Special Review Article

Involvement of Zinc in Neuronal Death in the Hippocampus

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Abstract

Zinc is released with glutamate from neuron terminals in the hippocampus. Zinc may serve as a negative-feedback factor of presynaptic activity and negatively modulate postsynaptic calcium mobilization. On the other hand, the hippocampus is vulnerable to glutamate excitotoxicity, a final common pathway for numerous pathological processes such as Alzheimer's disease and amyotrophic lateral sclerosis, in addition to stroke/ischemia, temporal lobe epilepsy. The excitotoxicity is linked to the excessive influx of zinc and calcium. The crosstalk between zinc and calcium via calcium channels may play a role in both synaptic plasticity and excitotoxicity. This reviewer summarizes the involvement of zinc in neuronal death in the hippocampus focused on the crosstalk. The enhanced excitotoxicity in the hippocampus in zinc deficiency is also summarized.

Keywords : zinc, glutamate, excitotoxicity, hippocampus, calcium, crosstalk, zinc deficiency

1. Introduction

Zinc is the second most abundant trace element in the body and powerfully influences cell division and differentiation [1,2]. In microorganisms, plants and animals, over 300 enzymes require zinc for their functions. Zinc has three functions in zinc enzymes : catalytic, coactive (or cocatalytic) and structural [3]. In the brain, zinc turnover is strictly regulated via the brain-barrier system [4,5]. Averaged intracellular zinc concentration is estimated to be approximately 150 mM, judging from zinc concentration in the total brain, while extracellular zinc concentration is estimated to be approximately 0.15–1 μM from zinc concentration in the cerebrospinal fluid and extracellular zinc concentration measured by in vivo microdialysis. Zinc serves as an intracellular and an extracellular signal factor in synaptic neurotransmission ; approximately 90% of the total brain zinc is zinc metalloproteins. The rest exists in the presynaptic vesicles and is histochemically reactive (as revealed by Timm's sulfide-silver staining method) [6,7].

Zinc concentration in the hippocampus is relatively high in the brain [8] and the action of zinc is closely linked to functions and pathological processes in the hippocampus [9]. There is a large number of evidence on zinc-containing glutamatergic neurons that sequester zinc in the presynaptic vesicles and release it in a calcium- and impulse-dependent manner [7,10]. Zinc concentration in the presynaptic vesicles is the highest in the giant boutons of hippocampal mossy fibers and is estimated to be approximately 300 μM there [11]. All giant boutons of mossy fibers contain zinc in the presynaptic vesicles, while approximately 45% of Schaffer collateral boutons is zinc-positive [12]. Vesicular zinc may serve as an endogenous neuromodulator of several important receptors including the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate receptor, N-methyl-D-aspartate (NMDA) and γ-amino butyric acid (GABA) receptors [13-15]. However, the extracellular concentration of zinc reached after the release is a matter of debate. Es-

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timates after tetanic stimulation range between 10 and 100 μM [16,17], even up to 300 μM under extreme conditions [18]. Excess of extracellular zinc become neurotoxic because of the translocation of zinc to postsynaptic neurons [19-23].

This review summarizes zinc action via crosstalk between zinc and calcium in both functional and pathological aspects and also enhanced glutamate excitotoxicity in zinc deficiency.

2. Zinc action via crosstalk between zinc and calcium in functional aspect

Neural circuits of the zinc-containing glutamatergic neurons are considered to be associated with the episodic memory function and are important for behavior, emotional expression and cognitive-mnemonic operations [4]. Lu et al. [24] demonstrated that endogenous zinc is required for the induction of long-term potentiation (LTP) in hippocampal mossy fiber synapses. Li et al. [25] demonstrated that the induction of LTP in hippocampal mossy fiber synapses requires translocation of synaptically released zinc. On the other hand, the impairment of spatial learning, memory or sensorimotor function was not observed in zinc transporter-3-null mice, which lack the histochemically reactive zinc in synaptic vesicles [26,27]. There is also some evidence that zinc has no role in the CA3 mossy fiber LTP [16,28]. Thus, the physiological significance of zinc as an endogenous neuromodulator is still poorly understood.

To clarify the presynaptic action of zinc released from mossy fibers, zinc action in presynaptic activity during tetanic stimulation was examined using rat hippocampal slices. In mossy fiber terminals preferentially double-stained with zinc and calcium indicators, the increase in calcium orange signal during delivery of tetanic stimuli (100 Hz, 1 s) to the dentate granule cell layer is enhanced by addition of 1 mM CaEDTA and attenuated by addition of 100 μM zinc [29]. It is likely that zinc released from mossy fiber terminals suppresses the increase in calcium signal in the presynaptic terminals induced by stimulation of depolarization, followed by inhibitory modulation of the presynaptic activity (Fig. 1). Presynaptic calcium influx through voltage-dependent calcium cannel (VDCC) triggers vesicular exocytosis. FM4-64 is known as a fluorescent indicator of synaptic vesicle recycling and is taken up into presynaptic vesicles in an activity-dependent manner. Subsequent rounds of exocytosis arising from depolarization lead to the release of the dye from the presynaptic terminals (destaining) [30,31].

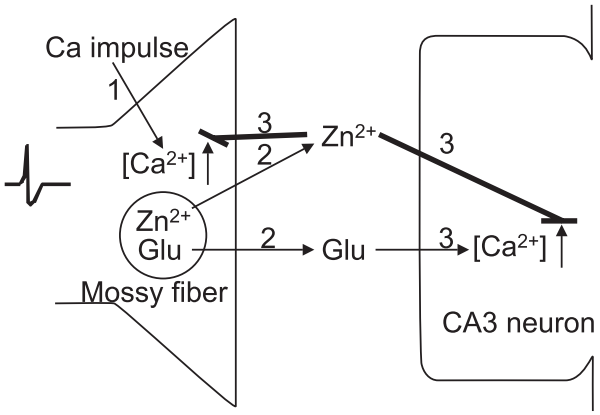

Fig. 1 Zinc action in calcium mobilization in the mossy fiber synapses.
When the action potential is delivered to mossy fibers, calcium influx occurs via voltage-dependent calcium channel (VDCC) and calcium concentration is increased in the terminals (1), followed by exocytosis (2). Zinc released from mossy fiber terminals may negatively modulate the presynaptic activity via suppression of the increase in calcium concentration (3). The negative modulation of the presynaptic activity by zinc leads to suppression of postsynaptic calcium mobilization (3). Zinc also negatively modulates the increase in calcium concentration in postsynaptic CA3 neurons (3).

When tetanic stimuli at 10 Hz for 180 s, which induce mossy fiber LTP, are delivered to the dentate granule cell layer, the decrease in FM4-64 signal is enhanced by addition of 1 mM CaEDTA and suppressed by addition of 100 μM zinc [29]. Zinc released from mossy fiber terminals during tetanic stimulation may suppress vesicular exocytosis, probably via inhibitory modulation of intracellular calcium mobilization (Fig. 1). The hippocampal mossy fiber LTP is expressed by presynaptic mechanisms leading to persistent enhancement of neurotransmitter release. The induction of mossy fiber LTP is critically dependent on the increase in presynaptic calcium induced by stimulation of depolarization [32-34], which activates the calcium-calmodulin-sensitive adenyl cyclase I [35]. Therefore, mossy fiber zinc seems to be involved in the presynaptic mechanism leading to the LTP.

On the other hand, the increase in calcium concentration in postsynaptic CA3 pyramidal cells is required for the initiation and modulation of numerous cellular processes including synaptic plasticity such as LTP [36-39]. It occurs via influx through NMDA receptors [37,39] and VDCC [40,41] or release from internal calcium stores [39,42]. Zinc blocks NMDA receptors [43], in addition to VDCC [44]. However, the action of intracellular zinc

in calcium release from internal stores via calcium channels, i.e., inositol 1,4,5 trisphosphate (IP_3) and ryanodine receptors, is unknown. Zinc uptake into CA3 pyramidal cells and its significance was examined using rat hippocampal slices with ZnAF-2DA, a membrane-permeable zinc indicator [45]. Intracellular ZnAF-2 signal in the CA3 pyramidal cell layer is increased during delivery of tetanic stimuli to the dentate granule cell layer. This increase is completely blocked in the presence of CNQX, an AMPA/kainate receptor antagonist. These results suggest that zinc is taken up into CA3 pyramidal cells via activation of AMPA/kainate receptors. AMPA/kainate receptors consist of calcium-impermeable and calcium-permeable (GluR2-lacking) receptors. The calcium-permeable AMPA/kainite receptors, which are involved in zinc influx, may play an important role in both synaptic plasticity and excitotoxicity [46,47]. The action of zinc taken up into CA3 pyramidal cells in the increas in intracellular calcium via group I metabotropic glutamate receptors is examined by regional delivery of tADA, a group I metabotropic glutamate receptor agonist, to the stratum lucidum after blockade of AMPA/kainate receptor-mediated calcium and zinc influx [45]. Intracellular calcium orange signal in the CA3 pyramidal cell layer is increased by stimulation with *t*ADA, suggesting that *t*ADA induces calcium release from internal stores in CA3 pyramidal cells. The increase in calcium orange signal by *t*ADA is enhancedby perfusion with pyrithione, a zinc ionophore that decreases basal ZnAF-2 signal in the CA3 pyramidal cell layer. On the other hand, it is blocked by perfusion with pyrithione and zinc that increases basal ZnAF-2 signal. These results indicate that the increase in calcium levels via the metabotropic glutamate receptor pathway is inversely related to zinc levels in CA3 pyramidal cells (Fig. 1). The cross talk between calcium and zinc via this pathway seems to be important for CA3 neuronal activity.

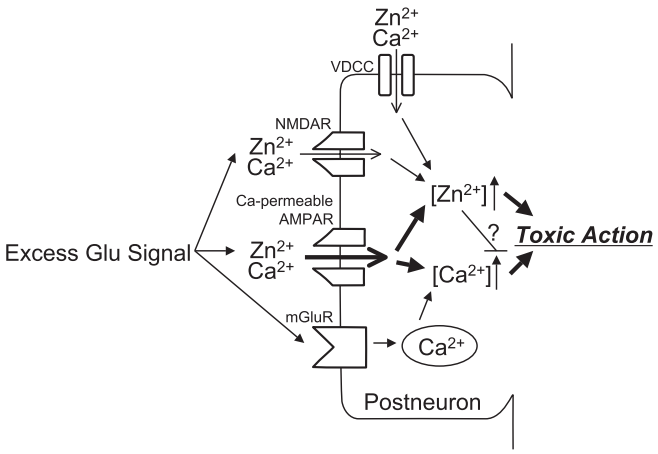

Fig. 2 Toxic action of zinc in pathological processes. Excess of extracellular glutamate triggers excessive influx of zinc and calcium in postsynaptic neurons via glutamate receptors and VDCC, followed by neurodegeneration. Calcium-permeable AMPA/kainite receptors play an important role in the neurodegenerative processes. Zinc suppresses calcium mobilization into postsynaptic CA3 neurons via blockade of NMDA receptors and VDCC. The increase in intracellular zinc may suppress calcium release from internal stores, whereas it is toxic in postsynaptic CA3 neurons.

3. Zinc action via crosstalk between zinc and calcium in pathological aspect

When 1 mM glutamate was regionally delivered to the stratum lucidum, in which mossy fiber synapses exist, in hippocampal slices double-stained with zinc and calcium indicators, extracellular zinc signal is markedly increased in the stratum lucidum and intracellular calcium signal is increased in the CA3 pyramidal cell layer [48]. Excessive delivery of exogenous glutamate may lead to the release of zinc and glutamate from mossy fibers and excite mossy fiber synapses. The persistent increase in calcium signal in the CA3 pyramidal cell layer during stimulation with glutamate is significantly attenuated in the presence of 100 μM zinc, while significantly enhanced in the presence of 1 mM CaEDTA. Zinc released from mossy fibers may attenuate the increase in intracellular calcium signal in mossy fiber synapses and postsynaptic CA3 neurons after excessive inputs to dentate granular cells (Fig. 1 and 2). The zinc may negatively modulate the activity of mossy fiber synapses even under excitation via excess of extracellular glutamate. However, it is possible that the zinc becomes neurotoxic via the translocation of the zinc to CA3 neurons. There is a lot of evidence that excessive zinc influx via calcium-permeable AMPA/kainate receptors is involved in neurodegeneration [22,46,49]. In excessive excitation, zinc release from mossy fibers seems to act protectively for CA3 pyramidal cells initially via negative modulation of presynaptic activity and postsynaptic calcium mobilization (Fig. 1). However, zinc taken up into CA3 pyramidal cells may damage the cells (Fig. 2).

In global ischemia, CA1 pyramidal neurons degenerate, whereas CA3 pyramidal neurons remain intact [46,50]. Degeneration of CA1 neurons can be protected by blockade of calcium-permeable AMPA/kainite receptors [46,51]. Excessive influx of zinc and calcium via

calcium-permeable AMPA/kainite receptors results in neurodegeneration in ischemia (Fig. 2).

On the other hand, zinc concentration in the brain may be decreased by epileptic seizures [7,52]. Kainate is an agonist of glutamate receptor subtypes and kainate-challenged mice and rats are experimental models of human temporal lobe epilepsy. They have been used to understand brain zinc movement in epileptic seizures. Zinc concentration in the hippocampus is significantly decreased in kainate-challenged mice [52]. A selective loss of Timm's stain is observed in the hippocampal mossy fibers after electrical stimulation of the perforant path, which evokes hippocampal granule spikes and epileptiform discharges [53,54]. Extracellular concentrations of zinc and glutamate are significantly increased in the hippocampus of young rats challenged with kainate [55]. Thus, the attenuation of Timm's stain is linked to excessive excitation of zinc-containing glutamatergic neurons and implies the translocation of zinc to postsynaptic neurons. Neuronal loss is observed in the CA1, CA2 and CA 3 pyramidal cell layers after challenge with kainite [56], probably followed by the loss of zinc from the hippocampus [52].

4. Enhanced glutamate excitotoxicity in zinc deficiency

Dietary zinc deficiency causes anorexia, weight loss and growth retardation [57-59]. It is possible that the stress of severe food restriction leads to the increase in serum corticosterone concentration via activation of the hypothalamic-pituitary-adrenal (HPA) axis ; Serum corticosterone concentration is significantly increased in young rats after 2-week zinc deprivation (Fig. 3) [60]. Zinc-deficient young rats exhibit behavioral abnormality in the open-field test, suggesting that activation of the HPA axis is associated with behavioral abnormality in zinc deficiency. On the other hand, a novel environment used for the open-field test can also activate the HPA axis [61,62]. The hippocampus is linked with the HPA axis activity and is involved in stress response [63,64]. Thus, hippocampal function seems to be influenced by 2-week zinc deprivation, although zinc concentration in the hippocampus is not decreased after 2-week zinc deprivation [65]. On the other hand, hippocampal calcium mobilization is altered by glucocorticoids [63]. Glucocorticoids increase voltage-dependent calcium conductance and calcium-dependent afterhyperpolarization [66,67]. They also increase calcium mobilization into the cytosolic compartment, as well as the decrease in its removal [68]. The basal signal of intracellular calcium (fluo-4 FF) is significantly increased in the dentate gyrus, CA3 and CA1 after 2-week zinc deprivation, suggesting the increase in intracellular Ca^{2+} levels in the hippocampus and the change in excitability of hippocampal neurons via corticosterone in zinc deficiency (Fig. 3) [69]. In kainite-challenged rats after 2-week zinc deprivation, the latency in myoclonic jerks is significantly shorter than in the control [65]. Susceptibility to kainite-induced seizures in zinc deficiency seems to be linked to the increase in basal Ca^{2+} levels in the hippocampus.

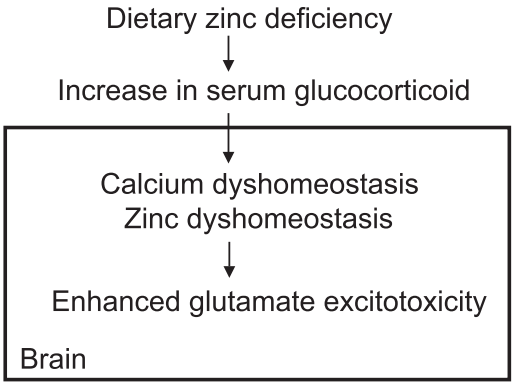

Fig. 3 Enhanced glutamate excitotoxicity in the hippocampus in zinc deficiency.
Zinc deficiency activates the HPA axis, followed by the increase in serum corticosterone, and increases the basal levels of intracellular Ca^{2+} in the hippocampus prior to the decrease in extracellular zinc. Intracellular calcium dyshomeostasis, in addition to zinc dyshomeostasis, may be linked to the enhanced glutamate excitotoxicity in the hippocampus in zinc deficiency.

When mice and rats are fed a zinc-deficient diet for 4 weeks, extracellular zinc concentration in the brain is decreased and Timm's stain is also attenuated [55]. Susceptibility to kainate-induced seizures is markedly enhanced after 4-week zinc deprivation. Enhanced release of glutamate associated with a decrease in GABA concentrations is a possible mechanism for the enhanced seizure susceptibility in zinc deficiency. Neuronal loss and TUNEL-positive cells are more observed in the CA1, CA2 and CA3 pyramidal cell layers of zinc-deficient group than those of the control group after challenge with kainite [56]. Glutamate excitotoxcity, which is induced with kainite, is enhanced by zinc deficiency (Fig. 3). Glutamate excitotoxicity is a final common pathway for numerous pathological processes such as Alzheimer's disease and amyotrophic lateral sclerosis, in addition to stroke/ischemia, temporal lobe epilepsy [70,71]. It is likely that pathological processes associated with glutamate excito-

toxicity are aggravated by zinc deficiency. Therefore, adequate zinc supply to the brain is important for prevention of neurological diseases.

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