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REVIEW

Calcium and neurodegeneration

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Summary

When properly controlled, Ca^{2+} fluxes across the plasma membrane and between intracellular compartments play critical roles in fundamental functions of neurons, including the regulation of neurite outgrowth and synaptogenesis, synaptic transmission and plasticity, and cell survival. During aging, and particularly in neurodegenerative disorders, cellular Ca^{2+}-regulating systems are compromised resulting in synaptic dysfunction, impaired plasticity and neuronal degeneration. Oxidative stress, perturbed energy metabolism and aggregation of disease-related proteins (amyloid β-peptide, α-synuclein, huntingtin, etc.) adversely affect Ca^{2+} homeostasis by mechanisms that have been elucidated recently. Alterations of Ca^{2+}-regulating proteins in the plasma membrane (ligand- and voltage-gated Ca^{2+} channels, ion-motive ATPases, and glucose and glutamate transporters), endoplasmic reticulum (presenilin-1, Herp, and ryanodine and inositol triphosphate receptors), and mitochondria (electron transport chain proteins, Bcl-2 family members, and uncoupling proteins) are implicated in age-related neuronal dysfunction and disease. The adverse effects of aging on neuronal Ca^{2+} regulation are subject to modification by genetic (mutations in presenilins, α-synuclein, huntingtin, or Cu/Zn-superoxide dismutase; apolipoprotein E isotype, etc.) and environmental (dietary energy intake, exercise, exposure to toxins, etc.) factors that may cause or affect the risk of neurodegenerative disease. A better understanding of the cellular and molecular mechanisms that promote or prevent disturbances in cellular Ca^{2+} homeostasis during aging may lead to novel approaches for therapeutic intervention in neurological disorders such as Alzheimer's and Parkinson's diseases and stroke.

Key words: Alzheimer's disease; amyloid; apoptosis; endoplasmic reticulum; *N*-methyl-D-aspartate; Parkinson's disease; presenilin.

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Calcium and neuronal death: the basics

Neurons are excitable cells that rapidly transfer electrochemical signals in a highly controlled spatio-temporal manner. A major intracellular messenger that mediates many physiological responses of neurons to chemical and electrical stimulation is Ca^{2+} (Fig. 1). The influx of Ca^{2+} through voltage-dependent and ligand-gated channels in the plasma membrane is a critical signal for the release of neurotransmitters from presynaptic terminals and for responses of the postsynaptic neuron (Yuste *et al*., 2000; Burnashev & Rozov, 2005; Hartmann & Konnerth, 2005). Glutamate, the major excitatory neurotransmitter in the central nervous system (CNS), induces an increase in the concentration of cytoplasmic Ca^{2+} by directly activating α-amino-3-hydroxy-5-methylisoxazole-4-propionate acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptor channels and by indirectly activating voltage-dependent Ca^{2+} channels (VDCC). Accordingly, antagonists of AMPA and NMDA receptors, or VDCC, have been reported effective in protecting CNS neurons against glutamate-mediated neuronal death (excitotoxicity) (Weiss *et al*., 1990; Mattson, 2003). In addition, activation of metabotropic glutamate receptors coupled to the GTP-binding protein G_{q11} stimulates the release of inositol triphosphate (IP_3), which activates Ca^{2+} channels in the endoplasmic reticulum (ER). Ca^{2+} is removed from the cytoplasm by the activities of the plasma membrane Na^+/Ca^{2+} exchanger, plasma membrane and ER Ca^{2+}-ATPases, and Ca^{2+}-binding proteins such as calbindin and parvalbumin (Mattson *et al*., 1989a,b, 1991; Hof *et al*., 1999). By buffering intracellular Ca^{2+} loads, Ca^{2+}-binding proteins such as calbindin may serve as endogenous anti-excitotoxic proteins (Mattson *et al*., 1991). Ca^{2+} can also be transported into and released from mitochondria (Werth & Thayer, 1994; Duchen, 2000; Nicholls *et al*., 2003).

During normal physiological activity, the intracellular Ca^{2+} concentration increases only transiently (seconds to a few minutes) and has no adverse effects on the neurons. However, in pathological states, and more insidiously in normal aging, the ability of neurons to control Ca^{2+} fluxes and recover from a Ca^{2+} load is compromised. Oxidative stress is an important factor implicated in the disruption of neuronal Ca^{2+} homeostasis and neuronal death. Sources of oxidative stress include superoxide anion radical produced during oxidative phosphorylation; hydrogen peroxide, generated from superoxide in a reaction catalyzed by superoxide dismutases; hydroxyl radical, produced from hydrogen peroxide in a reaction catalyzed by Fe^{2+} and Cu^+ and peroxynitrite, produced by the interaction of nitric oxide with superoxide.

Particularly disruptive to Ca^{2+} homeostasis is membrane-associated oxidative stress (MAOS), which typically involves lipid peroxidation caused by hydroxyl radical and peroxynitrite

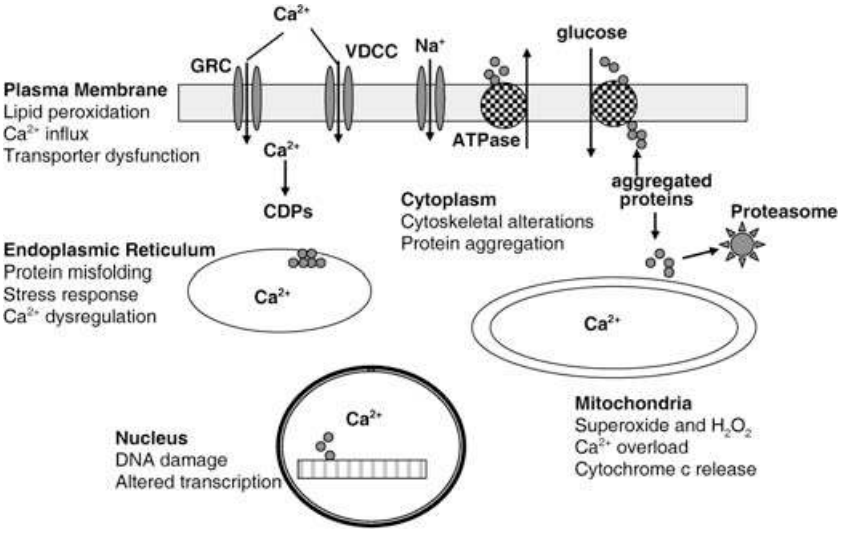

Fig. 1 Subcellular systems involved in the disruption of neuronal Ca^{2+} homeostasis in aging and neurodegenerative disorders. Oxidative stress resulting from the aging process and disease-specific mechanisms causes peroxidation of lipids in the plasma membrane that impairs the function of ion-motive ATPases and glucose transporter proteins. This promotes membrane depolarization and cellular energy depletion, which results in excessive Ca^{2+} influx through glutamate receptor channels (GRC) and voltage-dependent Ca^{2+} channels (VDCC), and accumulation of Ca^{2+} within the cell. Perturbed Ca^{2+} homeostasis may also result from endoplasmic reticulum stress and mitochondrial dysfunction. Abnormal aggregation of proteins such as Aβ and α-synuclein likely contribute to the damage and dysfunction of Ca^{2+}-regulating systems. Impaired function of the proteasome may contribute to the accumulation of protein aggregates throughout the cell. Excessive amounts of Ca^{2+} within the neuron can cause dysfunction of a myriad of cellular processes, including mitochondrial oxidative phosphorylation, protein production, and proper folding in the endoplasmic reticulum, and transcriptional regulation in the nucleus. Perturbed Ca^{2+} homeostasis may first adversely affect synaptic plasticity, followed by degeneration and death of neurons. Calcium dependent proteases (CDPs).

(Fig. 2). MAOS impairs the function of ion-motive ATPases (Na^+/K^+-ATPase and Ca^{2+}-ATPase), and glutamate and glucose transporters, thereby promoting membrane depolarization and Ca^{2+} influx through NMDA receptors and VDCC (Mattson, 1998). Thus, oxidative stress renders neurons vulnerable to a form of Ca^{2+}-mediated death called excitotoxicity in which glutamate receptors are overactivated even as the intracellular Ca^{2+} concentrations rise beyond tolerable levels (Arundine & Tymianski, 2003).

An important role for Ca^{2+} release from the ER in excitotoxicity has been demonstrated in studies showing that blockers of the two different types of ER Ca^{2+} channels, IP_3 receptors and ryanodine receptors, can protect neurons against excitotoxic injury (Frandsen & Schousboe, 1991; Mattson *et al.*, 2000). In addition, mitochondria play important roles in the regulation of neuronal Ca^{2+} homeostasis (Werth & Thayer, 1994), and it has been shown that genetic and pharmacological manipulations that enhance mitochondrial Ca^{2+} sequestration can protect neurons against excitotoxicity (Keller *et al.*, 1998; Duchen, 2000). Several proteins have been identified that are located in the ER or mitochondria that can protect neurons against Ca^{2+}-mediated death, including glucose-regulated protein 78 (Yu *et al.*, 1999), Bcl-2 (Guo *et al.*, 1997) and Herp (Chan *et al.*, 2004) in the ER, and manganese superoxide dismutase (Mn-SOD) (Keller *et al.*, 1998), Bcl-2 (Murphy *et al.*, 1996; Kruman & Mattson, 1999) and uncoupling proteins (Liu *et al.*, 2006) in mitochondria.

How does Ca^{2+} kill neurons? Considerable evidence for several different, cross-amplifying, cascades has been obtained (Fig. 1). First, Ca^{2+} activates (either directly or indirectly) cysteine proteases called calpains and caspases that degrade a variety of substrates, including cytoskeletal proteins, membrane receptors and metabolic enzymes (Chan & Mattson, 1999; Nixon, 2003). Calpains may also play an important role in the triggering of apoptotic cascades by virtue of their ability to activate caspases (Leist *et al.*, 1997; Stefanis, 2005). Second, Ca^{2+} induces oxidative stress (Lafon-Cazal *et al.*, 1993; Mattson, 2003). This occurs through several different mechanisms, including activation of oxygenases such as those in the arachidonic acid metabolism cascade, perturbation of mitochondrial Ca^{2+} and energy metabolism, and induction of MAOS. The reactive oxygen species (ROS) generated in response to glutamate-induced Ca^{2+} influx include superoxide anion radical, hydrogen peroxide, hydroxyl radical, nitric oxide and peroxynitrite (Lipton *et al.*, 1993; Mattson, 1998). Third, Ca^{2+} triggers apoptosis, a form of programed cell death (Ankarcrona *et al.*, 1995). This might occur by Ca^{2+}-mediated induction/activation of pro-apoptotic proteins such as Bax, Par-4, and p53 leading to mitochondrial membrane permeability changes, release of cytochrome *c* and caspase activation (Duan *et al.*, 1999; Dargusch *et al.*, 2001; Culmsee & Mattson, 2005).

Aging and perturbed neuronal calcium homeostasis

As in most other tissues, the normal aging process in the nervous system is associated with increased amounts of oxidative stress (Floyd & Hensley, 2002; Poon *et al.*, 2004; Hyun *et al.*, 2006) and perturbed cellular energy metabolism involving impaired mitochondrial function (Calabrese *et al.*, 2001; Drew & Leeuwenburgh,

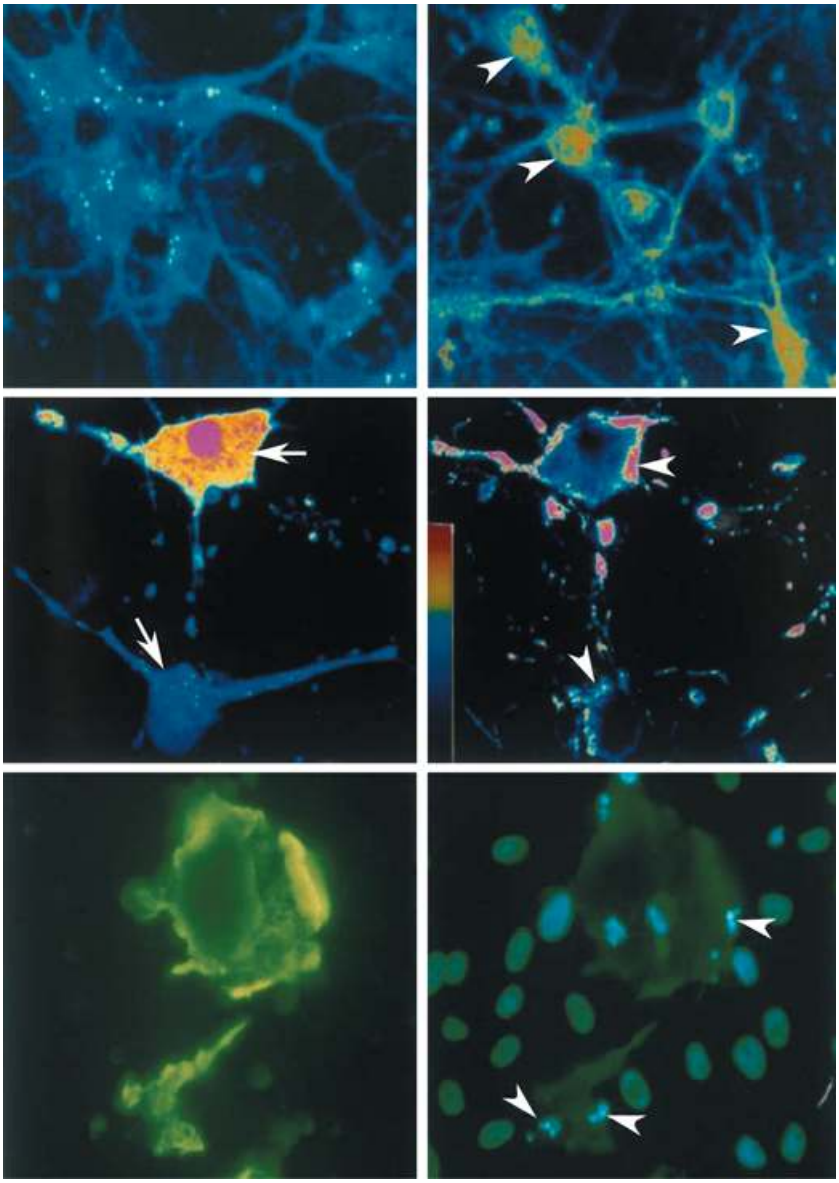

Fig. 2 Amyloid β-peptide induces membrane-associated oxidative stress, cellular Ca^{2+} overload and apoptosis. Upper panels: primary rat hippocampal neurons in culture were exposed to vehicle (left) or Aβ (right) for 24 h. Cells were then processed using a fluorescence-based method for visualization of sites of membrane lipid peroxidation. Neurons exposed to Aβ exhibited high levels of lipid peroxidation (yellow and red). Middle panels: cultured hippocampal neurons were exposed to Aβ for 24 h, an image showing intracellular free Ca^{2+} levels was acquired using fura-2 (left) and then the cells were immunostained with an Aβ antibody (right). The neuron with high amounts of Aβ immunoreactivity (pink) associated with its cell surface exhibited a very high concentration of intracellular Ca^{2+} (upper neuron). In contrast the neuron with little Aβ on its surface had a low intracellular Ca^{2+} concentration (lower neuron). Lower panels: cultured vascular endothelial cells were exposed to aggregated Aβ for 24 h, and were then stained with the DNA-binding dye bisbenzamide. Note that cells in contact with the Aβ exhibit apoptotic (condensed and fragmented) nuclear chromatin, whereas those not contacted by Aβ exhibit nuclei with normal appearing (diffuse and lightly stained) chromatin. These images were modified from Mark *et al*. (1997c), Mattson *et al*. (1993c), and Blanc *et al*. (1997).

2004). Measurements of oxidative stress and mitochondrial function in brain cells of animals of different ages have demonstrated increases in oxidative modifications of proteins, lipids and DNA, and reduced mitochondrial function (activity levels of electron transport chain enzymes) during aging (Floyd & Hensley, 2002). Data from studies of patients, and animal and cell culture models, have established pivotal roles for oxidative stress and impaired energy metabolism in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), stroke, and related neurodegenerative disorders (for a review, see Gardian & Vecsei, 2004; Mattson, 2004; Przedborski & Ischiropoulos, 2005; Saito *et al*., 2005; Abou-Sleiman *et al*., 2006; Mattson & Magnus, 2006). The specific molecular alterations that result in oxidative stress may differ among disorders; for example, amyloid β-peptide (Aβ) in AD (Chan *et al*., 2002), mitochondrial alterations in PD (Greenamyre *et al*., 1999), mutant huntingtin in HD (Brustovetsky *et al*., 2005), and ischemia in stroke (Kristian & Siesjo, 1998). However, the reactive oxygen (and nitrogen) species produced, and their consequences for neuronal function and viability, are similar among disorders. Superoxide, hydrogen peroxide, hydroxyl radical, nitric oxide and peroxynitrite have each been implicated in all of the major neurodegenerative disorders. ROS can directly damage proteins and nucleic acids, which could perturb neuronal Ca^{2+} homeostasis. Examples include peroxynitrite-mediated modification of VDCC and NMDA receptors (Leist *et al*., 1997; Ohkuma *et al*., 2001), and oxidative damage to mitochondrial DNA (Lee *et al*., 2002a).

Neurons expend relatively large amounts of energy to maintain ion gradients across membranes; Na^+/K^+- and Ca^{2+}-ATPases in the plasma membrane and Ca^{2+}-ATPases in the ER membrane are major ATP sinks. During normal aging of the CNS, there is a decrease in the efficiency of mitochondria in generating ATP (Navarro, 2004). Together with oxidative stress and activation

of glutamate receptors, prolonged membrane depolarization can deplete ATP from neurons, thereby compromising ion-motive ATPase activities and promoting Ca^{2+} overload (Collins *et al*., 1989). The latter mechanisms are perhaps best typified in ischemic brain injury where cellular Ca^{2+} overload is believed to play a key role in the death of neurons caused by a stroke. Accordingly, glutamate receptor antagonists, VDCC blockers, and intracellular Ca^{2+} chelators can protect neurons in experimental models of stroke (Weiss *et al*., 1990; Turski *et al*., 1991; Tymianski *et al*., 1993).

As mitochondria are the major source of both ATP and ROS in neurons, they represent an organelle that plays a pivotal role in determining whether or not neurons succumb to injury or disease during aging. The complex processes involved in mitochondrial energy, ROS and Ca^{2+} metabolism have been investigated (Mattson & Kroemer, 2003; Polster & Fiskum, 2004). Several mitochondrial proteins that may have particularly important roles in mediating or protecting against Ca^{2+}-mediated neuronal death include pro-apoptotic (Bax and Bad) and antiapoptotic (Bcl-2 and Bcl-xL) proteins that modify mitochondrial membrane permeability (Beal, 1998a; Murphy & Fiskum, 1999; Springer *et al*., 2000; Camandola *et al*., 2005), and uncoupling proteins that decrease mitochondrial ROS production (Maragos & Korde, 2004; Liu *et al*., 2006). Mitochondrial alterations, including membrane depolarization and permeability, Ca^{2+} overload, and release of apoptotic proteins such as cytochrome *c* and apoptosis-inducing factor have been implicated in the pathogenesis of AD, PD, HD, amyotrophic lateral sclerosis (ALS), and stroke (Dawson & Dawson, 2003; Mattson, 2004).

Alterations in the ER have been associated with age-related dysfunction and degeneration of neurons. ER stress, characterized by the accumulation of misfolded proteins and uncontrolled Ca^{2+} release, is implicated in the dysfunction and death of neurons in a range of age-related neurodegenerative conditions (Lindholm *et al*., 2006). As with other aspects of neuronal Ca^{2+} dysregulation, oxidative stress and metabolic impairment promote ER dysfunction. In regards to specific neurodegenerative conditions, ER dysfunction has clearly been shown to contribute to the death of neurons following a stroke (Paschen, 2003).

Involvement of perturbed calcium homeostasis in neurodegenerative disorders

Studies of patients, and animal and cell culture models, have provided a wealth of data supporting the involvement of alterations in Ca^{2+} regulation in the pathogenesis of stroke and chronic neurodegenerative disorders. Stroke is a major cause of disability and death in elderly populations worldwide (Ingall, 2004). Evidence that perturbed cellular Ca^{2+} homeostasis is pivotal to the death of neurons following a stroke is strong. Neurons in the affected brain regions exhibit increased activities of Ca^{2+}-dependent proteases, and inhibitors of calpains protect neurons against ischemic injury in animal models of stroke (Hong *et al*., 1994). Studies of animal and cell culture models have clearly demonstrated that neuronal Ca^{2+} overload occurs in neurons subjected to ischemia (Kristian & Siesjo, 1998). Activation of glutamate receptors and VDCC and impairment of Na^{+}/Ca^{2+} exchangers and ion-motive ATPases contribute to neuronal Ca^{2+} overload and cell death after a stroke (Kristian & Siesjo, 1998; Nellgard & Wieloch, 1992).

Analyses of brain tissue from patients with a neurodegenerative disease have revealed evidence that alterations in cellular Ca^{2+} homeostasis contribute to the neurodegenerative process. For example, amounts of free and protein-bound Ca^{2+}, and the activity of Ca^{2+}-dependent proteases, are increased in neurons containing neurofibrillary tangles as compared with tangle-free neurons in brain tissue from AD patients (Murray *et al*., 1992; Nixon, 2003). Studies of experimental models of AD have shown that overactivation of glutamate receptors can induce changes in the cytoskeleton of neurons similar to those seen in neurofibrillary tangles (Mattson, 1990; Stein-Behrens *et al*., 1994). In AD, the proteolytic processing of the β-amyloid precursor protein (APP) is altered; cleavage by β- and/or γ-secretases is increased resulting in increased production of neurotoxic Aβ (Mattson, 2004). In the most common late-onset form of AD, it is likely that age-related increases in oxidative stress, metabolic impairment, and inflammatory processes contribute to increased Aβ production.

Amyloid β-peptide disrupts neuronal Ca^{2+} homeostasis by generating ROS (hydrogen peroxide and hydroxyl radical) in a process catalyzed by Cu^{+} and Fe^{2+} (Hensley *et al*., 1994). Aβ accumulates on cell membranes and the ROS generated by Aβ oligomers induce MAOS, which can impair the function of membrane ion-motive ATPases (Na^{+}/K^{+}- and Ca^{2+}-ATPases), and glucose and glutamate transporters. The latter actions of Aβ cause an elevation of basal intracellular Ca^{2+} levels and sensitize neurons to excitotoxicity and apoptosis (Fig. 2) (Mattson *et al*., 1992; Mark *et al*., 1995, 1997a,b; Keller *et al*., 1997). Aβ induces lipid peroxidation, which disrupts Ca^{2+} homeostasis by a mechanism involving the production of 4-hydroxy-2,3-nonenal (HNE), an aldehyde that can covalently modify proteins on cysteine, lysine, and histidine residues. HNE has been shown to modify and impair the function of ion-motive ATPases, the neuronal glucose transporter GLUT3 and the astrocyte glutamate transporter GLT-1 (Keller *et al*., 1997; Mark *et al*., 1997a,b; Blanc *et al*., 1998). Increased levels of HNE have been detected in association with degenerating neurons in tissue samples from patients with AD (Cutler *et al*., 2004) and even in the cerebrospinal fluid of AD patients (Lovell *et al*., 1997). In addition to inducing oxidative stress, Aβ oligomers may disrupt Ca^{2+} homeostasis by forming Ca^{2+}-conducting pores in cell membranes (Kawahara & Kuroda, 2000).

Analyses of CNS tissues from patients with PD, HD, and ALS suggest a role for cellular Ca^{2+} overload in the death of the vulnerable neurons in these disorders. Excitotoxicity and excessive Ca^{2+}-mediated nitric oxide production are believed to contribute to the death of dopaminergic neurons in PD (Beal, 1998b). Dopaminergic neurons expressing relatively high levels of the Ca^{2+}-binding proteins calbindin and calretinin appear to be resistant to degeneration in PD (Yamada *et al*., 1990; Mouatt-Prigent *et al*., 1994). The medium spiny neurons that succumb in HD have low levels of Bcl-2 and parvalbumin and are highly

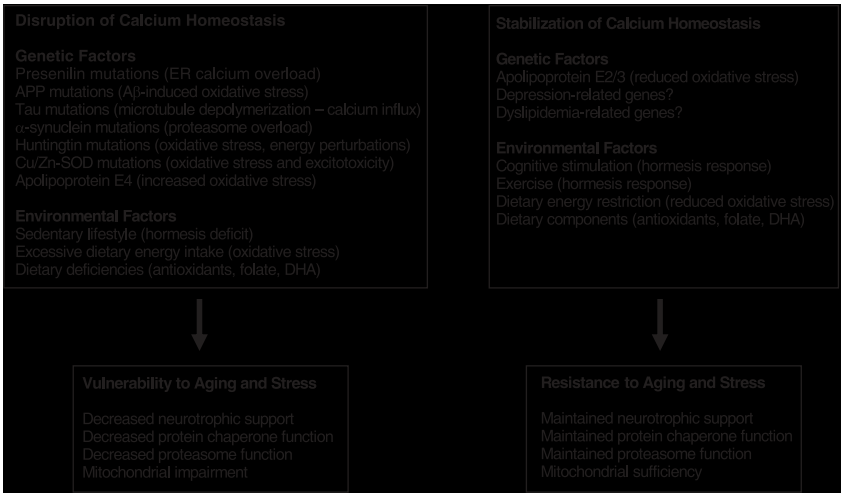

Fig. 3 Examples of genetic and environmental factors that have been shown to either disrupt (left) or stabilize (right) neuronal calcium homeostasis in the context of aging and neurodegenerative disorders. Modified from Mattson & Magnus (2006).

vulnerable to excitotoxicity compared to other populations of striatal neurons (Liang *et al*., 2005). Medium spiny neurons from transgenic mice expressing mutant huntingtin exhibit enhanced mitochondrial Ca^{2+} overload when exposed to glutamate compared to medium spiny neurons from control mice (Tang *et al*., 2005). Evidence that perturbed Ca^{2+} homeostasis contributes to the demise of motor neurons in ALS includes laser-activated microprobe mass analysis of spinal cord tissue sections from ALS and control subjects documented a significant increase in the Ca^{2+} content of motor neurons in the ALS patients (Kasarskis *et al*., 1995); motor neurons resistant to ALS express high levels of Ca^{2+}-binding proteins (Alexianu *et al*., 1994); motor neurons may die by an excitotoxic mechanism, and the only drug proven effective in slowing the progression of ALS (riluzole) targets excitotoxicity (Van Damme *et al*., 2005). In addition, MAOS occurs in neurons affected in PD, HD and ALS (Yoritaka *et al*., 1996; Beal, 1998b; Pedersen *et al*., 1998; Smith *et al*., 1998; Cutler *et al*., 2002) and, through the mechanisms described above, may disrupt neuronal Ca^{2+} homeostasis in each disorder.

Abnormal intracellular and extracellular accumulations of aggregated proteins are conspicuous features of neurodegenerative disorders that are strongly implicated in the disease process (Mattson & Sherman, 2003). Chronic inhibition of mitochondrial complex I results in aggregation of α-synuclein, which is associated with apoptosis of neural cells (Sherer *et al*., 2002). Transgenic mice expressing PD-causing mutations of α-synuclein exhibit intracellular aggregates of α-synuclein and neuronal degeneration in several brain regions (Lee *et al*., 2002c). Similarly, when mutant α-synuclein is expressed in cells of the substantia nigra of rats, dopaminergic neurons exhibited α-synuclein inclusions, neuritic degeneration and cell death (Lo Bionco *et al*., 2002). Mutations in α-synuclein and huntingtin may promote cell death through protein aggregation and impaired clearance by the proteasome (Moulder *et al*., 1999; Ostrerova-Golts *et al*., 2000; Bence *et al*., 2001). In contrast to Aβ, where the mechanism by which the aggregating peptide disrupts Ca^{2+} homeostasis is beginning to be elucidated, little is known about if and how mutations in α-synuclein, parkin, DJ-1, and huntingtin affect neuronal Ca^{2+}-regulating systems. However, induction of oxidative stress and disruption of membrane integrity may be involved (Lee *et al*., 2002d; Kegel *et al*., 2005; Firdaus *et al*., 2006; Furukawa *et al*., 2006).

Genetic factors, Ca^{2+} dysregulation and neurodegeneration

The work of molecular geneticists has been invaluable in our efforts to understand the mechanisms responsible for neuronal dysfunction and death in age-related neurodegenerative disorders. Data obtained from studies of cultured cells and mice expressing disease-causing mutations support roles for perturbed neuronal Ca^{2+} homeostasis in the demise of neurons (Fig. 3). Some cases of inherited early onset AD are caused by mutations in APP, presenilin-1 or presenilin-2. APP mutations result in increased production of neurotoxic forms of Aβ that, as described above, disrupt neuronal Ca^{2+} homeostasis by inducing MAOS. Presenilin mutations that cause AD result in an abnormality in ER Ca^{2+} regulation characterized by an increased capacity of the ER to release Ca^{2+} in response to IP_3 and Ca^{2+} influx through plasma membrane channels (Ca^{2+}-induced Ca^{2+} release) (Guo *et al*., 1997, 1999). Stutzmann *et al*. (2006) provided convincing evidence that presenilin-1 mutations cause an increase in the level of ryanodine receptors and Ca^{2+} release through those channels in response to Ca^{2+} influx or release from IP_3 stores. The consequences of the latter abnormality include increased vulnerability of neurons to excitotoxic, metabolic and oxidative insults (Guo *et al*., 1997, 1999; Mattson *et al*., 2000). Tau mutations that cause frontotemporal lobe dementia have been reported to disrupt neuronal Ca^{2+} homeostasis by enhancing Ca^{2+} influx through VDCC (Furukawa *et al*., 2003).

Individuals with the E4 isoform of apolipoprotein E are at increased risk of AD compared to those with E2 or E3 isoforms (Mahley *et al*., 2006). The mechanism by which apolipoprotein Es modify the neurodegenerative process in AD may involve, in

part, effects on neuronal Ca^{2+} homeostasis. The apoE4 isoform (which increases the risk of AD) may amplify Ca^{2+} signaling directly (Hartmann *et al*., 1994; Tolar *et al*., 1999). It has also been suggested that apoE4 is less effective than E2 and E3 in scavenging 4-hydroxynonenal, suggesting that individuals with apoE4 are compromised in their ability to protect cells against age- and disease-related increases in membrane-associated oxidative stress (Pedersen *et al*., 2000).

Mutations in several different genes have been linked to early-onset inherited PD; they include α-synuclein, Parkin, and DJ-1 (Moore *et al*., 2005). PD α-synuclein mutations have been shown to perturb Ca^{2+} homeostasis in cultured neurons by increasing membrane ion permeability (Volles & Lansbury, 2002; Furukawa *et al*., 2006). Parkin has been shown to interact with the synaptic vesicle-associated protein synaptotagmin XI, suggesting a potential mechanism whereby Parkin mutations impair synaptic signaling (Huynh *et al*., 2003).

Huntington's disease is caused by trinucleotide (CAG) repeat expansions in the huntingtin gene resulting in polyglutamine repeat expansions in the huntingtin protein. Studies of cells from HD patients, and of cultured cells and transgenic mice expressing mutant huntingtin, support a role for perturbed Ca^{2+} homeostasis in the degeneration of neurons that occurs in HD (Bezprozvanny & Hayden, 2004). For example, Ca^{2+} regulation is abnormal in mitochondria from HD patient lymphoblasts and from brains of HD mice. Mutant huntingtin causes a potentiation of NMDA receptor activity in medium spiny striatal neurons from HD mice. In addition, mutant huntingtin binds to IP_3 receptors and enhances their opening to release Ca^{2+} from the ER.

The selective vulnerability of spinal cord motor neurons in ALS is believed to result, in part, from their large size and their particular complement of AMPA receptors and VDCC (von Lewinski & Keller, 2005). The work of Simpson *et al*. (2002) have provided considerable evidence that cellular Ca^{2+} overload is of central importance in the death of motor neuron sin ALS. Mutations in Cu/Zn-SOD are responsible for some cases of inherited ALS (Bruijn *et al*., 2004). When expressed in cultured neurons and transgenic mice, the ALS Cu/Zn-SOD mutations render neurons vulnerable to oxidative stress and excitotoxicity (Kruman *et al*., 1999). ALS Cu/Zn-SOD mutations can impair synaptic glucose and glutamate transport and render neurons vulnerable to ischemic injury (Guo *et al*., 2000). Overexpression of the Ca^{2+}-binding protein parvalbumin protects motor neurons and delays disease onset in Cu/Zn-SOD mutant mice (Beers *et al*., 2001). Calcium influx through AMPA receptor channels has been implicated in motor neuron damage in ALS, and may damage the neurons by causing the misfolding and aggregation of Cu/Zn-SOD (Tateno *et al*., 2004).

Diet, lifestyle and neuronal vulnerability

It has become apparent in recent years that the risk of developing a neurodegenerative disease as one ages can be modified depending on certain environmental factors including the quantity and molecular composition of food consumed, exercise (of the body and the brain), and exposure to environmental hazards (Fig. 3). In many cases, the same factors that increase the risk of type 2 diabetes and cardiovascular disease also increase the risk of neurodegenerative disorders. This is most apparent in stroke; risk is increased by diets high in calories and saturated fats, and a sedentary lifestyle (Ingall, 2004). However, overeating and lack of exercise may also be risk factors for AD and PD (Mayeux, 2003). In addition, cognitively challenging lifestyles may protect neurons against AD (Stern, 2006). Animal studies suggest cause–effect relationships between dietary and lifestyle factors and neuronal vulnerability to disease (Martin *et al*., 2006). For example, rats maintained on an intermittent fasting regimen exhibit reduced brain damage and improved functional outcome in a stroke model (Yu & Mattson, 1999). In addition, dietary energy restriction protects hippocampal neurons and improves cognitive function in animal models relevant to AD (Bruce-Keller *et al*., 1999; Zhu *et al*., 1999; Duan *et al*., 2001; Patel *et al*., 2005; Wang *et al*., 2005a). Dietary energy restriction has also been shown to protect dopaminergic neurons in mouse (Duan & Mattson, 1999) and monkey (Maswood *et al*., 2004) models of PD, and striatal and cortical neurons in an HD model (Duan *et al*., 2003). On the other hand, dietary energy restriction was detrimental (Pedersen & Mattson, 1999), whereas a high energy diet was beneficial (Dupuis *et al*., 2004) in mouse models of ALS.

Exercise and cognitive stimulation were reported to have beneficial effects on disease pathogenesis and functional outcome in some, but not all, animal models of neurodegenerative disorders. Studies of AD mouse models have suggested that environmental enrichment (cognitive stimulation) can reduce (Lazarov *et al*., 2005), exacerbate (Jankowsky *et al*., 2003), or have no effect on (Arendash *et al*., 2004) Aβ accumulation. However, environmental enrichment did improve cognitive function in multiple models (Arendash *et al*., 2004; Jankowsky *et al*., 2005), suggesting the possibility that cognitive stimulation may act downstream of Aβ production. In other studies, it was shown that voluntary exercise decreases Aβ accumulation in a mouse model of AD (Adlard *et al*., 2005). In regards to other neurodegenerative disorders, exercise and/or environmental enrichment have been shown to improve the outcome in animal models of stroke, PD and HD (Young *et al*., 1999; Endres *et al*., 2003; Spires *et al*., 2004).

Direct evidence that environmental factors impact on neurodegenerative processes by modifying neuronal Ca^{2+} homeostasis is lacking. However, inference and indirect evidence supports mechanism(s) involving Ca^{2+} regulation. Perhaps the strongest evidence comes from the literature concerning the effects dietary energy restriction and excess on neuronal vulnerability. As described above, dietary energy restriction protects neurons against damage in models in which Ca^{2+} plays a major role in the cell death process, including severe epileptic seizures (Bruce-Keller *et al*., 1999) and stroke (Yu & Mattson, 1999). Conversely, diabetes renders neurons vulnerable to Ca^{2+}-mediated cell death (Li *et al*., 1998; Vannucci *et al*., 2001). Exercise and environmental enrichment have also been shown to modify the vulnerability

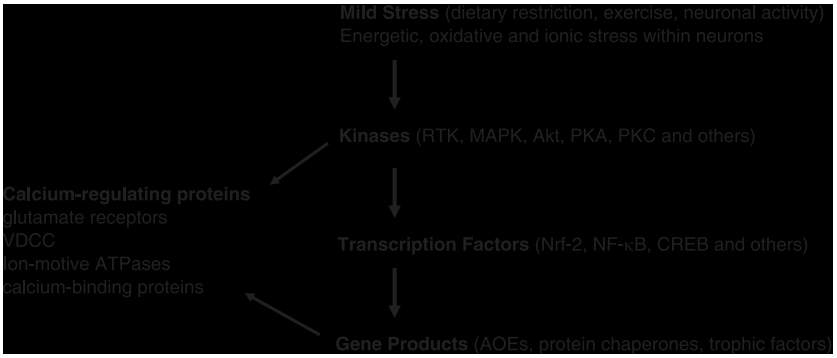

Fig. 4 Hormesis-based Ca^{2+} stabilization mechanisms. Environmental factors such as dietary energy restriction, exercise, and cognitive stimulation impose a mild and beneficial stress on neurons. Within the neurons, this stress manifests as reduced energy availability or increased energy demand, increased oxyradical production, and/or increased ionic fluxes. The latter types of stress result in the activation of kinases (RTK, receptor tyrosine kinases; MAPK, mitogen-activated protein kinases; Akt, xxxxxxxx; PKA, cyclic AMP-dependent protein kinase; PKC, protein kinase C). Kinases activate (or inhibit) transcription factors (Nrf-2, nuclear factor E2-related factor 2; NF-κB, nuclear factor kappa of B cells; CREB, cyclic AMP response element binding protein). Such transcription factors modify the expression of various genes that mediate adaptive responses of the neuron to the stress, including antioxidant enzymes (AOE), protein chaperones, and neurotrophic factors. Among the proteins whose function (through phosphorylation by kinases) and levels (through transcriptional regulation) affected by mild stress are those involved in regulation of cellular Ca^{2+} homeostasis, including glutamate receptor channel proteins (GRC), voltage-dependent Ca^{2+} channels (VDCC), and Ca^{2+}-binding proteins.

of neurons to excitotoxicity and related forms of Ca^{2+}-mediated death. In most cases, the effects of exercise and enrichment are beneficial (Endres *et al*., 2003; Gobbo & O'Mara, 2005), although detrimental effects have also been reported in some models (Ramsden *et al*., 2003).

How might diet and lifestyle affect neuronal Ca^{2+} homeostasis? One possibility is that the environmental factors modify neurotrophic factor signaling, which, in turn, affects Ca^{2+} homeostasis. For example, dietary energy restriction (Lee *et al*., 2002a,b; Maswood *et al*., 2004) and exercise (Smith & Zigmond, 2003; Vaynman & Gomez-Pinilla, 2006) can increase brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) signaling. Conversely, BDNF levels were reported to be decreased in the sciatic nerve of diabetic rats (Rodriguez-Pena *et al*., 1995), and both BDNF and GDNF can ameliorate adverse effects of diabetes on the nervous system (Nitta *et al*., 2002; Anitha *et al*., 2006). Both BDNF and GDNF have been shown capable of protecting neurons against Ca^{2+}-mediated death (Cheng & Mattson, 1994; Perez-Navarro *et al*., 1996; Tomac *et al*., 2002). Additional mechanisms by which dietary factors, exercise and cognitive stimulation may affect neuronal Ca^{2+} homeostasis are by modifying the expression of protein chaperones (heat-shock proteins, glucose-regulated protein 78, etc.) and mitochondrial uncoupling proteins (Lee *et al*., 1999; Yu & Mattson, 1999; Liu *et al*., 2006).

Hormesis and the stabilization of neuronal Ca^{2+} homeostasis

Hormesis is a general term describing any process in which exposure of a cell or organism to a moderate level of stress (oxidative, metabolic, thermal, etc.) results in adaptive changes in the cell/organisms that confer resistance to more severe stress that would otherwise cause damage, disease and/or death (Arumugam *et al*., 2006; Mattson & Cheng, 2006). The heat-shock response (Giffard *et al*., 2004), ischemic preconditioning (Kirino, 2002) and electroconvulsive shock therapy (Altar *et al*., 2004) are examples of hormesis. In the following paragraphs, I describe examples of how neuronal Ca^{2+} homeostasis can be enhanced through hormesis-based mechanisms; a schematic representation of this concept is shown in Fig. 4.

Because of the potential for Ca^{2+} to damage and kill neurons, several different mechanisms have evolved to prevent Ca^{2+} overload. Not surprisingly, Ca^{2+} itself activates hormetic pathways. One Ca^{2+}-stabilizing neuroprotective mechanism involves activation of the transcription factor CREB (cyclic AMP response element binding protein) by Ca^{2+} and calmodulin. CREB induces the expression of genes that encode proteins that promote neuronal survival and plasticity, including BDNF (Soriano *et al*., 2006). Nuclear factor-κB (NF-κB) is a transcription factor activated in response to Ca^{2+} release from the ER; NF-κB has been shown to stabilize Ca^{2+} homeostasis by modifying the expression of glutamate receptor subunits (Furukawa & Mattson, 1998) and down-regulating the expression of IP_3 receptor channels (Camandola *et al*., 2005). NF-κB is also activated by some cytokines and neurotrophic factors that are released from neurons and glial cells when they are under stress; examples include tumor necrosis factor (Barger *et al*., 1995; Mattson *et al*., 1997), BDNF (Cheng & Mattson, 1994), nerve growth factor (Carter *et al*., 1996) and a secreted form of APP (Barger & Mattson, 1996). Several different neurotrophic factors induced by mild hormetic stress have been shown to protect neurons against excitotoxicity and other forms of Ca^{2+}-mediated death, in part, by modifying the expression of Ca^{2+}-regulating proteins, including AMPA and NMDA receptor subunits, antioxidant enzymes, and Ca^{2+}-binding proteins (Cheng & Mattson, 1991, 1992; Mattson *et al*., 1993b, 1995; Cheng *et al*., 1995; Fawcett *et al*., 2000).

The hormesis mechanisms described in the previous paragraph typically function over time periods of hours to days. However, more rapid neuroprotective responses to Ca^{2+} influx have been

described. For example, phosphorylation of glutamate receptor channels and VDCC by the Ca^{2+}-dependent kinases has been shown to modulate Ca^{2+} influx (Bartschat & Rhodes, 1995; Lu *et al*., 2000; Leonard *et al*., 2002). Another rapid response mechanism involves activation of the Ca^{2+}-responsive actin-severing protein gelsolin (Furukawa *et al*., 1997). Actin filaments enhance opening of NMDA receptor channels and VDCC by reducing channel rundown. Sustained Ca^{2+} influx results in depolymerization of actin filaments, resulting in channel rundown and a reduction in Ca^{2+} influx. Actin filaments may also regulate Ca^{2+} release from the ER (Wang *et al*., 2002).

Other hormesis pathways that are not directly activated by Ca^{2+} may also stabilize neuronal Ca^{2+} homeostasis. It is well established that exposure of neurons to a mild metabolic stress, such as occurs during a brief ischemia, can protect them against excitotoxicity and other Ca^{2+}-mediated neurodegenerative processes. This type of metabolic hormesis is mediated by transcription factors such as hypoxia inducible factor 1 and production of cytoprotective proteins such as basic fibroblast growth factor and erythropoietin (Grimm *et al*., 2002; Liu *et al*., 2005). Exposure of neurons to subtoxic levels of noxious chemicals is increasingly recognized as a means of inducing hormesis. This has been well established for mitochondrial toxins such as cyanide (Jensen *et al*., 2002), but may also be a major mode of action of many of the health-promoting phytochemicals present in vegetables and fruits (Mattson & Cheng, 2006). Examples include sulforaphane (present at high levels in broccoli) (Gao & Talalay, 2004), curcumin from tumeric root (Wang *et al*., 2005b), and resveratrol from red grapes (Parker *et al*., 2005). Pathways that may mediate the beneficial effects of these phytochemicals in neurons include Nrf-2 – ARE (antioxidant response element pathway) and histone deacetylases called sirtuins.

Targeting Ca^{2+} regulation to prevent and treat neurodegenerative disease

The findings described above and elsewhere (Mattson, 2003; Braunewell, 2005) suggest that therapeutic approaches that stabilize neuronal Ca^{2+} homeostasis may be capable of retarding or preventing neuronal degeneration in acute and chronic neurodegenerative conditions. Although many different drugs that target Ca^{2+} influx have demonstrated efficacy in animal models of stroke, AD and other neurodegenerative disorders, very few have been successful in clinical trials. However, significant beneficial effects of the L-type Ca^{2+} channel blocker nimodipine (Tollefson, 1990) and the NMDA open channel blocker memantine (Bullock, 2006) in AD patients, and of the glutamate-modulating agent riluzole in ALS patients (Miller *et al*., 2003) have shown that Ca^{2+}-regulating systems are viable targets. However, drugs that suppress Ca^{2+} influx may compromise the normal functions of neurons, which is a particularly important concern in neurodegenerative disorders that require long-term treatment including AD, PD and ALS. Therapeutic strategies aimed at enhancing endogenous Ca^{2+} removal and buffering mechanisms would be expected to have fewer side-effects. In this regard, activation of neurotrophic factor-signaling pathways, as described above, might prove beneficial.

Perhaps the most exciting development in therapeutics for neurodegenerative disorders has been the possible use of immunization. Data obtained from studies of mouse models of AD, and of AD patients, suggest that Aβ aggregation and accumulation in the brain can be modified by the immune system. Immunization of APP mutant mice with human Aβ results in reduction in the accumulation of Aβ in, and removal of aggregated Aβ from, the brain (Gelinas *et al*., 2004). In an initial clinical Aβ vaccination trial, a few of the patients developed severe CNS inflammation, but some of the patients who tolerated the treatment appeared to benefit as indicated by magnetic resonance imaging analyses and cognitive testing (Fox *et al*., 2005; Gilman *et al*., 2005). Other studies have shown that, depending upon the particular Aβ antibody, and presumably the epitopes with which it interacts, Aβ antibodies may either inhibit peptide aggregation and toxicity, or they may exacerbate the toxicity of the peptide (Mattson & Chan, 2003). Accordingly, clinical trials are in progress in which AD patients are treated with well-characterized Aβ antibodies (passive immunization), an approach that is expected to have fewer side-effects and more consistent therapeutic efficacy.

As with other major age-related diseases, the burden of neurodegenerative disorders may best be lessened through the implementation of preventative changes in diet and lifestyle. As described above, a reduction in dietary energy intake, exercise and cognitive stimulation may each enhance the ability of neurons to control Ca^{2+} fluxes during aging. A better understanding of how this is accomplished at the cellular and molecular levels may identify additional targets and strategies for neuroprotective therapeutic interventions.

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