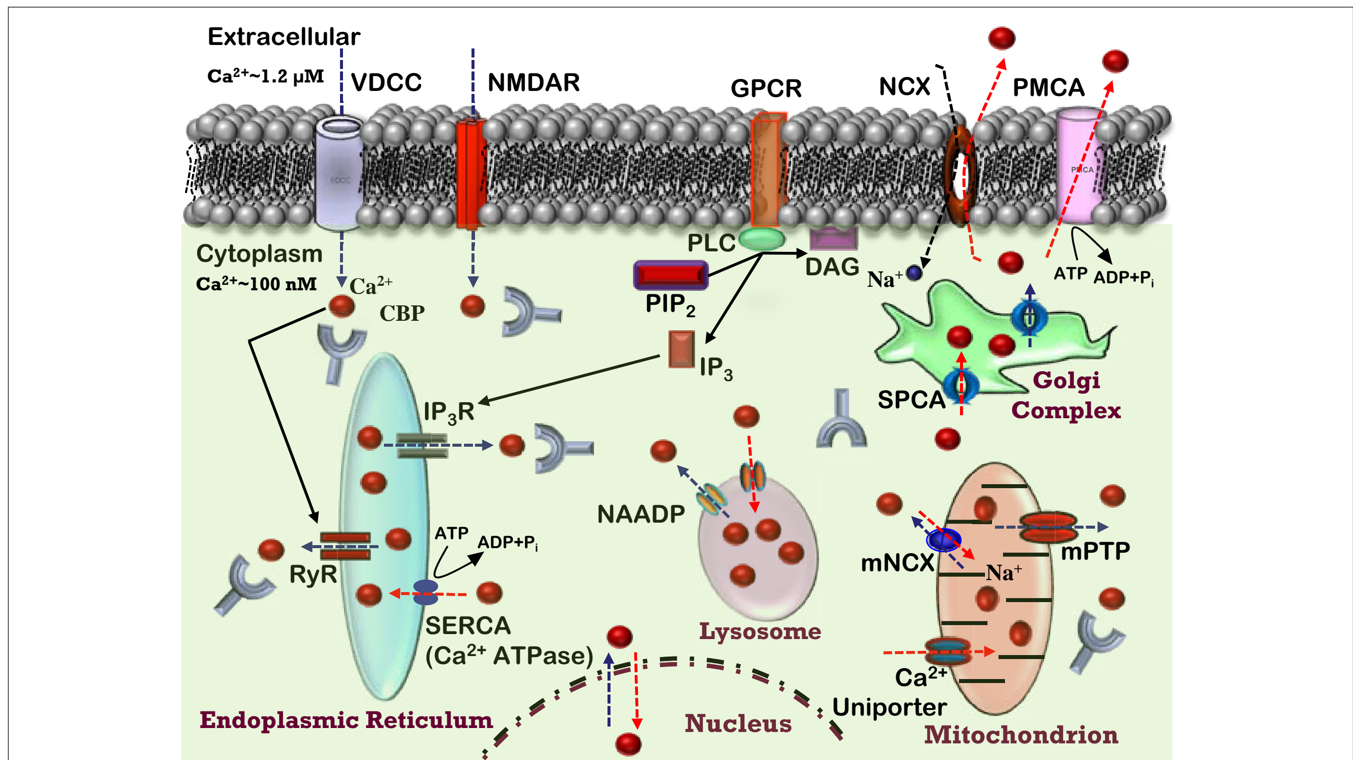

FIGURE 1 | Ca^{2+} homeostasis in the neuron. Model depicting various Ca^{2+} sources, sequestrating, buffering mechanisms, and Ca^{2+} signaling events in a healthy neuron. Indicated are the voltage-dependent Ca^{2+} channels (*VDCC*), *N*-methyl-D-aspartate receptor (*NMDAR*), and G protein-coupled receptor (*GPCR*) involved in Ca^{2+} (*red balls*) influx into the cytosol (*blue dashed arrows*). The release of Ca^{2+} into the cytoplasm also occurs from the intracellular Ca^{2+} stores (*ICS*) through inositol (1,4,5)-trisphosphate receptor (*IP_3R*) and ryanodine receptors (*RyR*). Organelles, including the endoplasmic reticulum (*ER*), mitochondria, and lysosomes act as a Ca^{2+} buffering system, releasing and sequestering Ca^{2+}. Further, the model depicts Ca^{2+} buffering and extrusion pathways (*red dashed arrows*), involving Na^+/Ca^{2+} exchanger (*NCX*) and plasma membrane Ca^{2+} ATPase (*PMCA*), sarcoplasmic reticulum Ca^{2+} ATPases (*SERCA*), nicotinic acid adenine dinucleotide phosphate (*NAADP*), various Ca^{2+} binding proteins (*CBP*). Mitochondrial permeability transition pore (*mPTP*) and mitochondrial Na^+/Ca^{2+} exchanger (*mNCX*) and secretory pathway Ca^{2+}-ATPases (*SPCA*) contribute to Ca^{2+} regulation.

influx of Na^+ and Ca^{2+} ions (Chen et al., 2005). However, between the two predominant ionotropic glutamate receptors subtypes, the NMDARs are the most permeable to Ca^{2+} ions (Garaschuk et al., 1996).

There is considerable evidence to indicate that aging is associated with a decline in NMDAR function within brain regions involved in higher brain function including learning and memory (Gonzales et al., 1991; Pittaluga et al., 1993; Barnes et al., 1997; Magnusson, 1998; Eckles-Smith et al., 2000; Gore et al., 2002; Liu et al., 2008b; Zhao et al., 2009). Perhaps the strongest evidence for a reduction in NMDAR function comes from physiological studies which indicate that the NMDAR mediated excitatory post synaptic potentials in the Schaeffer collateral pathway of the hippocampus are reduced by approximately 50% in aged animals (Barnes et al., 1997; Eckles-Smith et al., 2000; Bodhinathan et al., 2007). However, age-related changes in the amplitude of NMDA-evoked responses were not observed in dissociated cortical neurons suggesting the possibility of regional specificity in the loss of NMDAR function (Kuehl-Kovarik et al., 2003). Several studies indicate a decrease in the level of NMDAR protein expression in the hippocampus during aging (Bonhaus et al., 1990; Kito et al., 1990; Miyoshi et al., 1991; Tamaru et al., 1991; Wenk et al., 1991; Magnusson, 1995; Magnusson et al., 2006; Billard and Rouaud, 2007; Das and Magnusson, 2008; Liu et al., 2008b; Zhao et al., 2009); further, the decrease has primarily been localized to region CA1 (Magnusson and Cotman, 1993; Gazzaley et al., 1996; Magnusson, 1998; Wenk and Barnes, 2000). These studies report reduced binding of [^{3}H] glutamate (agonist site), [^{3}H] glycine (NR1 site), [^{3}H] CPP (a competitive antagonist to the L-glutamate binding site), and [^{3}H] MK-801 (an open channel blocker) in the hippocampus and cerebral cortex of aged rats. However, others have reported no age-related change in antagonist binding (Kito et al., 1990; Miyoshi et al., 1991; Araki et al., 1997; Shimada et al., 1997) or an increased MK-801 binding in animals with learning and retention deficits (Ingram et al., 1992; Topic et al., 2007). It is interesting to note that MK-801 binds to the hydrophobic channel domain of NMDAR, exclusively labeling open channels. Thus, an apparent increase in NMDAR channel open time may act as a compensatory mechanism for the decrease in receptor number (Serra et al., 1994). However, the majority of reports, including our recent findings, indicate that the net function of the NMDARs decreases at CA3-CA1 hippocampal synaptic contacts during senescence (Bodhinathan et al., 2007).

One of the potential mechanisms for the observed decrease in the NMDAR function is related to altered expression of specific NMDAR subunits (Magnusson, 2000). Significant decreases have been observed in the expression of NR1 protein (Eckles-Smith

et al., 2000; Mesches et al., 2004; Liu et al., 2008a) and NR1 mRNA (Adams et al., 2001) levels in the aged hippocampus. In contrast, other studies report no age-related decrease in NR1 protein expression in the whole hippocampus (Sonntag et al., 2000; Zhao et al., 2009). Despite the lack of congruent changes in the expression levels in the hippocampus, other brain regions exhibit a decline in NR1 mRNA expression during aging. Indeed, senescence-related decrease in the NR1 mRNA expression has been observed in the medial basal hypothalamus-median eminence (Gore et al., 2002), in the medial and lateral prefrontal cortices (Magnusson et al., 2005), and in the insular, orbital, and somatosensory cortices (Das and Magnusson, 2008).

Some studies indicate age-related changes in the modulatory NR2 subunits. A decrease in the NR2A protein expression has been observed in the hippocampus (Sonntag et al., 2000; Liu et al., 2008b), which is not observed in the frontal cortex (Sonntag et al., 2000). Furthermore, NR2A mRNA expression was reported to decline in the ventral hippocampus (Adams et al., 2001). In contrast, other studies report no significant change in the NR2A protein expression levels in the hippocampus and cortex (Sonntag et al., 2000; Martinez Villayandre et al., 2004). Age-related changes have also been reported for NR2B subunit of the NMDAR; in particular the expression of NR2B protein (Mesches et al., 2004; Zhao et al., 2009) and NR2B mRNA (Adams et al., 2001; Magnusson, 2001) declines in the hippocampus. This effect may be region specific since a decline in NR2B protein is not observed in the frontal cortex (Sonntag et al., 2000). In contrast, NR2B mRNA decreases in the frontal cortices of aging macaque monkeys, but not in the hippocampus (Bai et al., 2004).

From a physiological standpoint, the changes in the expression of specific NR2 subunits could have dramatic influences on NMDAR function through the regulation of mean channel open time and conductance of the NMDARs. Studies on recombinant NMDAR expressed in *Xenopus* oocytes demonstrate that NMDARs containing the NR2A subunit (NR2A-NMDARs) have faster deactivation kinetics relative to NR2B containing NMDARs (NR2B-NMDARs) (Cull-Candy et al., 2001), such that smaller ion flux is observed for the NR2A-NMDARs, relative to the NR2B-NMDARs. Thus, a shift in the level of NR2 subunit expression could modify the time course and magnitude of the Ca^{2+} signal leading to reduced Ca^{2+} influx associated with loss of NR2B. A shift in NR2A and NR2B expression is thought to contribute to developmental changes in cognition and synaptic function (Dumas, 2005).

Alternatively it is possible that alterations in the NMDAR localization, through the insertion of receptors into the membrane or recruitment of extra-synaptic receptors into the synapse, may have important effects on NMDAR function during aging. It has been suggested that NR2B containing receptors may be more prevalent at extra-synaptic sites (Massey et al., 2004), which could temporarily house the NMDARs, before being internalized into the cytoplasm (Blanpied et al., 2002; Lau and Zukin, 2007). In the frontal cortex, the expression of the NR2B subunit is reduced in the synaptic membrane fraction, but not in the whole homogenate of senescent mice suggesting that NR2B containing receptor sequestration at the extra-synaptic sites may be the mechanism by which the NR2B levels decline during aging (Zhao et al., 2009). Finally, recent work indicates that extra-synaptic NMDARs couple to different signaling cascades, and initiate mechanisms that oppose synaptic potentiation, by shutting off the activity of cAMP response element binding protein and decreasing expression of brain-derived neurotropic factor (Hardingham et al., 2002; Vanhoutte and Bading, 2003). However, it remains to be determined whether altered localization of the NMDARs (specifically extra-synaptic localization) is the mechanism by which the NMDAR function declines during senescence.

Another likely candidate mechanism for regulating NMDAR function during aging is posttranslational modification of the receptor. In particular, the function of the NMDAR is influenced by its phosphorylation state. Activation of the tyrosine kinase (Wang et al., 1994; Heidinger et al., 2002), protein kinase C (Ben-Ari et al., 1992; Chen and Huang, 1992) and protein kinase A (Raman et al., 1996) increases NMDAR mediated currents. In contrast, protein phosphatases, including calcineurin and protein phosphatase 1, decrease NMDAR currents (Lieberman and Mody, 1994; Wang et al., 1994; Raman et al., 1996). Phosphorylation state of NR2A and NR2B subunits can rapidly regulate surface expression and localization of these receptors (Gardoni et al., 2001; Chung et al., 2004; Hallett et al., 2006; Lin et al., 2006). For example, phosphorylation of serine residues within the alternatively spliced cassettes of the C-terminal tail of NR1 promotes receptor trafficking from the endoplasmic reticulum (ER) and insertion into the postsynaptic membrane (Scott et al., 2001; Carroll and Zukin, 2002). Finally, increased phosphatase activity has been linked to the internalization of NMDARs (Snyder et al., 2005). Thus, the kinases and phosphatases act like molecular switches which increase or decrease NMDAR function, respectively. Interestingly, aging is associated with a shift in the balance of kinase/phosphatase activity, favoring an increase in the phosphatase activity (Norris et al., 1998a; Foster et al., 2001; Foster, 2007). Thus alterations in the phosphorylation state of the NMDAR could underlie the decrease in the NMDAR function during aging (Coultrap et al., 2008).

NMDAR function can be altered by the oxidation and reduction of sulfhydryl moieties on their structure. Previous research demonstrates that oxidizing agents like 5,5′-dithiobis(2-nitrobenzoic acid) (Aizenman et al., 1989), hydroxyl radicals generated by xanthine/xanthine oxidase (Aizenman, 1995) and oxidized glutathione (Sucher and Lipton, 1991) decrease NMDAR function in the neuronal cell cultures. The decrease in NMDAR function under oxidizing conditions is thought to result from the formation of disulfide bonds on the sulfhydryl group containing amino acid residues in NMDARs (Aizenman et al., 1990; Sullivan et al., 1994; Choi et al., 2001). The aging brain is associated with an increase in the levels of oxidative stress and/or a decrease in redox buffering capacity (Foster, 2006; Poon et al., 2006; Parihar et al., 2008), conditions that should promote a decrease in NMDAR function.

Finally, NMDAR function in neurons is regulated by local supporting cells, astrocytes and microglia, thus acting as an additional possible mechanism for the age-related changes to NMDAR function. Astrocytes are a major source of D-serine an endogenous co-agonist for the NMDAR, which binds to the glycine site (Schell et al., 1995). An age-related loss of D-serine is observed in the hippocampus and cortex of rats (Williams et al., 2006). Furthermore, the age-related decline in the NMDAR function is rescued by D-cycloserine (Billard and Rouaud, 2007). Microglia

contribute to the brain's immune system and activated microglia can release D-serine (Wu and Barger, 2004; Wu et al., 2004). In accordance with this idea, recent reports suggest that microglia can potentiate the NMDAR-mediated synaptic responses in cortical neurons (Moriguchi et al., 2003; Hayashi et al., 2006). Markers of neuroinflammation increase with age and in certain neurodegenerative disorders. Finally, there is evidence for a feedback reduction in NMDARs due to excess synaptic glutamate activity during microglial activation (Rosi et al., 2004, 2006).

In light of the interaction of NMDARs and microglia, it is important to consider the possibility that the decrease in NMDAR function might represent a compensatory neuroprotective mechanism associated with inappropriate receptor activity or increased Ca^{2+} due to other mechanisms (see below). Thus, impaired NMDAR-dependent synaptic plasticity and memory decline may be epiphenomena due to processes for cell preservation (Foster, 1999). Indeed, over expression of NR2B subunits improves synaptic plasticity and memory in aged mice (Cao et al., 2007) indicating that increased NMDAR function can ameliorate physiological aging. However, cognition and synaptic plasticity are also improved by treating with the low-affinity voltage-dependent NMDAR channel blocker, memantine (Barnes et al., 1996; Norris and Foster, 1999; Pieta Dias et al., 2007), possibly by reducing inappropriate NMDAR activity (Rosi et al., 2006; Matute, 2007; Chang and Gold, 2008). In the case of neurodegenerative disease, decreased expression of NR1 mRNA has been observed in brain regions that are most at risk for cell death, including Huntington's disease, wherein a decrease in NR1 mRNA expression is observed in the neostriatum (Arzberger et al., 1997). Furthermore, there is evidence for decreased NMDA receptors expression in the hippocampus during the early stages of Alzheimer's disease (Jacob et al., 2007; Mishizen-Eberz et al., 2004). Thus, it will be important for future research to determine whether enhancing or inhibiting NMDAR function will be beneficial in preserving memory during normal aging and in the face of neurodegenerative disease.

VOLTAGE-DEPENDENT Ca^{2+} CHANNELS

VDCCs are ion channels in the plasma membrane, which open in response to membrane depolarization and allow Ca^{2+} influx into the cell from the extracellular space. VDCCs, which are heteromultimers and are composed of an α_1 subunit and three auxiliary subunits, $\alpha_2\delta$, β_{1-4}, and γ (Jones, 1998; Catterall, 2000; Kang et al., 2001; Dolphin, 2006), provide one of the most effective sources of Ca^{2+} influx into the neuron (Bertolino and Llinas, 1992). The pore forming α_1 subunit (190 kDa) is the primary subunit necessary for channel functioning. Each α_1 subunit has four homologous domains (I–IV), which are composed of six transmembrane helices. The fourth transmembrane helix of each domain contains the voltage-sensing motif. Two classes of VDCCs have been described; high-voltage-gated and low-voltage-gated channels, which are activated by strong and weak depolarization, respectively. On the basis of differential biophysical properties and sensitivity to pharmacological agents, high-voltage-gated channels are further classified into the L (Ca_v1.1-3), P/Q (Ca_v2.1), and N (Ca_v2.2) type channels. The low-voltage-gated channels include the T (Ca_v3.1) type channels; in addition, an intermediate-voltage-gated channel, R (Ca_v2.3) type is expressed throughout the central nervous system (Veselovskii and Fedulova, 1983; Carbone and Lux, 1984; Fedulova et al., 1985; Nilius et al., 1985; Nowycky et al., 1985; Bean, 1989; Soong et al., 1993).

In hippocampal CA1 pyramidal neurons of the rat, the whole-cell L-type Ca^{2+} currents are increased (Campbell et al., 1996; Brewer et al., 2009) and an increase in the density of functional L-type VDCCs have been reported for aged animals (Thibault and Landfield, 1996). The idea that L-channels are increased in the hippocampus during senescence is also supported by mRNA and protein expression studies indicating an increase in Ca_v1.3 (Herman et al., 1998; Chen et al., 2000; Veng et al., 2003). Furthermore, posttranslational changes including the phosphorylation state of the Ca_v1.2 channel could contribute to age-associated increase in activity (Norris et al., 1998a; Norris et al., 2002; Davare and Hell, 2003). However, L-channel associated intracellular Ca^{2+} transients may show region specific variations within the hippocampus itself. For example, a recent report indicates that CA3 interneurons in aged hippocampus exhibit no alterations in intracellular Ca^{2+} transients at resting state; however larger Ca^{2+} transients are evident in the presence of external excitatory drive produced by kainate application (Lu et al., 2009). Several cellular biomarkers of senescent physiology in the hippocampus are dependent on VDCC function and L-type channel blockers can reverse age-related changes in the magnitude of the aftehyperpolarization and spike frequency adaptation (Moyer Jr. et al., 1992; Disterhoft et al., 1996; Norris et al., 1998b; Kumar and Foster, 2002). In turn, the reduction in the afterhyperpolarization permits increase activation of NMDAR, to shift the threshold for induction of synaptic plasticity (Shankar et al., 1998; Norris et al., 1998b). It should be noted that L-channel blockade does not completely ameliorate age-related differences. The afterhyperpolarization amplitude is reduced but not to the levels observed in young animals (Power et al., 2002). In aged rats, under L-channel blockade, the induction of long-term potentiation is facilitated for low level synaptic activation, which would not induce synaptic modification in young animals (Norris et al., 1998b). Regardless, L-channel blockers appear to improve hippocampal-dependent learning and memory in aged animals (Deyo et al., 1989; Straube et al., 1990; Thompson et al., 1990; Levy et al., 1991; Levere and Walker, 1992; Moyer Jr. et al., 1992; Quartermain et al., 1993; Kowalska and Disterhoft, 1994; Solomon et al., 1995; Woodruff-Pak et al., 1997; Quevedo et al., 1998; Veng et al., 2003; Rose et al., 2007), non-human primates (Sandin et al., 1990), and humans (Ban et al., 1990; Lopez de Armentia and Sah, 2004; Trompet et al., 2008).

It is unclear exactly why L-channels increase in the hippocampus with advanced age. The increase in L-channel function appears to be specific to hippocampal pyramidal cells. The expression of L-channels in the cortex does not change or is decreased by age (Tanaka and Ando, 2001; Iwamoto et al., 2004), and peak currents for high-voltage-gated channels are not increased in the basal forebrain (Murchison and Griffith, 1996). The expression of L-channels in the hippocampus is regulated by the sex steroid estrogen, such that an increased expression is associated with the decline of the hormone during aging (Foster, 2005) Finally, it is possible that the increased L-channel function, increased afterhyperpolarization, and reduction in cell excitability represent compensatory

mechanisms associated with Ca^{2+} dysregulation during senescence, which attempts to limit depolarization and further influx of Ca^{2+} through NMDARs (Foster, 1999).

In direct contrast to the hippocampus, altered Ca^{2+} homeostasis in basal forebrain neurons of rats appears to result from the inactivation of high-voltage-gated currents and an increase in Ca^{2+} from T-type, low-voltage-gated channels (Murchison and Griffith, 1995; Murchison and Griffith, 1996; Murchison and Griffith, 2007). T-channels have been localized on dendrites (Magee and Johnston, 1995a,b; Christie et al., 1996a,b; Yasuda et al., 2003) where they likely influence synaptic function (Komatsu and Iwakiri, 1992; Yoshimura et al., 2008; Uebele et al., 2009). Interestingly, the age-related shift in T-type channels in the basal forebrain appears to be specific to cholinergic neurons (Han et al., 2005) and may influence the magnitude of the afterhyperpolarization (Murchison et al., 2009). The influence of these changes on cell function and cognition remain to be determined. Similarly, much less is known concerning other high-voltage-gated channels and aging. N-channels may be decreased in the cortex with age (Tanaka and Ando, 2001). Animal models suggest that altered P/Q-type channel expression could contribute to age-related changes in cognition and motor function (Alonso et al., 2008). There is evidence that the expression of P/Q splice variants changes with age in different brain regions (Tanaka and Ando, 2001; Iwamoto et al., 2004; Chang et al., 2007; Martella et al., 2008). Thus, more research is required in order to determine how Ca^{2+} channels other than the L-channel contribute to Ca^{2+} regulation during aging.

Mounting evidence indicates that Ca^{2+} channels in the membrane contribute to the specificity of cell loss and the progression of Parkinson's and Alzheimer's disease. For example, in the substantia nigra, a high level of $Ca_v1.3$ L-type channel activity contributes to the discharge pattern of dopamine pacemaker neurons. This activity results in a large Ca^{2+} influx which is buffered by intracellular stores. However, in Parkinson's disease, disruption of this buffering process due to genetic or environmental stress results in toxic levels of Ca^{2+} leading to cell death (Chan et al., 2009). Furthermore, with advanced age, these neurons increase their reliance on L-channel activity to regulate pacemaker activity, increasing their liability (Chan et al., 2007). Thus, the activity of the L-channel provides the specificity for cell loss in Parkinson's disease.

Temporal lobe regions, including the hippocampus, exhibit marked cell loss associated with Alzheimer's disease. The beta amyloid protein of Alzheimer's disease, increases cytosolic Ca^{2+}, impairs synaptic plasticity, and increases cell death through an L-channel-dependent mechanism (Freir and Herron, 2003; Fu et al., 2006; Lopez et al., 2008). Polymorphism of a recently identified Ca^{2+} channel has been linked to late-onset Alzheimer's disease (Dreses-Werringloer et al., 2008). Interestingly, this gene is predominantly expressed in brain regions, such as the hippocampus, which exhibit early and profound cell loss. Together, the results indicate that Ca^{2+} channels provide a point of cross talk between age-related Ca^{2+} dysregulation and signaling in neurodegenerative diseases resulting in selectivity of cell loss.

INTRACELLULAR Ca^{2+} STORES

In addition to Ca^{2+} influx from outside the cell, intracellular Ca^{2+} stores (ICS) play a major role in regulating larger Ca^{2+} signals (Mattson et al., 2000; Ly and Verstreken, 2006). Organelles, including the ER, mitochondria, and lysosomes act as Ca^{2+} buffering systems – releasing and sequestering Ca^{2+} (Duchen, 2000; Nicholls and Budd, 2000; Toescu et al., 2000; Solovyova et al., 2002; Toescu and Verkhratsky, 2004; McGuinness et al., 2007; Murchison and Griffith, 2007). Thus, there are at least two possible mechanisms by which ICS regulate Ca^{2+} homeostasis: (1) release of stored Ca^{2+} to enhance Ca^{2+} signals and (2) removing cytosolic Ca^{2+} following a large influx.

Two pathways control the release of Ca^{2+} from the ER, Ca^{2+}-induced Ca^{2+} release (CICR) and the inositol (1,4,5)-trisphosphate (IP_3) pathway activated by G protein-coupled receptors (GPCR). GPCRs activate phospholipase C (PLC) to form diacylglycerol and IP_3 which act on IP_3 receptors (IP_3Rs) to release Ca^{2+} from ICS. While several studies indicate age-related changes in GPCRs or PLC (Roth, 1995; Mizutani et al., 1998; Nicolle et al., 1999), we will focus on Ca^{2+} release induced by IP_3R activation. Previous reports have observed a decrease in IP_3R in several brain regions (Burnett et al., 1990; Igwe and Ning, 1993; Martini et al., 1994; Simonyi et al., 1998). Despite a general decrease in the receptor, the literature suggests that a decrease in IP_3 induced Ca^{2+} release is either limited to cortical cells (Burnett et al., 1990) or no age-related change is observed (Stutzmann et al., 2006). The disconnect between a reduction in IP_3R expression and the apparent absence of an effect of age on IP_3-induced Ca^{2+} release may be due to increased oxidation of the IP_3Rs which has been demonstrated to increase IP_3R function in brain cells (Peuchen et al., 1996; Long et al., 2009). As such, reduced expression may act as compensation for an altered redox state, in order to maintain proper IP_3 signaling.

CICR is a Ca^{2+} amplification process that is initiated by influx of Ca^{2+} through membrane channels or from ICS through the activation of IP_3Rs. The intracellular Ca^{2+} binds ryanodine receptors (RyRs) to release additional Ca^{2+} into the cytosol from the ER. Accumulating evidence supports a role of altered CICR in contributing to altered physiology of normal aging. The increased involvement of RyRs does not appear to be due to increased RyR expression (Martini et al., 1994). Rather, an age-related increase in oxidative stress and a shift in the intracellular redox state may enhance the responsiveness of RyRs to intracellular Ca^{2+} (Hidalgo et al., 2004; Bull et al., 2007; Gokulrangan et al., 2007). Thus, like IP_3Rs, a shift in the redox state may provide a general aging mechanism to promote Ca^{2+} release from RyRs. Again, the contribution of this source of Ca^{2+} to Ca^{2+} dysregulation is cell specific and will depend on other Ca^{2+} regulating mechanisms. For example, CICR is decreased during senescence in peripheral synapses, due in part to decreased expression of RyRs (Buchholz et al., 2007) and a decrease in the amplitude of Ca^{2+} release in basal forebrain neurons is linked to enhanced mitochondrial buffering (Murchison and Griffith, 1999). Increased CICR appears to contribute to altered physiology in hippocampal neurons (Kumar and Foster, 2004; Kumar and Foster, 2005; Gant et al., 2006). As noted above, hippocampal cells exhibit increase Ca^{2+} from L-type Ca^{2+} channels, which could provide a source of Ca^{2+} to fill ICS and activate CICR from ICS. Thus, the contribution of CICR to aging physiology in hippocampal cells may be due to due to a summation of various mechanisms.

Similarly, RyRs and IP_3Rs are likely to interact with other Ca^{2+} regulating mechanisms and neurodegenerative diseases to contribute to cell specific vulnerability. The protein presenilin interacts

with several signaling pathways including Ca^{2+} signaling, contributing to the neurotoxicity and the pathology of familial Alzheimer's disease (Chan et al., 2000; Smith et al., 2005; Stutzmann, 2007). Presenilin and beta amyloid have been associated with increased RyR function (Supnet et al., 2006; Stutzmann, 2007; Hayrapetyan et al., 2008). The influence of increased RyR activity on cell function (e.g., synaptic transmission) in the hippocampus may initially be masked by compensatory mechanisms and emerge with age and the disruption of other Ca^{2+} regulatory mechanisms (Chakroborty et al., 2009). Polyglutamine expansion of the protein huntingtin in medium spiny neurons of the striatum results in Huntington's disease, and this protein enhances activation of IP_3Rs resulting in uncontrolled Ca^{2+} release and death of medium spiny neurons (Tang et al., 2003; Tang et al., 2005).

Recent studies suggest the possibility that lysosomes may act as a Ca^{2+} storage organelle (Lee, 2004; McGuinness et al., 2007; Brailoiu et al., 2009b; Pandey et al., 2009). Release of Ca^{2+} from lysosomes involves the pyridine nucleotide, nicotinic acid adenine dinucleotide phosphate (NAADP) which can stimulate a rise in cytosolic Ca^{2+} from bafilomycin-sensitive Ca^{2+} stores (Brailoiu et al., 2005, 2009a). There are a few studies, which have investigated role of NAADP-induce Ca^{2+} release in the regulation of neuronal Ca^{2+} homeostasis and Ca^{2+}-dependent processes. Findings from recent studies provide evidence for the presence of NAADP-sensitive Ca^{2+} stores in neurons (Brailoiu et al., 2009b; Pandey et al., 2009) and NAADP mediated Ca^{2+} release can act to increase neurotransmitter release (Brailoiu et al., 2001; Chameau et al., 2001; McGuinness et al., 2007). Furthermore, pharmacological manipulations indicate that NAADP is a likely candidate for regulating Ca^{2+} signaling in astrocytes (Singaravelu and Deitmer, 2006). It is unclear whether this source of Ca^{2+} regulation is altered by aging; however, the aging brain is characterized by increased lysosomal markers and decreased lysosomal function (Lynch and Bi, 2003; Keller et al., 2004; Stolzing et al., 2005). Thus, the role of this source of Ca^{2+} in susceptibility to Ca^{2+} dysregulation should be examined in the future.

Ca^{2+} BUFFERING, EXTRUSION, AND SEQUESTRATION

In most cases, a modest rise in intracellular Ca^{2+} level is handled by rapid Ca^{2+} buffering involving Ca^{2+} binding proteins (CBPs) in the cytosol and extrusion into the extracellular space by Ca^{2+} pumps or exchangers. In addition, Ca^{2+} can be pumped into the ER or mitochondria for sequestration. A decrease in Ca^{2+} buffering or delayed removal could result in the larger or prolonged Ca^{2+} responses, which is a characteristic of aged neurons (Verkhratsky and Toescu, 1998; Brewer et al., 2006).

Over 250 proteins can be described as CBPs and the brain is a particularly rich source of these proteins (Celio et al., 1996). CBPs are generally considered to be neuroprotective (Scharfman and Schwartzkroin, 1989; Mattson et al., 1991; Lukas and Jones, 1994; Berger et al., 1998). Age-related changes in the expression of cytosolic CBPs (parvalbumin, calbindin-D28K, calretinin, calmodulin, hippocalcin) are cell and region specific (Furuta et al., 1999; Bu et al., 2003; Geula et al., 2003a,b; Wu et al., 2003; Han et al., 2006; Ouda et al., 2008). In general, age-related changes involve a decline in expression, which may be associated with a loss of function, rather than a compensatory up regulation. However, in a series of studies, Murchison and Griffith and associates (Murchison and Griffith, 2007) demonstrate rapid Ca^{2+} buffering in aged basal forebrain neurons, likely mediated by CBPs, which can act as compensation for increased Ca^{2+} influx and impaired mitochondrial uptake.

Na^+/Ca^{2+} exchangers and plasma membrane Ca^{2+} ATPase are major transport system capable of rapidly extruding substantial amounts of Ca^{2+} from the cell cytosol, across the plasma membrane, to extracellular space. The Sarco/ER Ca^{2+} ATPases are Ca^{2+} ion ATPases, which resides in the membrane of sarco/ER and transport Ca^{2+} from the cytosol to the intracellular membranous compartment of the sarco/ER. An age-related decline in the function of these transports systems has been suggested to underlie altered Ca^{2+} homeostasis during brain aging and contribute to age-related neurodegenerative diseases (Michaelis et al., 1984, 1996; Zaidi et al., 1998; Hanahisa and Yamaguchi, 2001; Pottorf et al., 2001; Gomez-Villafuertes et al., 2007). The decrease in activity may be linked to oxidation of pump proteins or CBPs that regulate pump activity (Zaidi and Michaelis, 1999; Squier and Bigelow, 2000; Bartlett et al., 2003). As such, it is likely that altered pump activity will vary with regional differences in oxidative stress.

Reports of age-related changes in the buffering function of the ER and mitochondria are highly variable across different cell types and brain regions (Brown et al., 2004). For example, studies of the peripheral nervous system indicate that buffering of cytosolic Ca^{2+} by the ER is decreased during aging (Tsai et al., 1998) with no change in mitochondrial function (Buchholz et al., 2007). In contrast, ER-mediated Ca^{2+} buffering may be intact (Burnett et al., 1990; Pottorf et al., 2001) and mitochondrial buffering may be altered at synapses in the central nervous system (Martinez-Serrano et al., 1992; Satrustegui et al., 1996; Toescu and Verkhratsky, 2000, 2003, 2004; Toescu et al., 2000; Murchison et al., 2004).

Mitochondria from aged animals show structural alterations to mitochondrial DNA (Cortopassi and Arnheim, 1990; Toescu et al., 2000) and to the mitochondrial membrane (Yan and Sohal, 1998; Kwong and Sohal, 2000), which could contribute to a net decrease in the Ca^{2+} buffering capacity during senescence. More important is decreased Ca^{2+} uptake capacity of aged mitochondria, which arises as a direct consequence of the decreased electrochemical gradient across the mitochondrial membrane (Xiong et al., 2004). Mitochondrial depolarization may increase the threshold level of Ca^{2+} needed to initiate mitochondrial uptake. As such, an age-dependent delay in Ca^{2+} sequestration or recovery would become apparent under conditions of a large rise in intracellular Ca^{2+} (Xiong et al., 2002, 2004; Murchison et al., 2004). Finally, mitochondria provide a source for oxidative stress and regional variability in oxidative stress (Dubey et al., 1996; Rebrin et al., 2007) and mitochondrial damage has been reported (Corral-Debrinski et al., 1992; Filburn et al., 1996), which appear to correspond to regions that are vulnerable to neurodegenerative disease.

CONCLUSION

The Ca^{2+} ion is a central signaling molecule in numerous cellular functions including apoptosis, energy production, gene regulation, cell proliferation, membrane excitability, synaptic transmission and plasticity. Since the first observations in the 1980s that led to Ca^{2+} 'dysregulation' hypothesis of brain aging and Alzheimer's disease,

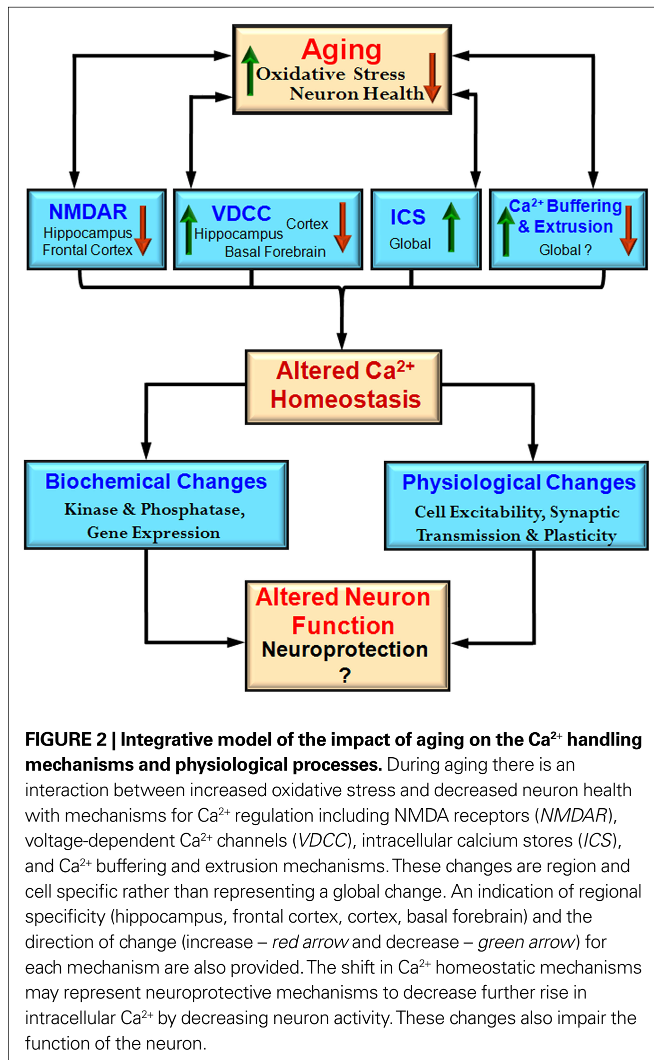

FIGURE 2 | Integrative model of the impact of aging on the Ca^{2+} handling mechanisms and physiological processes. During aging there is an interaction between increased oxidative stress and decreased neuron health with mechanisms for Ca^{2+} regulation including NMDA receptors (*NMDAR*), voltage-dependent Ca^{2+} channels (*VDCC*), intracellular calcium stores (*ICS*), and Ca^{2+} buffering and extrusion mechanisms. These changes are region and cell specific rather than representing a global change. An indication of regional specificity (hippocampus, frontal cortex, cortex, basal forebrain) and the direction of change (increase – *red arrow* and decrease – *green arrow*) for each mechanism are also provided. The shift in Ca^{2+} homeostatic mechanisms may represent neuroprotective mechanisms to decrease further rise in intracellular Ca^{2+} by decreasing neuron activity. These changes also impair the function of the neuron.

new findings have shaped ideas concerning the mechanisms and the pervasiveness of Ca^{2+} dysregulation. It is becoming clear that Ca^{2+} dysregulation is not ubiquitous and mechanisms of dysregulation are restricted to specific cell populations. For example, an age-related increase in L-type Ca^{2+} channels is relatively specific to hippocampal pyramidal cells. Furthermore, an age-related decrease in NMDA receptor function, specifically in the hippocampus or frontal cortex, suggests a possible compensatory mechanism to limit intracellular Ca^{2+} levels. However, such a mechanism may protect the cell at the expense of cell function. Thus, memory decline associated with a decrease in NMDA receptor function might be considered an epiphenomenon due to the activation of mechanisms for cell survival.

Cell specific susceptibility to Ca^{2+} dysregulation depends on environmental and genomic factors in addition to the availability of mechanisms for handling Ca^{2+}. The level of neural activity may render some regions more susceptible to oxidative stress, resulting in multiple changes to increase intracellular Ca^{2+} including increased release of Ca^{2+} from ICS, impaired Ca^{2+} pumps, and weakened Ca^{2+} buffering (**Figure 2**). In turn, gene mutations may interact with age and cell specific alterations in Ca^{2+} regulation to produce the pattern of neuronal death which characterizes neurodegenerative diseases.

Due to the importance of Ca^{2+} as a central signaling molecule, selective regulation of Ca^{2+} in a particular set of neurons may be a daunting task for treating age-related diseases. Clearly future research will need to delineate contribution of several mechanisms in optimizing Ca^{2+} homeostasis or mediating Ca^{2+} dysregulation.

ACKNOWLEDGMENTS

Financial support by National Institutes of Health Grants AG014979, MH 059891, and the Evelyn F. McKnight Brain Research Grant and a University of Florida Alumni Fellowship (Karthik Bodhinathan) is highly appreciated.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 10 August 2009; paper pending published: 28 August 2009; accepted: 27 October 2009; published online: 27 November 2009.

*Citation: Kumar A, Bodhinathan K and Foster TC (2009) Susceptibility to calcium dysregulation during brain aging. Front. Ag. Neurosci. **1**:2. doi: 10.3389/neuro.24.002.2009*

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