

# Positive Modulation of Long-term Potentiation at Hippocampal CA1 Synapses by Low Micromolar Concentrations of Zinc

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Hippocampal formation that plays an important role in learning, memory and recognition of novelty receives major input from the entorhinal cortex via the perforant pathway; the dentate granule cells project to the CA3 pyramidal cells via the mossy fibers. The CA3 pyramidal cells project to the CA1 pyramidal cells via the Schaffer collaterals. The three pathways are glutamatergic and terminals of them are stained by Timm's sulfide-silver method, which detects histochemically reactive zinc in the presynaptic vesicles. All giant boutons of mossy fibers contain zinc in the presynaptic vesicles, while approximately 45% of Schaffer collateral/commissural pathway is zinc-positive. Zinc may serve as an endogenous neuromodulator. However, the role of zinc in synaptic plasticity in the hippocampus remains to be clarified and the role of zinc, an endogenous N-methyl-D-aspartate (NMDA) receptor antagonist, in long-term potentiation (LTP) at hippocampal CA1 synapses is poorly understood.

In the present study, the effect of exogenous zinc and zinc chelators on CA1 LTP was examined by using hippocampal slices. CA1 LTP after tetanic stimulation (100 Hz, 1 s) was potentiated in the presence of 5  $\mu\text{M}$   $\text{ZnCl}_2$ , but not in the presence of 30  $\mu\text{M}$ . In varying the frequency (10-100 Hz, 1 s), zinc (5  $\mu\text{M}$ ) caused a significant shift of the frequency-response curve and lowered the threshold in LTP induction. The present study is the first to demonstrate that CA1 LTP is potentiated by low micromolar concentrations of zinc. Endogenous zinc is likely to reach low micromolar concentrations in the extracellular compartment in CA1 LTP induction. On the other hand, zinc has no effect on field excitatory postsynaptic potentials (fEPSPs) after tetanic stimulation in the presence of 2-amino-5-phosphonovalerate (APV), a NMDA receptor antagonist, in which LTP was abolished, indicating that NMDA receptor activation is necessary for the potentiation of CA1 LTP by zinc. The pretreatment with ZnAF-2DA, a membrane-permeable zinc chelator, which was used to block the increase in intracellular  $\text{Zn}^{2+}$ , inhibited LTP and also LTP potentiated by zinc. It is likely that  $\text{Zn}^{2+}$  taken up during LTP induction potentiates CA1 LTP via NMDA receptor activation.