Introduction
Brain zinc, in its free ionic form (Zn\textsuperscript{2+}), is present within synaptic vesicles at glutamatergic nerve terminals and is synaptically released during neuronal activity. Zn\textsuperscript{2+} is also bound to metalloproteins and intracellularly mobilized upon oxidative stress. A growing and exciting body of evidence indicates that Zn\textsuperscript{2+} plays a dynamic role in both the physiology and pathophysiology of brain function.

Synaptic activation releases vesicular Zn\textsuperscript{2+}, bringing its concentrations in the synaptic cleft to transiently rise. The exact amount of such release is controversial, but many laboratories have indicated (with the limitation of the current imaging techniques) that transient Zn\textsuperscript{2+} increases may reach 1–100 µM (Vogt et al., 2000; Qian and Noebels, 2005; Frederickson et al., 2006). Others have indications for lower (submicromolar) concentrations (Komatsu et al., 2005). Fuelling the controversy is the fact that measurement of actual Zn\textsuperscript{2+} levels within the synaptic cleft is technically challenging, given the short time in which the free ion is present in the synapse (Hurst et al., 2010). Some authors have alternatively suggested that the ion does not diffuse in the cleft and is actually only externalized following exocytosis. In this view, Zn\textsuperscript{2+} remains bound to the plasma membrane, forming a “veneer” on presynaptic terminals (Kay, 2003; Kay and Töth, 2008). While this is an intriguing hypothesis, the interpretation of these results needs to take into account the variability in preexisting vesicular Zn\textsuperscript{2+} levels, as these are known to be affected by changes in previous synaptic activity (i.e., sensory experience), the animal age, and the methods used in the preparation of brain slices (Frederickson et al., 2006; Nakashima and Dyck, 2009).

Future studies combining electrophysiology with state-of-the-art synaptic Zn\textsuperscript{2+} imaging are likely to give a more accurate description of the precise dynamics and concentrations of the ion during activity-dependent synaptic activity.

Exogenously applied Zn\textsuperscript{2+} profoundly affects the activity of glutamate, GABA\textsubscript{A}, and glycine ionotropic receptors. Extracellular Zn\textsuperscript{2+} therefore is likely to be intimately linked to the balance of excitation and inhibition in the brain. Indeed following stimulation of Zn\textsuperscript{2+}-containing fibers, endogenous Zn\textsuperscript{2+} has been shown to block postsynaptic NMDA (Vogt et al., 2000; Molnár and Nadler, 2001a) and GABA\textsubscript{A} (Ruiz et al., 2004) receptors. However, the modulation of postsynaptic receptors by Zn\textsuperscript{2+} is likely complex, as other investigators have failed to find effects of vesicular Zn\textsuperscript{2+} on GABA\textsubscript{A} receptors (Molnár and Nadler, 2001b) and neuronal excitability (Lopantsev et al., 2003; Laviole et al., 2007).

More recent findings also indicate that synthetically released Zn\textsuperscript{2+} activates a specific metabotropic Zn\textsuperscript{2+}-sensing receptor (Fig. 1B) (Besser et al., 2009; Chorin et al., 2011). Zn\textsuperscript{2+} can flux into neurons and be taken up in organelles such as mitochondria (Sensi et al., 2000; Caporale et al., 2009; Dittmer et al., 2009), and recent evidence in non-neuronal cells indicates that some uptake might occur in the endoplasmic reticulum and the Golgi apparatus (Qin et al., 2011) as well. Neurons also keep cytosolic [Zn\textsuperscript{2+}] levels very low by using several Zn\textsuperscript{2+} transporters (such as ZnT families, ZIP transporters, and Zn\textsuperscript{2+} buffering metallothioneins (MTs) as well as other transporters such as a putative Na\textsuperscript{+}/Zn\textsuperscript{2+} exchanger (Sensi et al., 2009).

On the dark side, Zn\textsuperscript{2+} is also a potent neurotoxin (Fig. 2) involved in variety of conditions that have been associated with
excitotoxicity, including ischemia, epilepsy, and brain trauma (Sensi et al., 2009). Zn$^{2+}$ promotes both neuronal and glial death in vitro and in vivo (Choi et al., 1988). Landmark in vivo studies have shown that the transsynaptic movement of Zn$^{2+}$, a process also called “Zn$^{2+}$ translocation,” plays a role in neuronal death associated with transient global ischemia (TGI) (Tønder et al., 1990; Koh et al., 1996). However, more recent evidence indicates that Zn$^{2+}$ mobilization from intracellular pools is also a crucial contributor to neuronal injury (Aizenman et al., 2000; Lee et al., 2000, 2003; Hwang et al., 2008).

Finally, Zn$^{2+}$ can play an important role in the development of Alzheimer’s disease (AD). The cation is a key component of amyloid plaques, and it is now suggested that Zn$^{2+}$ deregulation in the brain facilitates the synaptic deficits and cognitive decline observed in AD, while re-storing brain Zn$^{2+}$ homeostasis may represent an important and novel therapeutic avenue (Corona et al., 2010) (Fig. 3A).

In this Mini-Symposium, we review novel, exciting, and sometimes controversial, findings that substantiate a major role for Zn$^{2+}$ in the physiological and pathological functioning of the brain.

**Zn$^{2+}$ and synaptic function**

Free or “chelatable” Zn$^{2+}$ is concentrated within synaptic vesicles at glutamatergic terminals through the activity of the specific transporter ZnT3 (Paoletti et al., 2009). The role of synaptic Zn$^{2+}$ in regulating plasticity has been addressed either using extracellular metal chelators or in animal models lacking synaptic Zn$^{2+}$ (ZnT3 KO and the Mocha mutation), but the precise roles this ion plays in synaptic function is still controversial. While some studies suggest that long-term potentiation (LTP) and synaptic excitability in CA3 hippocampal neurons are unaffected by Zn$^{2+}$ under physiological conditions (Vogt et al., 2000; Lopantsev et al., 2003), others reports have shown the opposite (Li et al., 2001; Huang et al., 2008). In CA3 hippocampal neurons, Zn$^{2+}$ can directly promote the transactivation of the BDNF-related TrkB pathway (Huang et al., 2008); however, TrkB signaling can also be activated by extracellular Zn$^{2+}$ in a metalloproteinase-dependent manner by releasing pro-BDNF and converting it to mature BDNF (Hwang et al., 2005).

Paralleling these in vitro Zn$^{2+}$-mediated neurotrophic effects, chronic dietary treatment with Zn$^{2+}$ has been found to induce an increase of brain levels of BDNF (Nowak et al., 2004; Corona et al., 2010) (Fig. 3B). It should be noted that in CA3 neurons, BDNF has been shown to activate a Zn$^{2+}$-independent Ca$^{2+}$ current that is mediated by TRPC3 channels (Li et al., 2010).

Zn$^{2+}$ also modulates LTP in the amygdala through regulation of feedforward GABAergic inhibition (Kodirov et al., 2006). A direct role for synaptic Zn$^{2+}$ in learning and memory has been only recently uncovered. ZnT3 KO mice exhibit clear cognitive deficits, but only in animals aged beyond 6 months (Adlard et al., 2010). In other studies, 3- to 4-month-old ZnT3 KO animals show impaired contextual discrimination, spatial working mem-
Figure 2. Zn\(^{2+}\)-mediated neuronal death and dysfunction. A, NMDAR activation induces \([\text{Zn}^{2+}]_{\text{i}}\), mobilization in neuronal soma and dendrites. Neurons loaded with the Zn\(^{2+}\)-selective probe FluoZin3-AM (a, d) were exposed to NMDA (20 \(\mu M\)) for 5 min. NMDAR activation induces \([\text{Zn}^{2+}]_{\text{i}}\) rises (b, e) that show a different profile when analyzing changes in neuronal somata (Figure legend continues.)
ory, or learned fear extinction (Martel et al., 2010; Martel et al., 2011; Sindreu et al., 2011).

Among the targets of synaptic Zn\(^{2+}\), NMDA receptors (NMDARs) are rather unique as they display very high sensitivity to extracellular Zn\(^{2+}\) (Paolotti et al., 1997; Traynelis et al., 1998). At low nanomolar concentrations, Zn\(^{2+}\) allosterically inhibits the activity of NMDARs containing the GluN2A subunit, a subunit that is widespread in the adult CNS. The cation acts on a discrete Zn\(^{2+}\)-binding site located in the large bilobate N-terminal domain of the GluN2A subunit (Fig. 1A) (Paolotti et al., 2000). The Zn\(^{2+}\)–GluN2A interaction likely mediates tonic inhibition of NMDARs by ambient Zn\(^{2+}\) levels. At higher Zn\(^{2+}\) concentrations (micromolar range), such as may occur during phasic synaptic release, Zn\(^{2+}\) binds to the N-terminal domain of the GluN2B subunit, thereby inhibiting GluN2B-containing receptors (Rachline et al., 2005). The in vivo relevance of the high-affinity Zn\(^{2+}\) inhibition of NMDARs has been recently addressed using a knock-in (KI) mouse line in which the GluN2A Zn\(^{2+}\) site has been specifically eliminated. GluN2A-KI mice display a pronounced pain phenotype, showing both hypersensitivity to acute nociceptive stimuli and increased allostery in models of inflammatory and neuropathic pain (Nozaki et al., 2011). Moreover, in the KI animals, analgesia produced by exogenous Zn\(^{2+}\) administrations is completely suppressed, revealing an essential role of the Zn\(^{2+}\)–GluN2A interaction in the pain-relieving effects of the cation (Nozaki et al., 2011).

Synaptic Zn\(^{2+}\) also interacts with a selective metabotropic receptor, the mZnR, which has been recently identified as the previously orphan G-protein-linked receptor GPR39 (Fig. 1B) (Besser et al., 2009). Zn\(^{2+}\) released from mossy fibers directly and specifically activates the mZnR in CA3 hippocampal neurons. The mZnR response is mediated by a G\(_{q}\)-coupled pathway that shows both hypersensitivity to acute thermal and chemical nociception and enhanced allodynia in models of inflammatory and neuropathic pain (Nozaki et al., 2011). Moreover, in the KI animals, analgesia produced by exogenous Zn\(^{2+}\) administrations is completely suppressed, revealing an essential role of the Zn\(^{2+}\)–GluN2A interaction in the pain-relieving effects of the cation (Nozaki et al., 2011).

Synaptic Zn\(^{2+}\) also interacts with a selective metabotropic receptor, the mZnR, which has been recently identified as the previously orphan G-protein-linked receptor GPR39 (Fig. 1B) (Besser et al., 2009). Zn\(^{2+}\) released from mossy fibers directly and specifically activates the mZnR in CA3 hippocampal neurons. The mZnR response is mediated by a G\(_{q}\)-coupled pathway that shows both hypersensitivity to acute thermal and chemical nociception and enhanced allodynia in models of inflammatory and neuropathic pain (Nozaki et al., 2011). Moreover, in the KI animals, analgesia produced by exogenous Zn\(^{2+}\) administrations is completely suppressed, revealing an essential role of the Zn\(^{2+}\)–GluN2A interaction in the pain-relieving effects of the cation (Nozaki et al., 2011).

Synaptic Zn\(^{2+}\) also interacts with a selective metabotropic receptor, the mZnR, which has been recently identified as the previously orphan G-protein-linked receptor GPR39 (Fig. 1B) (Besser et al., 2009). Zn\(^{2+}\) released from mossy fibers directly and specifically activates the mZnR in CA3 hippocampal neurons. The mZnR response is mediated by a G\(_{q}\)-coupled pathway that shows both hypersensitivity to acute thermal and chemical nociception and enhanced allodynia in models of inflammatory and neuropathic pain (Nozaki et al., 2011). Moreover, in the KI animals, analgesia produced by exogenous Zn\(^{2+}\) administrations is completely suppressed, revealing an essential role of the Zn\(^{2+}\)–GluN2A interaction in the pain-relieving effects of the cation (Nozaki et al., 2011).

Synaptic Zn\(^{2+}\) also interacts with a selective metabotropic receptor, the mZnR, which has been recently identified as the previously orphan G-protein-linked receptor GPR39 (Fig. 1B) (Besser et al., 2009). Zn\(^{2+}\) released from mossy fibers directly and specifically activates the mZnR in CA3 hippocampal neurons. The mZnR response is mediated by a G\(_{q}\)-coupled pathway that shows both hypersensitivity to acute thermal and chemical nociception and enhanced allodynia in models of inflammatory and neuropathic pain (Nozaki et al., 2011). Moreover, in the KI animals, analgesia produced by exogenous Zn\(^{2+}\) administrations is completely suppressed, revealing an essential role of the Zn\(^{2+}\)–GluN2A interaction in the pain-relieving effects of the cation (Nozaki et al., 2011).

Synaptic Zn\(^{2+}\) also interacts with a selective metabotropic receptor, the mZnR, which has been recently identified as the previously orphan G-protein-linked receptor GPR39 (Fig. 1B) (Besser et al., 2009). Zn\(^{2+}\) released from mossy fibers directly and specifically activates the mZnR in CA3 hippocampal neurons. The mZnR response is mediated by a G\(_{q}\)-coupled pathway that shows both hypersensitivity to acute thermal and chemical nociception and enhanced allodynia in models of inflammatory and neuropathic pain (Nozaki et al., 2011). Moreover, in the KI animals, analgesia produced by exogenous Zn\(^{2+}\) administrations is completely suppressed, revealing an essential role of the Zn\(^{2+}\)–GluN2A interaction in the pain-relieving effects of the cation (Nozaki et al., 2011).
Interestingly, Zn$^{2+}$ deprivation can also be a trigger for neuronal death and a converging set of evidence indicates that, most likely, neurons possess a finely tuned “Zn$^{2+}$ set-point.” In this respect, even though chelation of deregulated [Zn$^{2+}$], is neuroprotective, excessive depletion of [Zn$^{2+}$], by high-affinity cell-permeable Zn$^{2+}$ chelators can be lethal (Lee et al., 2008). Zn$^{2+}$ depletion can enhance endonuclease activity (Vincent and Maiese, 1999; Vincent et al., 1999) as well as counteract neuronal apoptosis by inhibiting Bax and Bak activation (Ganju and Eastman, 2003). In addition Zn$^{2+}$ chelation by TPEN promotes neuronal apoptosis by inducing caspase-11 and caspase-3 activation (Lee et al., 2008). TPEN-induced Zn$^{2+}$ depletion also favors a “dying-back” pattern of axon and dendrite degeneration due to Zn$^{2+}$-mediated ATP depletion and autophagy (Yang et al., 2007).

The possibility of neuronal injury triggered by Zn$^{2+}$ depletion should be considered in light of the fact that Zn$^{2+}$-chelating strategies have been proposed as therapeutic measures in the aftermath of an ischemic insult as well as for the treatment of AD (Corona et al., 2011). The idea of a Zn$^{2+}$ set-point is further substantiated within the context of AD as recent findings indicate that, in an AD mouse model, dietary supplementation of the cation starting as early as 1-month-old animals largely prevents the development of age-dependent mitochondrial dysfunction and hippocampal-dependent cognitive deficits and induces a potential increase in BDNF levels (Fig. 3B) (Corona et al., 2010).

**Zn$^{2+}$ dyshomeostasis and ischemic neuronal injury**

A series of recent studies has promoted a reevaluation of the “calcium-centric” hypothesis that has dominated the field of ischemic neuronal death in the past three decades (Choi, 1988). Real-time “single-cell” imaging techniques have in fact shown that Ca$^{2+}$ works in synergy with Zn$^{2+}$ to promote ischemic death. Ca$^{2+}$ imaging in acute hippocampal slices undergoing oxygen and glucose deprivation (OGD; an in vitro model of brain ischemia) using a low-affinity Ca$^{2+}$-sensitive probe has shown that the OGD-driven increase in the probe fluorescence is substantially stunted (by 70%) by TPEN, indicating that, at least in some models, ischemia promotes a parallel, and possibly interdependent, surge of [Ca$^{2+}$] and [Zn$^{2+}$], (Stork and Li, 2006).

Indeed, analyzing the ionic changes of CA1 pyramidal neurons exposed to OGD, a more recent study has dissected the interplay between the two cations. The study showed that, within few minutes after OGD induction, neurons undergo Ca$^{2+}$ deregulation and irreversible alteration of plasma membrane permeability (Medvedeva et al., 2009). Surprisingly, both processes are to APP and inhibits its ferroxidase activity and ability to facilitate iron release from neurons, leading to pro-oxidant intraneuronal iron accumulation as a downstream consequence of extracellular Zn$^{2+}$ accumulation. B, Zn$^{2+}$ supplementation is beneficial in an animal model of AD. 3xTg-AD mice chronically fed (11–13 months) with water containing 30 ppm of ZnSO$_4$ are protected from the appearance at 12–14 months of age of hippocampus-dependent memory deficits (as assessed with the Morris water maze test). Mice were tested when the platform was removed 1.5 h (a, left panel; to investigate short-term memory) and 24 h (a, right panel; to investigate long-term memory) after the last training trial. Zn$^{2+}$-fed 3xTg-AD mice exhibited a marked recovery in their long-term memory as indicated by the decreased time (latency) they used to reach the point where the platform used to be. b, Zn$^{2+}$ supplementation promotes metalloproteinase (MMPs) activation in 3xTg-AD mice as shown by gelatin zymography indicating a significant increase of MMP-2 and MMP-9 induction in 3xTg-AD mouse brains. c, BDNF immunoblotting reveals that Zn$^{2+}$-fed 3xTg-AD mice showed a fourfold increase in BDNF levels compared to untreated mice (modified from Corona et al., 2010). Error bars indicate mean values ± SEM. * indicates $p < 0.05$ in a and c and $p < 0.01$ in b.

---

**Figure 3.** Zn$^{2+}$ in Alzheimer’s disease. A, Zn$^{2+}$ released during neurotransmission is trapped by amyloid, depriving targets essential for LTP. In addition, the Zn$^{2+}$ transfers inappropriately...
preceded by elevations in $[\text{Zn}^{2+}]$, and associated with mitochondrial Zn$^{2+}$ uptake as well as with depolarization and $[\text{Zn}^{2+}]$, chelation with TPEN results in delaying the phenomena (Memedvedeva et al., 2009). A novel link explaining the synergistic deregulation of the two cations is offered by the downstream effects produced by glutamate and Ca$^{2+}$ influx on the acidification of the neuronal cytosol. Acidosis is a potent trigger for Zn$^{2+}$ mobilization from MTs and a recent study indicates that glutamate/Ca$^{2+}$ influx leads to acidification of the neuronal cytosol, and that this is key to promote neuronal $[\text{Zn}^{2+}]$, rises (Kiedrowski, 2011). Synaptically released Zn$^{2+}$ can promote ischemic neuronal death (especially in TGI) by entering postsynaptic neurons through routes that are used by Ca$^{2+}$, such as NMDARs and voltage-sensitive Ca$^{2+}$ channels (VSCC), however most Zn$^{2+}$ preferentially fluxes through Ca$^{2+}$-and Zn$^{2+}$-permeable GluA2-lacking AMPA receptors (Ca/ARs; for review, see Sensi et al., 2009). Ca/ARs are highly expressed and dynamically upregulated after TGI (Pellegrini-Giampietro et al., 1997) on postsynaptic membranes in the dendritic tree of TGI-vulnerable neurons and their pharmacological inhibition prevents Zn$^{2+}$ influx and is highly neuroprotective in brain slices undergoing OGD or in animals exposed to TGI (Yin et al., 2002; Noh et al., 2005).

TGI-related apoptosis is also modulated by Zn$^{2+}$ as the cation induces mPTP opening in isolated postsynaptic mitochondria extracted immediately after TGI and these intramitochondrial Zn$^{2+}$ increases are linked to increased proteolytic cleavage of BCL-xL and the accumulation of the pro-apoptotic byproduct, deltaN-BCL-xL (Bonanni et al., 2006). Furthermore, the extracellular Zn$^{2+}$ chelator, cliquinol (CQ), is neuroprotective and decreases the expression levels of caspase-3 and -9 and AIF in the hippocampus of CQ-treated gerbils undergoing ischemia (Wang et al., 2010).

Neurons can be also killed by intraneuronal mobilization of the metal. Studies using ZnT3KO mice have, in fact, shown that glutamate-driven $[\text{Zn}^{2+}]$, accumulation can result from Zn$^{2+}$ released from sources such as MTs, mitochondria, and lysosomes (for review, see Sensi et al., 2009). MTs are key players in excitotoxic and ischemic injury as they release Zn$^{2+}$ upon oxidative stress, a phenomenon occurring in neurons and glia (Aizenman et al., 2000; Malaiyandi et al., 2001, 2004) that can lead to both caspase-dependent and caspase-independent forms of cell death (Aizenman et al., 2000; McLaughlin et al., 2001; Du et al., 2002). In the case of caspase-dependent cell death, the liberated Zn$^{2+}$ triggers a signaling cascade that creates a permissive environment for the effective activation of proteases and nucleases. K$^+$ is a key modulator of this process as cells undergoing caspase-mediated death develop an early, robust drop of intracellular K$^+$ levels (Yu et al., 1997; Hughes and Cidlowski, 1999) reaching, in some cases, a final concentration of 50 mM (Hughes et al., 1997). This loss of $[\text{K}^+]$, favors the activation of caspases, including caspase 3, while the process and the subsequent neuronal death is inhibited when $[\text{K}^+]$, is maintained at physiological levels (Bortner et al., 1997; Hughes et al., 1997; Yu et al., 1997). In cortical and midbrain neurons, K$^+$ efflux is facilitated by a dramatic enhancement of acidosis is also a key modulator of Zn$^{2+}$ dyshomeostasis upon cerebral ischemia. Ischemic acidosis can increase Zn$^{2+}$ influx through VS3C and Ca/ARs and promote Zn$^{2+}$ release from MTs, thereby favoring an overall neurotoxic increase in $[\text{Zn}^{2+}]$, levels (Jiang et al., 2000; Sensi et al., 2003; Frazzini et al., 2007). As protons also block NMDARs, ischemic acidosis can therefore serve as a switch to decrease NMDAR-mediated neuronal death while potentiating injury triggered by the activation of VS3C and AMPAR. Data from cultured neurons indicate that, in fact, AMPAR activation promotes ROS-mediated $[\text{Zn}^{2+}]$, rises that are enhanced by mild acidosis (Frazzini et al., 2007). Interestingly, Zn$^{2+}$ can itself disrupt the neuronal acid–base equilibrium by blocking the Na$^+$/H$^+$ exchanger, thereby creating a feedforward loop as the cation promotes intracellular acidification and also delays recovery from intracellular acidification (Dineley et al., 2002).

Zn$^{2+}$ in Alzheimer’s disease

Aβ accumulation in the neocortex in AD is pathognomonic of AD, yet the mere production of this ubiquitously expressed 39–43 residue peptide does not offer explanations for why amyloid only forms in the neocortex, why mice and rats do not develop amyloid pathology with age, or why women and APP transgenic mice have accelerated amyloid formation. The exceptional colocalization of Aβ and Zn$^{2+}$ in the glutamatergic synapses of the neocortex offers plausible explanations (Fig. 3A). Zn$^{2+}$ induces the rapid, but reversible, aggregation of Aβ into amyloid precipitates (Bush et al., 1994; Cherny et al., 1999), the pathological hallmark of AD. The rat/mouse Aβ possesses three amino acid substitutions that attenuate the interaction of Zn$^{2+}$ and prevent Zn$^{2+}$-induced precipitation (Bush et al., 1994). As
described earlier, Zn\(^{2+}\) is released in a dissociable form by glutamatergic fibers in the cortex and hippocampus, and ZnT3 loads Zn\(^{2+}\) into these synaptic vesicles. The distribution of ZnT3 expression closely approximates with the anatomical sites of Aβ deposition. ZnT3 is not appreciably expressed outside of the brain, and therefore the synaptic release of Zn\(^{2+}\) in the neocortex is a cogent explanation for why Aβ, which is released in the same vicinity, is liable to precipitate only in the brain. While several reports have found Zn\(^{2+}\) to be enriched in extracellular amyloid deposits (Lovell et al., 1998; Lee et al., 1999; Miller et al., 2006; Adlard et al., 2008), this represents only a small fraction of the total cortical volume, and the tissue total Zn\(^{2+}\) concentrations only rise during advanced pathology (Religa et al., 2006).

Genetic ablation of ZnT3 abolishes interstitial (Lee et al., 2002) and vessel-wall (Friedlich et al., 2004) amyloid pathology in transgenic mice overexpressing human Aβ. The increase in the levels of soluble Aβ in the brains of the APP transgenic × ZnT3 KO mice (Lee et al., 2002) confirmed that Zn\(^{2+}\) holds the amyloid mass in a dissociable equilibrium (Huang et al., 1997). Ablation of ZnT3 also abolished the difference in genders for this model in amyloid burden. Female mice have greater levels of dissociable Zn\(^{2+}\) in this system (Lee et al., 2002), and ovarectomy raises hippocampal synaptic vesicle Zn\(^{2+}\) levels further, whereas estrogen replacement opposed this rise (Lee et al., 2004).

As mentioned above, Zn\(^{2+}\) may be a key modulator of synaptic activity and substrate for LTP. This may explain why ZnT3 KO mice develop a cognitive and memory loss by the age of 6 months, becoming a phenocopy for the cognitive loss seen in the AD model transgenic Aβ overexpressers (Adlard et al., 2010). Therefore, by trapping extracellular Zn\(^{2+}\), amyloid pathology may deprive these targets of physiological Zn\(^{2+}\) and so contribute to downstream cognitive loss through a variety of mechanisms. At the same time, Zn\(^{2+}\) flux through the NMDAR promotes the attachment of Aβ oligomers to the NR2B subunit, which may also impair LTP, but can be reversed by treatment with the Zn\(^{2+}\) ionophore, CQ (Deshpande et al., 2009). This ionophoric mechanism that liberates Zn\(^{2+}\) from Aβ oligomers, returning Zn\(^{2+}\) to the relatively deficient neighboring cells, may explain the rapid benefits of PBT2 (an analog of CQ) on cognition and neurite outgrowth in AD animal and cell culture models (Adlard et al., 2008, 2011), as well as the rapid efficacy of the drug candidate in a phase 2 clinical trial of AD patients (Lannfelt et al., 2008; Faux et al., 2010).

The trapping of Zn\(^{2+}\) by extracellular amyloid also impacts upon neuronal iron homeostasis. The amyloid protein precursor (APP) is a ferroxidase that catalytically loads Fe\(^{3+}\) into transferrin, and is required for optimal iron export from neurons (Duce et al., 2010). Brain neuronal iron levels are increased in APP knock-out mice, as well as in AD, which provokes oxidative damage (Smith and Goldin, 1997; Duce et al., 2010). APP ferroxidase activity is 75% decreased in AD cortical tissue, caused by dissociation of Zn\(^{2+}\) from amyloid, and not caused by a decrease in APP levels (Duce et al., 2010). Abnormal iron homeostasis can also have broad sequelae on heme synthesis, and is another of the downstream ramifications of Zn\(^{2+}\) trapping by amyloid.

One major question to be answered is why extracellular Zn\(^{2+}\) begins to react with soluble Aβ with advanced aging. Extracellular Aβ concentrations are elevated in uncommon familial AD mutations, but there is no evidence of an elevation with age in sporadic cases. The prediction is that extracellular Zn\(^{2+}\) levels may rise with age. Zn\(^{2+}\) coreleased with glutamate in the synapse must be, like glutamate, taken back into the cells by a very rapid transport with a pattern of Zn\(^{2+}\) levels in the synaptic cleft that is likely to not be steady, but rather rapidly sinusoidal. There is no evidence for increased synaptic Zn\(^{2+}\) in AD, but it is possible that Zn\(^{2+}\) reuptake, which is energy dependent, may be fatigued with aging. Recent data have implicated the presenilins (PSs), whose mutations cause familial AD, in Zn\(^{2+}\) uptake (Greenough et al., 2011). Together, these data indicate that PS may be able to influence Aβ aggregation by metal ion clearance in the extra-neuronal vicinity, which is currently being studied further.

Conclusions

Critical new findings have begun to uncover the many physiological roles for synthetically released Zn\(^{2+}\), as well as for intracellularly mobilized Zn\(^{2+}\), acting as an important player in the modulation of neuronal excitability and survival. New territories, however, need to be explored. For instance, the physiopathological activity of Zn\(^{2+}\) in glial cells and how this is factored within the context of neuron–glia interaction requires further investigation. A more detailed road map of the regulatory processes that affect Zn\(^{2+}\) homeostasis and Zn\(^{2+}\)–dependent signaling is also needed. All these steps are crucial to find better pharmacological tools able to modulate cellular Zn\(^{2+}\). These drugs are urgently needed as they are likely to have an important impact in the management of major neurological conditions like AD, epilepsy, and stroke.

References

Adlard PA, Cherry RA, Finkelstein DJ, Gautier E, Robb E, Cortes M, Volitakis I, Liu X, Smith JP, Perez K, Laughton K, Li QX, Charman SA, Nicolazzo JA, Wilkins S, Deleva K, Lynch T, Kok G, Ritchie CW, Tanzi RE, et al. (2008) Rapid restoration of cognition in Alzheimer’s transgenic mice with 8-hydroxy quinoline analogs is associated with decreased interstitial Abeta. Neurot 59:43–55.

Adlard PA, Parncutt JM, Finkelstein DI, Bush AI (2010) Cognitive loss in zinc transporter-3 knock-out mice: a phenocopy for the synaptic and memory deficits of Alzheimer’s disease? J Neurosci 30:1631–1636.

Adlard PA, Bica L, White AB, Nurjono M, Filiz G, Crouch PJ, Donnelly PS, Cappai R, Finkelstein DI, Bush AI (2011) Metal ionophore treatment restores dendritic spine density and synaptic protein levels in a mouse model of Alzheimer’s disease. PLoS ONE 6:e17669.

Aizenman E, Stout AK, Hartnett KA, Dineley KE, McLaughlin B, Reynolds JJ (2000) Induction of neuronal apoptosis by thiol oxidation: putative role of intracellular zinc release. J Neurochem 75:1878–1888.

Aras MA, Aizenman E (2005) Obligatory role of ASKJ in the apoptotic surge of K+ currents. Neurosci Lett 387:136–140.

Aras MA, Aizenman E (2011) Redox regulation of intracellular zinc: molecular signaling in the life and death of neurons. Antioxid Redox Signal 15:2249–2263.

Besser L, Chorin E, Sekler I, Silverman WF, Atkin S, Russell JT, Hershfinkel M (2009) Synaptically released zinc triggers metabotropic signaling via a zinc-sensing receptor in the hippocampus. J Neurosci 29:2890–2901.

Blasco-Ibáñez JM, Poza-Aznar J, Crespo C, Marqués-Mari AI, Gracia-Llanes FJ, Martínez-Guijarro FJ (2004) Chelation of synaptic zinc induces overexcitability in the hilar mossy cells of the rat hippocampus. Neurosci Lett 355:101–104.

Bonanni L, Chachar M, Jover-Mengual T, Li H, Jones A, Yokota H, Ofengeim D, Flannery RJ, Miyawaki T, Cho CH, Polster BM, Pypaert M, Hardwick JM, Sensi SL, Zukin RS, Jonas EA (2006) Zinc-dependent multiconductance channel activity in mitochondria isolated from ischemic brain. J Neurosci 26:6851–6862.

Bortner CD, Hughes FM Jr, Cidlowski JA (1997) A primary role for K+ and Na+ efflux in the activation of apoptosis. J Biol Chem 272:32346–32342.

Bush AI, Pettingell WH, Multhaup G, d Paradis M, Vonsattel JP, Gusella JF, Beyreuther K, Masters CL, Tanzi RE (1994) Rapid induction of Alzheimer A beta amyloid formation by zinc. Science 265:1464–1467.

Cai AL, Zipfel GJ, Sheline CT (2006) Zinc neurotoxicity is dependent on the synaptic cleft. J Neurosci 26:2169–2176.

Caporale T, Ciavardelli D, Di Ilio C, Lanuti P, Drago D, Sensi SL (2009)
Ratiometric-pericam-mt, a novel tool to evaluate intramitochondrial zinc. Exp Neurol 218:228–234.

Carter RE, Aiba I, Dietz RM, Sheline CT, Shuttleworth CW (2011) Spread depression and related events are significant sources of neuronal Zn2+ release and accumulation. J Cereb Blood Flow Metab 31:1073–1084.

Chen M, Chen Q, Cheng XW, Lu TJ, Liu HX, Jia JM, Zhang C, Xu L, Xiong QZ (2009) Zn2+ mediates ischemia-induced impairment of the ubiquitin-proteasome system in the rat hippocampus. J Neurochem 111:1094–1103.

Cherny RA, Legg JT, McLean CA, Fairlie DP, Huang X, Atwood CS, Beyreuther K, Tanzi RE, Masters CL, Bush AI (1999) Aqueous dissolution of Alzheimer’s disease Aβ amyloid deposits by biodepletion. J Biol Chem 274:23223–23228.

Choi DW (2009) Calcium-mediated neurotoxicity: relationship to specific channel types and role of ischemic damage. Trends Neurosci 11:465–469.

Choi DW, Yokoyama M, Koh J (1988) Zinc neurotoxicity in cortical cell culture. Neuroscience 24:67–79.

Chorin E, Vinograd O, Fleidervish I, Gilad D, Herrmann S, Sekler I, Aizenman E, Hershfinkel M (2011) Upregulation of KCC2 activity by zinc-mediated neurotransmission via the mZnR/GPR39 receptor. J Neurosci 31:12916–12926.

Cole TB, Robbins CA, Wenzel HJ, Schwartzkroin PA, Palmiter RD (2000) Seizures and neuronal damage in mice lacking vesicular zinc. Epilepsy Res 39:153–169.

Corona C, Marcon, M., coppo F, Silvestri E, Viscoo AD, Lattanzio R, Sorda RL, Ciardiarelli D, Goglia F, Piantelli M, Canzoniero LM, Sensi SL (2010) Dietary zinc supplementation of 3×Tg-AD mice increases BDNF levels and prevents cognitive deficits as well as mitochondrial dysfunction. Cell Death Dis 1:e91.

Corona C, Pensalfini A, Frazzini V, Sensi SL (2011) New therapeutic targets in Alzheimer’s disease: brain deregulation of calcium and zinc. Cell Death Dis 2:e176.

Deshpande A, Kawai H, Metherate R, Glabe CG, Busciglio J (2009) A role for hippocampal zinc in regulating mGluR1-dependent pathway. J Neurosci 29:4004–4015.

Dineley KE, Brocard JB, Reynolds IJ (2002) Elevated intracellular zinc and altered proton homeostasis in forebrain neurons. Neuroscience 114:439–449.

Dineley KE, Richards LL, Votyakova TV, Reynolds IJ (2005) Zinc causes loss of membrane potential and elevates reactive oxygen species in rat brain mitochondria. Mitochondrion 5:55–65.

Dittmer PJ, Miranda JG, Gorski JA, Palmer AE (2009) Genetically encoded sensors to elucidate spatial distribution of cellular zinc. J Biol Chem 284:16289–16297.

Du S, McLaughlin B, Pal S, Aizenman E (2002) In vitro neurotoxicity of methylisothiazolinone, a commonly used industrial and household bio-icide, proceeds via a zinc and extracellular signal-regulated kinase mitogen-activated protein kinase-dependent pathway. J Neurosci 22:7408–7416.

Ducet JA, Tsatsanis A, Cate MA, James SA, Robb E, Wilke K, Leong SL, Perez K, Johanns T, Greenough MA, Cho HH, Galatius D, Moir RD, Masters CL, McLean C, Tanzi RE, Cappai R, Barnham KJ, Ciccotosto GD, Rogers JT, et al. (2010) Iron-export ferroxidase activity of beta-amyloid precursor protein is inhibited by zinc in Alzheimer’s disease. Cell 142:857–867.

Faux NG, Ritchie CW, Gunn A, Rembach A, Tsatsanis A, Bedo J, Bush AI (2011) Presenilin promotes the cellular uptake of copper and zinc and maintains Cu-chaperone of sod1-dependent Cu/Zn superoxide dismutase activity. J Biol Chem 286:9776–9786.

Frazzini V, Rapposelli IG, Corona C, Rockabrand E, Canzoniero LM, Sensi SL (2007) Mild acidosis enhances AMPA receptor-mediated intracellular zinc. Exp Neurol 212:228–234.

Frederickson CJ, Giblin LJ 3rd, Balaji RV, Masala R, Frederickson CJ, Zeng Y, Lopez EV, Koh JY, Chorin U, Besser L, Hershfinkel M, Li Y, Thompson RB, Krezel A (2006) Synchronous release of zinc from brain slices: factors governing release, imaging, and accurate calculation of concentration. J Neurosci Methods 154:19–29.

Friedlich AL, Lee JY, van Groen T, Cherry RA, Volitakis I, Cole TB, Palmeter RD, Koh JY, Bush AI (2004) Neuronal zinc exchange with the blood vessel wall promotes cerebral amyloid angiopathy in an animal model of Alzheimer’s disease. J Neurosci 24:3435–3439.

Fukahori M, Itoh M (1990) Effects of dietary zinc status on seizure susceptibility and hippocampal zinc content in the El (epilepsy) mouse. Brain Res 529:16–22.

Ganju N, Eastman A (2003) Zinc inhibits Bax and Bak activation and cytochrome c release induced by chemical inducers of apoptosis but not by death-receptor-initiated pathways. Cell Death Differ 10:652–661.

Gazaryan IG, Krassianskaia YP, Kristal BS, Brown AM (2007) Zinc irreversibly damages major enzymes of energy production and antioxidant defense prior to mitochondrial permeability transition. J Biol Chem 282:24373–24380.

Greenough MA, Volitakis I, Li QX, Laughton K, Evin G, Ho M, Daziel AH, Chen M, Busch AI (2011) Presenilins promote the cellular uptake of copper and zinc and maintain Cu-chaperone of sod1-dependent Cu/Zn superoxide dismutase activity. J Biol Chem 286:9776–9786.

Hershfinkel M, Kandler K, Knoch ME, Dagan-Rabin M, Aras MA, Abramovitch-Dahan C, Sekler I, Aizenman E (2009) Intracellular zinc inhibits KCC2 transporter activity. Nat Neurosci 12:725–727.

Hwang X, Atwood CS, Moir RD, Hartshorn MA, Vonsattel JP, Tanzi RE, Bush AI (1997) Zinc-induced Alzheimer’s Abeta1–40 aggregation is mediated by conformational factors. J Biol Chem 272:26484–26470.

Hwang YZ, Pan E, Xiong QZ, McNamara JO (2008) Zinc-mediated trans-activation of TrkB potentiates the hippocampal mossy fiber-CA3 pyramidal neuron. Neuron 57:525–535.

Hughes FM Jr, Bortter CD, Purdy GD, Cidlowski JA (1997) Intracellular Z+ suppresses the activation of apoptosis in lymphocytes. J Biol Chem 272:30567–30576.

Hughes FM Jr, Cidlowski JA (1999) Potassium is a critical regulator of apoptotic enzymes in vitro and in vivo. Adv Enzyme Regul 39:157–171.

Hurst TK, Wang D, Thompson RB, Fierke CA (2010) Carbonic anhydride II-based metal ion sensing: advances and new perspectives. Biochem Biophys Acta 1804:393–403.

Hwang JJ, Park MH, Choi SY, Koh JY (2005) Activation of the Trk signaling pathway by extracellular zinc: role of metalloproteinases. J Biol Chem 280:11995–12001.

Hwang JJ, Lee SJ, Kim TY, Cho JH, Koh JY (2008) Zinc and 4-hydroxy-2-nonenal mediated lysosomal membrane permeabilization induced by H2O2 in cultured hippocampal neurons. J Neurosci 28:6847–6855.

Kay AR, Töth K (2008) Is zinc a neuromodulator? Sci Signal 1:re3.

Kchedrowski L (2011) Cytosolic zinc release and clearance in hippocampal neurons exposed to glutamate—the role of pH and sodium. J Neurochem 111:237–243.

Kim YH, Koh JY (2002) The role of NADPH oxidase and neuronal nitric oxide synthase in zinc-induced poly(ADP-ribos)e polymerase activation and cell death in cortical culture. Exp Neurol 177:407–418.

Kim YH, Kim EY, Gwag BJ, Sohn S, Koh JY (1999) Zinc-induced cortical neuronal death with features of apoptosis and necrosis: mediation by free radicals. Neuroscience 89:175–182.

Kodirov SA, Takizawa S, Joseph J, Kandel ER, Shumyatsky GP, Bolshakov VV (2006) Synchronized release of zinc gates long-term potentiation in fear-conditioning pathways. Proc Natl Acad Sci U S A 103:2503–2508.

Kay AR (2003) Evidence for chelatable zinc in the extracellular space of the hippocampus, but little evidence for synaptic release of Zn. J Neurosci 23:8647–8655.

Kay AR, Töth K (2008) Is zinc a neuromodulator? Sci Signal 1:re3.

Kim YH, Koh JY (2002) The role of NADPH oxidase and neuronal nitric oxide synthase in zinc-induced poly(ADP-ribos)e polymerase activation and cell death in cortical culture. Exp Neurol 177:407–418.

Kim YH, Koh JY, Gwag BJ, Sohn S, Koh JY (1999) Zinc-induced cortical neuronal death with features of apoptosis and necrosis: mediation by free radicals. Neuroscience 89:175–182.

Kchedrowski L (2011) Cytosolic zinc release and clearance in hippocampal neurons exposed to glutamate—the role of pH and sodium. J Neurochem 111:237–243.

Kim YH, Koh JY (2002) The role of NADPH oxidase and neuronal nitric oxide synthase in zinc-induced poly(ADP-ribos)e polymerase activation and cell death in cortical culture. Exp Neurol 177:407–418.

Kim YH, Koh JY, Gwag BJ, Sohn S, Koh JY (1999) Zinc-induced cortical neuronal death with features of apoptosis and necrosis: mediation by free radicals. Neuroscience 89:175–182.

Kchedrowski L (2011) Cytosolic zinc release and clearance in hippocampal neurons exposed to glutamate—the role of pH and sodium. J Neurochem 111:237–243.
modifying therapy for Alzheimer’s disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol [Erratum (2009) 8:981].

Lavada N, Peralta MR, Jrd, Chiasson M, Lafortune K, Pellegrini L, Seress L, Toth K (2007) Extracellular chelation of zinc does not affect hippocampal excitability and seizure-induced cell death in rats. J Physiol 578:275–289.

Lee JM, Kim YJ, Ra H, Kang SJ, Han S, Koh JY, Kim YH (2008) The involvement of caspase-11 in TPEN-induced apoptosis. FEBS Lett 582:1871–1876.

Lee JY, Mook-Jung I, Koh JY (1999) Histochemically reactive zinc in plaques of the Swedish mutant β-amyloid precursor protein transgenic mice. J Neurosci 19:RC10.

Lee JY, Cole TB, Palmiter RD, Koh JY (2000) Accumulation of zinc in degenerating hippocampal nerve terminal of ZnT3-null mice after seizures: evidence of synaptic vesicle origin. J Neurosci 20:RC79.

Lee JY, Cole TB, Palmiter RD, Suh SW, Koh JY (2002) Contribution by synaptic zinc to the gender-disparate plaque formation in human Swedish mutant APP transgenic mice. Proc Natl Acad Sci U S A 99:7705–7710.

Lee JY, Kim JH, Palmiter RD, Koh JY (2003) Zinc released from metallothionein-iii may contribute to hippocampal CA1 and thalamic neuronal death following acute brain injury. Exp Neurol 184:337–347.

Lee J-Y, Kim J-H, Hong SH, Lee JY, Cherny RA, Bush AI, Palmiter RD, Koh J-Y (2004) Estrogen decreases zinc transporter 3 expression and synaptic vesicle zinc levels in mouse brain. J Biol Chem 279:8602–8607.

Li Y, Hough CJ, Frederickson CJ, Searvey JM (2001) Induction of mossy fiber—CA3 long-term potentiation requires translocation of synaptically released Zn++. J Neurosci 21:8015–8025.

Li Y, Calfa G, Inoue T, Amaral MD, Pozzo-Miller L (2010) Activity-dependent release of endogenous BDNF from mossy fibers evokes a TRPC3 current and Ca2+ elevations in CA3 pyramidal neurons. J Neurophysiol 103:2846–2856.

Lopantsev V, Wenzel HJ, Cole TB, Palmiter RD, Schwartzkroin PA (2003) Lack of vesicular zinc in mossy fibers does not affect synaptic excitability of CA3 pyramidal cells in zinc transporter 3 knockout mice. Neuroscience 116:237–248.

Lovell MA, Robertson JD, Teesdale WJ, Campbell JL, Markesbery WR (1998) Copper, iron and zinc in Alzheimer’s disease senile plaques. J Neurol Sci 158:47–52.

Malaiyandi LM, Dineley KE, Reynolds JI (2001) Metallothionein overexpression enhances oxidant-induced zinc release in astrocytes. Soc Neurosci Abstr 27:868.816.

Malaiyandi LM, Dineley KE, Reynolds JI (2004) Divergent consequences arise from metallothionein overexpression in astrocytes: zinc buffering and oxidant-induced zinc release. Glia 45:346–353.

Malaiyandi LM, Honick AS, Rintoul GL, Wang QJ, Reynolds IJ (2005) Copper, iron and zinc in Alzheimer’s disease senile plaques of the Swedish mutant APP transgenic mice. Proc Natl Acad Sci U S A 102:12230–12235.

Nowak G, Legutko B, Szewczyk B, Papp M, Sanak M, Plic A (2004) Zinc treatment induces cortical brain-derived neurotrophic factor gene expression. Eur J Pharmacol 492:57–59.

Nakashima AS, Dyck RH (2009) Zinc and cortical plasticity. Brain Res Rev 59:347–373.

Noh KM, Kim YH, Koh JY (1999) Mediation by membrane protein kinase C of zinc-induced oxidative neuronal injury in mouse cortical cultures. J Neurochem 72:1609–1616.

Noh KM, Yokota H, Mashiko T, Castillo PE, Zukin RS, Bennett MV (2005) Blockade of calcium-permeable AMPA receptors protects hippocampal neurons against global ischemia-induced death. Proc Natl Acad Sci U S A 102:12230–12235.

Pal SK, Takimoto K, Aizenman E, Levitan ES (2006) Apoptotic surface delivery of K+ channels. Cell Death Differ 13:661–667.

Pal S, Hartnett KA, Nerbonne JM, Levitan ES, Aizenman E (2003) Mediation of neuronal apoptosis by Kv2.1-encoded potassium channels. J Neurosci 23:4798–4802.

Pal S, He K, Aizenman E (2004) Nitrosative stress and potassium channel-mediated neuronal apoptosis: is zinc the link? Pflugers Arch 448:296–303.

Paoletti P, Paoletti P, Asher P, Neyton J (1997) High-affinity zinc inhibition of NMDA NR1-NR2A receptors. J Neurosci 17:5711–5725.

Paoletti P, Perin-Dureau F, Fayayzuddin A, Le Goff A, Callebaut I, Neyton J (2000) Molecular organization of a zinc binding N-terminal modulatory domain in a NMDA receptor subunit. Neuron 28:911–925.

Paoletti P, Vernagno AM, Barbour B, Casado M (2009) Zinc at glutamatergic synapses. Neuroscience 158:126–136.

Pellegrini-Giampietro DE, Gorter JA, Bennett MV, Zukin RS (1998) The GluR2 (GluR-B) hypothesis: Ca2+-permeable AMPA receptors in neurotoxic disorders. Trends Neurosci 20:464–470.

Qian J, Noebels JL (2005) Visualization of transmitter release with zinc fluorescence detection at the mouse hippocampal mossy fibre synapse. J Physiol 566:747–758.

Qin Y, Dittmer PJ, Park JG, Iansen KB, Palmer AE (2011) Measuring steady-state and dynamic endoplasmic reticulum and Golgi Zn2+ with genetically encoded sensors. Proc Natl Acad Sci U S A 108:7351–7356.

Rachline J, Perin-Dureau F, Le Goff A, Neyton J, Paoletti P (2005) The micromolar zinc-binding domain on the NMDA receptor subunit NR2B. J Neurosci 25:308–317.

Redman PT, Jefferson BS, Ziegler CB, Mortensen OV, Torres GE, Levitan ES, Aizenman E (2006) A vital role for voltage-dependent potassium channels in dopamine transporter-mediated 6-hydroxydopamine neurotoxicity. Neuroscience 143:1–6.

Redman PT, He K, Hartnett KA, Jefferson BS, Hu L, Rosenberg PA, Levitan ES (2007) Apoptotic surge of potassium currents is mediated by p38 phosphorylation of Kv2.1. Proc Natl Acad Sci U S A 104:3568–3573.

Redman PT, Hartnett KA, Aras MA, Levitan ES, Aizenman E (2009) Regulation of apoptotic potassium currents by coordinated zinc-dependent signalling. J Physiol 587:4393–4404.

Religa D, Strozyl D, Cherny RA, Volitakis I, Haroutunian V, Winblad B, Naslund J, Bush AI (2006) Elevated cortical zinc in Alzheimer disease. Neurology 67:69–75.

Ruíz A, Walker MC, Fabian-Fine R, Kullmann DM (2004) Endogenous zinc inhibits GABA(A) receptors in a hippocampal pathway. J Neurophysiol 91:1091–1096.

Sensi SL, Yin HZ, Carriedo SG, Rao SS, Weiss JH (1999) Preferential Zn2+ influx through Ca2+-permeable AMPA/kainate channels triggers prolonged mitochonrdial superoxide production. Proc Natl Acad Sci U S A 96:2414–2419.

Sensi SL, Yin HZ, Weiss JH (2000) AMPA/kainate receptor-triggered Zn2+ entry into cortical neurons induces mitochondrial Zn2+ uptake and persistent mitochondrial dysfunction. Eur J Neurosci 12:3813–3818.

Sensi SL, Ton-That D, Sullivan PG, Jonas EA, Gee KR, Kaczmarek LK, Weiss JH (2003) Modulation of mitochondrial function by endogenous Zn2+ pools. Proc Natl Acad Sci U S A 100:6157–6162.

Sensi SL, Paoletti P, Bush AI, Sekler I (2009) Zinc in the physiology and pathology of the CNS. Nat Rev Neurosci 10:780–791.
Sheline CT, Behrens MM, Choi DW (2000) Zinc-induced cortical neuronal death: contribution of energy failure attributable to loss of NAD(+) and inhibition of glycolysis. J Neurosci 20:3139–3146.

Sindreu C, Palmier RD, Storm DR (2011) Zinc transporter ZnT-3 regulates presynaptic Erk1/2 signaling and hippocampus-dependent memory. Proc Natl Acad Sci U S A 108:3366–3370.

Smith RD, Goldin AL (1997) Phosphorylation at a single site in the rat brain sodium channel is necessary and sufficient for current reduction by protein kinase A. J Neurosci 17:6086–6093.

Stork CJ, Li YV (2006) Intracellular zinc elevation measured with a “calcium-specific” indicator during ischemia and reperfusion in rat hippocampus: a question on calcium overload. J Neurosci 26:10430–10437.

Tønder N, Johansen FF, Frederickson CJ, Zimmer J, Diemer NH (1990) Possible role of zinc in the selective degeneration of dentate hilar neurons after cerebral ischemia in the adult rat. Neurosci Lett 109:247–252.

Traynelis SF, Burgess MF, Zheng F, Lyuboslavsky P, Powers JL (1998) Control of voltage-independent zinc inhibition of NMDA receptors by the NR1 subunit. J Neurosci 18:6163–6175.

Vincent AM, Maiese K (1999) Nitric oxide induction of neuronal endonuclease activity in programmed cell death. Exp Cell Res 246:290–300.

Vincent AM, TenBroeke M, Maiese K (1999) Neuronal intracellular pH directly mediates nitric oxide-induced programmed cell death. J Neurobiol 40:171–184.

Vogt K, Mellor J, Tong G, Nicoll R (2000) The actions of synaptically released zinc at hippocampal mossy fiber synapses. Neuron 26:187–196.

Wang T, Zheng W, Xu H, Zhou JM, Wang ZY (2010) Clioquinol inhibits zinc-triggered caspase activation in the hippocampal CA1 region of a global ischemic gerbil model. PLoS One 5:e11888.

Yang Y, Kawataki T, Fukui K, Koike T (2007) Cellular Zn2+ chelators cause “dying-back” neurite degeneration associated with energy impairment. J Neurosci Res 85:2844–2855.

Yin HZ, Sensi SL, Ogoshi F, Weiss JH (2002) Blockade of Ca2+-permeable AMPA/kainate channels decreases oxygen-glucose deprivation-induced Zn2+ accumulation and neuronal loss in hippocampal pyramidal neurons. J Neurosci 22:1273–1279.

Yu SP, Yeh CH, Sensi SL, Gwag BJ, Canzoniero LM, Farhangrazi ZS, Ying HS, Tian M, Dugan LL, Choi DW (1997) Mediation of neuronal apoptosis by enhancement of outward potassium current. Science 278:114–117.