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Corticosteroid receptor-mediated synaptic Zn^{2+} dynamics in the hippocampus and its significance

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Summary

Neuronal Zn^{2+} homeostasis is closely linked with not only cognitive function but also cognitive decline, while there is no hormone involved in zinc homeostasis unlike calcium homeostasis. Extracellular Zn^{2+} dynamics is modified by extracellular levels of glucocorticoids and glutamate, which are linked with stress response. Extracellular glucocorticoid signal is transmitted via not only glucocorticoid receptors but also mineralocorticoid receptors. Membrane corticosteroid receptors dynamically modifies synaptic Zn^{2+} dynamics in the hippocampus. Synaptic plasticity, i.e., long-term potentiation (LTP), which is a cellular mechanism of memory, is affected by rapid intracellular Zn^{2+} dysregulation via membrane corticosteroid receptor activation in the CA1; Corticosterone rapidly induces the increase in intracellular Zn^{2+} via membrane corticosteroid receptor activation, and decreases phosphorylated CaMKII level, resulting in attenuating CA1 LTP. The mechanism of intracellular Zn^{2+} dysregulation is different between membrane mineralocorticoid and glucocorticoid receptor-mediated signaling. In contrast, corticosterone-induced intracellular Ca^{2+} dysregulation is less crucial for affecting CA1 LTP. The basal concentration (~100 pM) of intracellular Zn^{2+} is much lower than that (~100 nM) of intracellular Ca^{2+}. Therefore, the precise mechanism is required to regulate intracellular Zn^{2+} homeostasis because of more critical neurotoxicity of Zn^{2+}. This review summarizes the physiological significance of intracellular Zn^{2+} homeostasis focused on signaling of corticosterone and glutamate in the extracellular compartment.

Key words: Zn^{2+}, membrane corticosteroid receptor, glucocorticoid, hippocampus, stress

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Introduction

Zrt-Irt-like proteins (ZIPs) are involved in the transport of Zn^{2+} into the cytoplasm, while the zinc transporter (ZnT) family is involved in the transport of Zn^{2+} out of the cytoplasm. ZIPs and ZnTs serve to regulate Zn^{2+} homeostasis in the living body including the brain [1-3]. The basal concentrations of extracellular Zn^{2+} and intracellular Zn^{2+} are approximately 10 nM [4] and 100 pM (**Fig. 1B**) [5,6], respectively, in the brain, while the basal concentrations of extracellular Ca^{2+}

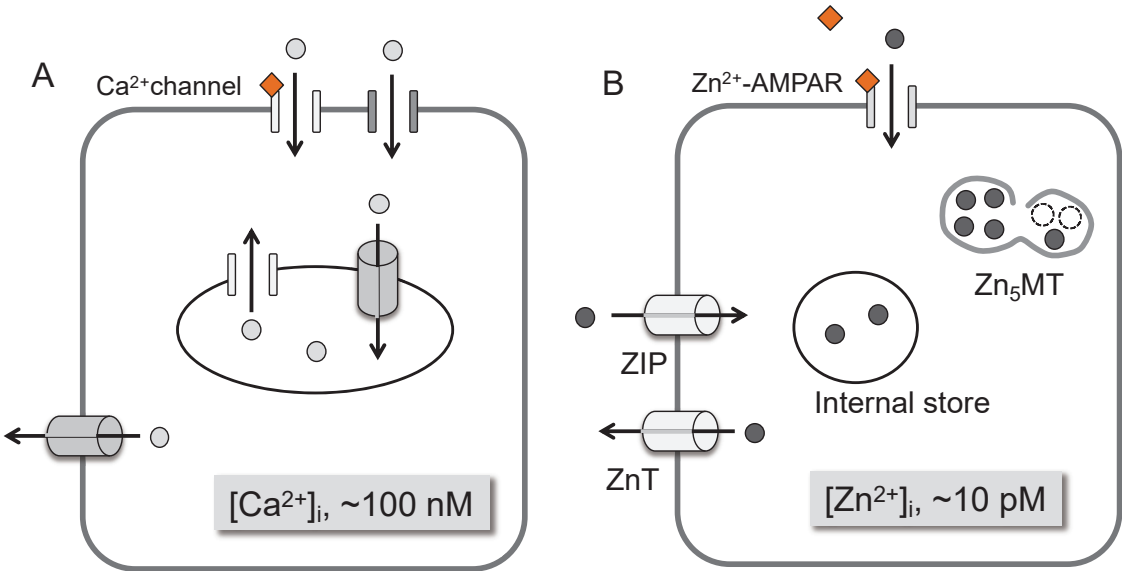

Figure 1. **Intracellular buffering systems of Ca^{2+} and Zn^{2+}**

A The influx of extracellular Ca^{2+} is dynamically induced through Ca^{2+} channels for intracellular Ca^{2+} signaling, while the basal concentration of intracellular Ca^{2+} is strictly regulated by the efflux of cytosol Ca^{2+} to the extracellular compartment and the reuptake of cytosol Ca^{2+} into the Ca^{2+} stores.

B The influx of extracellular Zn^{2+} is also dynamically induced through Zn^{2+}-permeable GluR2-lacking AMPA receptors (Zn^{2+}-AMPAR) for intracellular Zn^{2+} signaling. While the basal concentration of intracellular Zn^{2+} is regulated by the Zn^{2+}-buffering system, i.e., Zn^{2+} transporters (ZIPs and ZnTs), MTs, and internal stores containing Zn^{2+}, the mechanism is poorly understood.

and intracellular Ca^{2+}, which are 1.3 mM and 100 nM (**Fig. 1A**), respectively, are much higher than of extracellular Zn^{2+} and intracellular Zn^{2+}, resulting in much less attention paid to Zn^{2+} than Ca^{2+} to understand brain function and brain dysfunction. For understanding synaptic function, for example, no attention has been paid to Zn^{2+} in the extracellular compartment; Zn^{2+} is not added to artificial cerebrospinal fluid (ACSF), i.e., the brain extracellular medium widely used for *in vitro* and *in vivo* experiments. Not only neuronal excitation but also synaptic plasticity such as long-term potentiation (LTP), a cellular mechanism of memory, are modified in brain slices bathed in ACSF without Zn^{2+} where the original neurophysiology may be modified [7,8].

In the brain, approximately 80% of zinc is zinc metalloproteins. Approximately 20% is histochemically reactive as determined by Timm's sulfide-silver staining and concentrated in the synaptic vesicles of a subclass of glutamatergic neuron [9]. The latter serves as a signal factor, free Zn^{2+}, in both the intracellular and extracellular compartments. Synaptic Zn^{2+} dynamically functions in conjunction with synaptic activity, i.e., glutamatergic synapse activity in the limbic system including the hippocampus [10,11]. Synaptic Zn^{2+} plays a key role in not only cognitive function but also cognitive decline. However, there is no hormone involved in zinc homeostasis unlike calcium homeostasis. Extracellular Zn^{2+} dynamics, which is linked with intracellular Zn^{2+} homeostasis, is dynamically modified by the changes in extracellular circumstances. Dietary zinc deficiency activates the hypothalamo-pituitary-adrenocortical (HPA) system and increases glucocorticoid secretion from the adrenal cortex [12]. Extracellular levels of glucocorticoids modify extracellular Zn^{2+} dynamics followed by modifying intracellular Zn^{2+} level [13]. Extracellular levels of glucocorticoids and glutamate, which are linked with stress response, affects not only intracellular Ca^{2+} homeostasis but also intracellular Zn^{2+} homeostasis.

This review summarizes the physiological significance of intracellular Zn^{2+} homeostasis focused on signaling of corticosterone and glutamate in the extracellular compartment.

Intracellular buffering of Ca^{2+} and Zn^{2+}

Vulnerability to Ca^{2+} dysregulation is facilitated with brain aging [14-16]. Ca^{2+} dysregulation is not ubiquitous in the brain, and has been observed in specific cell populations and areas. For example, the expression of L-type Ca^{2+} channels is age-relatedly

elevated in hippocampal pyramidal cells [17]. *N*-Methyl-*D*-aspartate (NMDA) receptor function is age-relatedly reduced in the frontal cortex and the hippocampus [18], suggesting that a compensatory mechanism is induced in the process of brain aging to regulate the availability of intracellular Ca^{2+} signaling. On the other hand, intracellular Ca^{2+} buffering is involved not only in cognitive function but also in cognitive decline, and is weakened with brain aging (**Fig. 1A**) [15].

To regulate the availability of intracellular Zn^{2+} signaling, a compensatory mechanism is also induced in the process of brain aging. The zinc concentration in presynaptic vesicles is reduced by the decrease in ZnT3 protein with aging [19,20], while the extracellular zinc concentration is age-relatedly increased in the hippocampus [21]. Intracellular Zn^{2+} buffering is also involved not only in cognitive function but also in cognitive decline. However, the Zn^{2+}-buffering system is more poorly understood than the Ca^{2+}-buffering system (**Fig. 1**). Weakened intracellular Ca^{2+} buffering, with a net decrease in the Ca^{2+}-buffering capacity, is linked with both normal aging [15] and neurological disorders such as AD [22].

The Zn^{2+}-buffering system is composed of Zn^{2+} transporters (ZIPs and ZnTs), Zn^{2+}-binding proteins such as metallothioneins (MTs), internal stores containing Zn^{2+}, and Ca^{2+}-permeable channels, which is dynamically linked with synaptic excitation (**Fig. 1B**). Judging from the increased concentration of extracellular Zn^{2+} [21], it is estimated that intracellular Zn^{2+} buffering is modified in the aged brain of rats [23]. The characteristics (easiness) of extracellular Zn^{2+} influx may lead to reduced intracellular Zn^{2+}-buffering capacity in the aged dentate gyrus, which represents weakened intracellular Zn^{2+} buffering [23]. Because MT synthesis in the hippocampus is induced even in aged rats, it is estimated that MT-mediated Zn^{2+}-buffering capacity is not significantly different between young and aged hippocampus [24]. MTs are of benefit to maintaining intracellular Zn^{2+} homeostasis under acute changes in intracellular Zn^{2+} concentration [24].

Corticosteroid receptor-mediated synaptic Zn^{2+} dynamics in the hippocampus

The HPA system is activated after exposure to stress followed by increase in glucocorticoid secretion from the adrenal cortex [25-27]. Glucocorticoids pass through the brain barrier system and modulate cognitive activity bidirectionally [28-30]. Under stressful circumstances, glucocorticoids are excessively and/or persistently secreted and considered a major factor for stress-related memory disorders [31,32]. Glucocorticoids (corticosterone in rodents) act on via both mineralocorticoid and glucocorticoid receptors, which exist on the plasma membrane and in the cytosolic compartment. Many of glucocorticoid actions require time to lead to changes in gene expression (>15–30 min), while glucocorticoids have rapid non-genomic actions via the membrane-bound receptors [33].

The hippocampus is enriched with mineralocorticoid and glucocorticoid receptors and is a target area under stressful circumstances. Glucocorticoids facilitate glutamate release from the neuron terminals via the rapid action of membrane mineralocorticoid receptors [34,35]. On the basis of the evidence on co-release of glutamate and Zn^{2+} from a subclass of glutamatergic neurons, i.e., zincergic neurons, it is estimated that glucocorticoids facilitate Zn^{2+} release from zincergic neuron terminals under stressful conditions [36] and that Zn^{2+} accumulation in the extracellular compartment plays a key role for cognitive decline in cooperation with glutamate accumulation in the extracellular compartment [36-38].

Synaptic plasticity, i.e., long-term potentiation (LTP) has been extensively studied in the hippocampus [39]. The entorhinal cortex is connected with the hippocampus and both areas play a key role for cognitive performance (**Fig. 2**). In the hippocampal CA1, pyramidal cells are innervated by the non-zincergic perforant pathway from the entorhinal cortex and also by zincergic Schaffer collateral from the hippocampal CA3 pyramidal cells (**Fig. 2**). Zn^{2+} released from Schaffer collateral is required to induce LTP at the Schaffer collateral-CA1 pyramidal cell synapses in the CA1 (**Fig. 3 and 4**) [40], while excess Zn^{2+} release attenuates the LTP [41]. In contrast, Zn^{2+} released from internal stores is required to induce LTP at the perforant pathway-CA1 pyramidal cell synapses in the CA1 (**Fig. 3 and 4**) [42]. Extracellular Zn^{2+} preferentially passes through Ca^{2+}- and Zn^{2+}-permeable GluR2-lacking α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors followed by intracellular Zn^{2+} dysregulation (toxicity) when glutamate accumulates in the extracellular compartment of the CA1, resulting in neurodegeneration including cognitive decline [43-46]. Extracellular glutamate-mediated cognitive decline, which is induced by stimulation with high K^+, is linked with intracellular Zn^{2+} dysregulation, but not intracellular Ca^{2+} dysregulation [47]. In 6-hydroxydopamine-induced Parkinson's disease in rats, nigral dopaminergic degeneration is also induced by intracellular Zn^{2+} dysregulation, but not intracellular Ca^{2+} dysregulation [48]. Ca^{2+}- and Zn^{2+}-permeable GluR2-lacking AMPA receptors are more closely linked with intracellular Zn^{2+} toxicity than intracellular Ca^{2+} toxicity [49,50], because the basal concentration of intracellular Zn^{2+} is much lower.

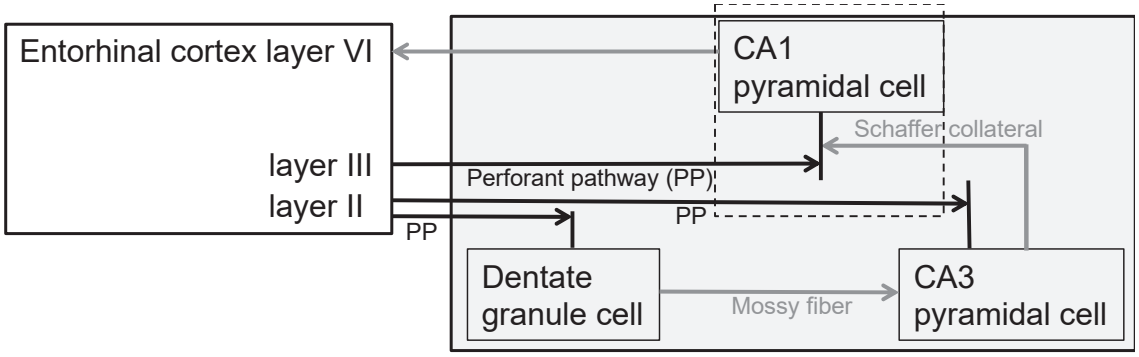

Figure 2. **The hippocampus is connected with the entorhinal cortex via the perforant pathway**
Mossy fiber and Schaffer collateral (the grey arrow) are zincergic and perforant pathway is non-zincergic.

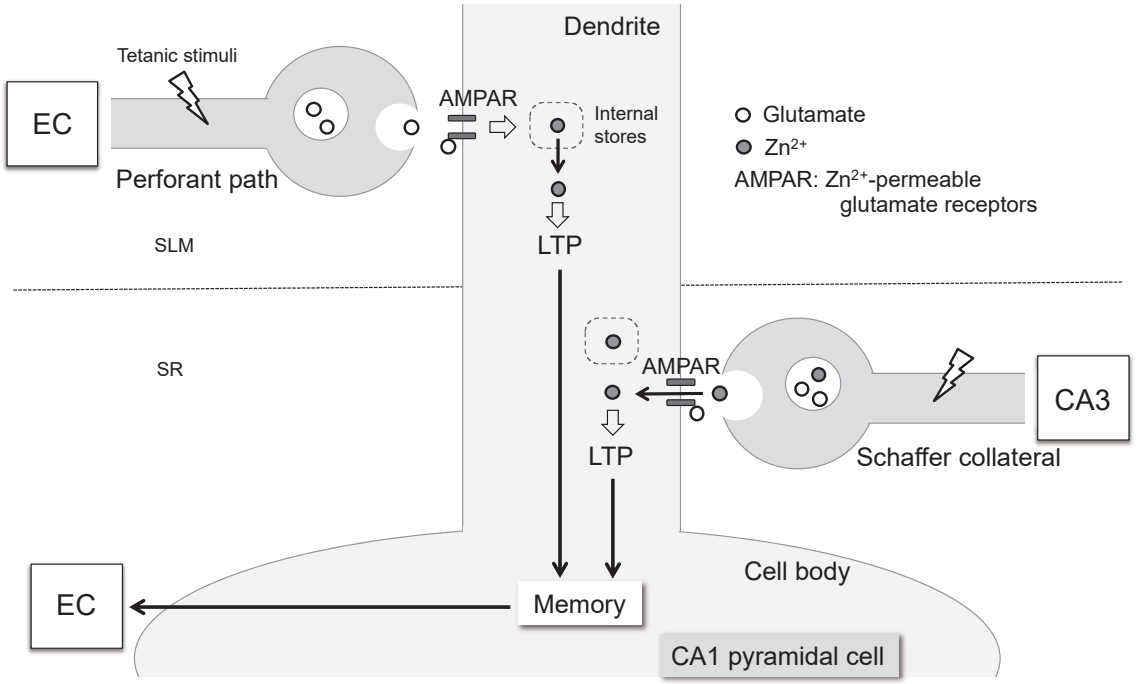

Figure 3. **Intracellular Zn^{2+} signaling is required for both perforant pathway LTP and Schaffer collateral LTP followed by hippocampus-dependent memory.**
The figure represents the area surrounded by the dotted line of Fig. 2. At perforant pathway synapses, Ca^{2+} signaling via NMDA receptor activation might be involved in Zn^{2+} release from the internal stores, which is required for perforant pathway LTP. At Schaffer collateral synapses, in contrast, transsynaptic Zn^{2+} influx through Zn^{2+}-permeable GluR2-lacking AMPA receptors is required for Schaffer collateral LTP. EC, entorhinal cortex; SLM, stratum lacunosum-moleculare; SR, stratum radiatum.

Acute stress induces a rapid corticosterone rise in the hippocampus of rats and impairs memory formation [51,52]. Non-genomic actions, especially via membrane mineralocorticoid receptor activation, are involved in the impairment of memory retrieval [53-55]. Although intracellular Zn^{2+} dysregulation is induced by excess signaling of extracellular glutamate, there has been no evidence on the relationship between synaptic Zn^{2+} dynamics and membrane corticosteroid receptors. We postulated that rapid modification of synaptic Zn^{2+} dynamics is linked with membrane corticosteroid receptors and leads to in vivo aberrant synaptic plasticity [38].

In the CA1, rapid changes in CA1 pyramidal cell function emerge via presyanptic and postsynaptic membrane mineralocorticoid receptors: corticosterone increases glutamate release probability pre-synaptically and causes a suppression in potassium current

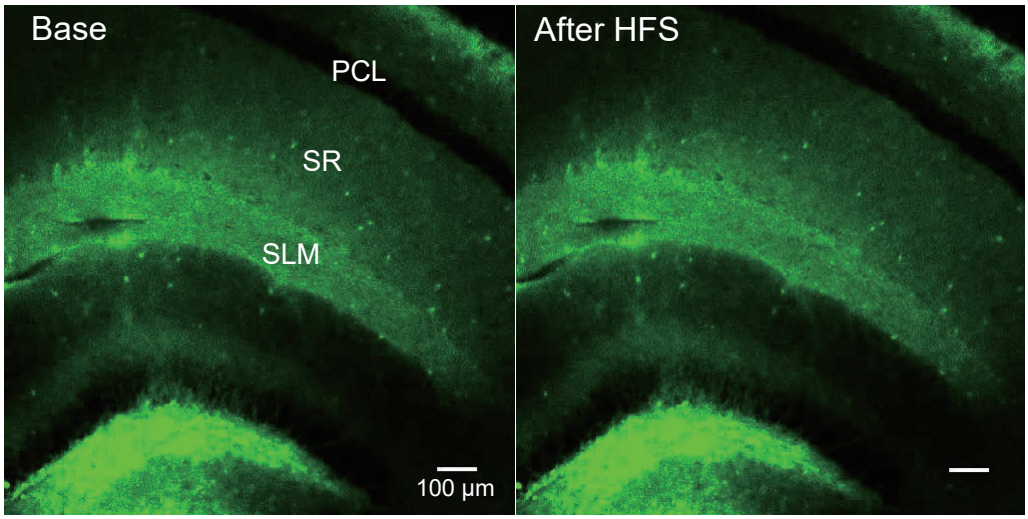

Figure 4. **Intracellular Zn^{2+} imaging in hippocampal CA1**
The basal level of intracellular Zn^{2+} in the CA1, which represents the area surrounded by the dotted line of Fig. 2, is imaged with intracellular ZnAF-2. Intracellular Zn^{2+} increases even in the stratum lacunosum-moleculare (SLM) where the perforant pathway connects with CA1 pyramidal cells after high-frequency stimulation (HFS) to induce LTP (Fig. 3). PCL, pyramidal cell layer; SLM, stratum lacunosum-moleculare; SR, stratum radiatum.

post-synaptically, leading to enhanced CA1 pyramidal cell excitability [56]. Corticosterone-induced increase in extracellular Zn^{2+}, which is linked with Schaffer collateral excitation, induces the subsequent attenuation of Schaffer collateral LTP in vivo [38]. Corticosterone-induced increase in extracellular Zn^{2+} may lead to intracellular Zn^{2+} dysregulation. In rat brain slices, corticosterone-induced rapid increases in extracellular and intracellular Zn^{2+} are canceled in the presence of spironolactone, a mineralocorticoid receptor antagonist that canceled corticosterone-induced attenuation of CA1 LTP. Corticosterone rapidly increases Zn^{2+} release from the Schaffer collateral via membrane mineralocorticoid receptor activation and then increases intracellular Zn^{2+} in CA1 pyramidal cells probably via Zn^{2+}-permeable GluR2-lacking AMPA receptor activation, resulting in the attenuated CA1 LTP (**Fig. 5B**). On the other hand, mifepristone, a glucocorticoid receptor antagonist, which canceled corticosterone-induced attenuation of CA1 LTP, also canceled corticosterone-induced rapid increase in intracellular Zn^{2+}, but not extracellular Zn^{2+}, suggesting that the short-term block of corticosterone-induced increase in intracellular Zn^{2+} with mifepristone is also benefit to canceling of the attenuated CA1 LTP. The mechanism of intracellular Zn^{2+} dysregulation is different between membrane mineralocorticoid and glucocorticoid receptor-mediated signaling (**Fig. 5B**). Corticosterone-induced rapid increase in intracellular Ca^{2+} is blocked by spironolactone, but not by mifepristone, suggesting that corticosterone-induced rapid intracellular Ca^{2+} dysregulation is less crucial for affecting CA1 LTP than rapid intracellular Zn^{2+} dysregulation.

Synaptic Zn^{2+} and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)

Corticosterone regulates AMPA receptors trafficking including Zn^{2+}-permeable GluR2-lacking AMPA receptors and facilitates LTP in the hippocampus [57-60]. Newly synthesized LTP-related proteins can be captured at new binding sites via CaMKII, a key molecule for LTP, for structural synapse enlargement, sustaining the potentiated state for a long term. The location of CaMKII is crucial for the construction of the potentiated state [61,62]. The interplay between the kinase and structural functions of CaMKII is important for defining a time window permissive for synaptic plasticity [63]. It is estimated that Zn^{2+} concentrates in the postsynaptic density (PSD) via intracellular Zn^{2+} signaling after LTP induction, which can be linked with membrane mineralocorticoid and glucocorticoid receptor activation (**Fig. 5A**), and is able to influence the recruitment of ProSAP/Shank proteins to PSDs in a family member-specific manner during the course of synaptogenesis and structural plasticity [64,65]. Intracellular Zn^{2+} concentration might reach a few nanomolar for synaptic plasticity.

Total and phosphorylated CaMKII are increased in the hippocampal CA1 after CA1 LTP induction [66,67]. In contrast, chronic stress decreases basal levels of phosphorylated CaMKII and then attenuates LTP induction [68]. It is possible that Zn^{2+}

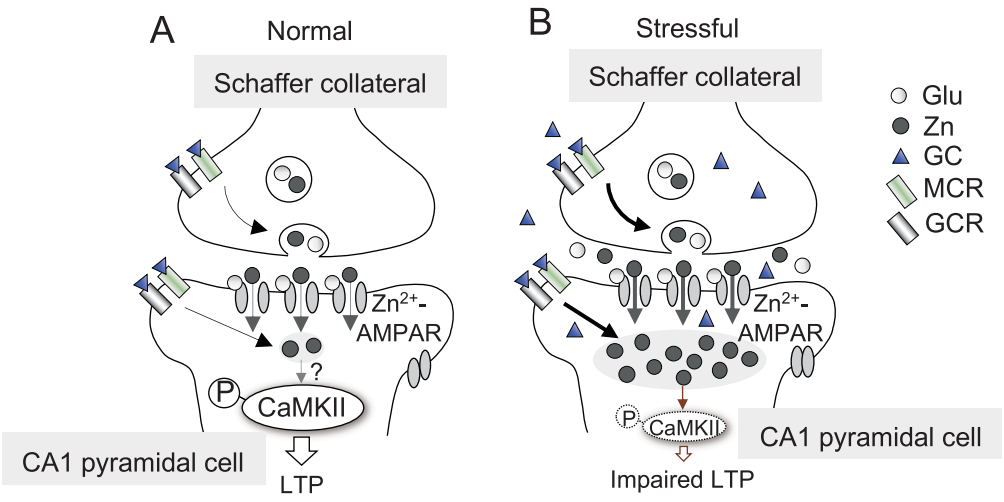

Figure 5. Schematic diagram on bidirectional synaptic Zn^{2+} dynamics via membrane corticosteroid receptor-mediated signaling in LTP induction

A The release of glutamate and Zn^{2+} is increased from Schaffer collateral by learning behavior and the increase is accelerated by glucocorticoid (GC): Presynaptic activation of membrane mineralocorticoid receptors (MCR) increases the release probability followed by the influx of extracellular Zn^{2+} through Zn^{2+}-permeable GluR2-lacking AMPA receptors (Zn^{2+}-AMPAR). Postsynaptic membrane corticosteroid receptors are also involved in the increase in intracellular Zn^{2+} in CA1 pyramidal cells followed by LTP (left).

B After exposure to stress, intracellular Zn^{2+} is excessively increased in CA1 pyramidal cells according to the bold arrows; presynaptic membrane mineralocorticoid receptors and postsynaptic membrane corticosteroid receptors, which are excessively activated, induce intracellular Zn^{2+} dysregulation followed by impaired LTP via the decrease in phosphorylated CaMKII (right). GCR, glucocorticoid receptor.

can directly modulate CaMKII activity for synaptic plasticity (**Fig. 5A**). At high micromolar concentrations (~400 μM), Zn^{2+} turns CaMKII into an increased mobility form on SDS-PAGE in vitro [69], while it is improbable in vivo. Intracellular Zn^{2+} concentration may reach low nanolmolar (~10 nM), an estimated concentration of extracellular Zn^{2+}, under the perfusion with $ZnCl_2$ and corticosterone prior to LTP induction, while the concentration may be neurotoxic [70].

Under stressful condition, on the other hand, corticosterone decreases the basal levels of phosphorylated CaMKII and the decreases are canceled by co-perfusion with CaEDTA, an extracellular Zn^{2+} chelator, or spironolactone, suggesting that the rapid influx of extracellular Zn^{2+} induced by corticosterone via presynaptic activation of membrane mineralocorticoid receptors into CA1 pyramidal cells leads to the decrease in the basal level of phosphorylated CaMKII (**Fig. 5B**).

Perspective

The basal concentration of intracellular Zn^{2+} is approximately 1000 times lower than that of intracellular Ca^{2+}, resulting in more critical neurotoxicity of Zn^{2+}. We need to understand the precise mechanism on regulation of intracellular Zn^{2+} homeostasis, i.e., the Zn^{2+}-buffering system under physiological and pathological conditions [71,72].

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