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Modulation of long-term potentiation, a mechanism of memory in the hippocampus by zinc, an essential trace metal

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The long-term potentiation (LTP) has been reported to be a mechanism of memory and the mechanism has been studied in the hippocampus. The LTP at hippocampal mossy fiber synapses is expressed by presynaptic mechanisms leading to persistent enhancement of neurotransmitter release. The induction of mossy fiber LTP is critically dependent on the rise in presynaptic calcium induced by high-frequency (tetanic) stimulation, which activates the calcium-calmodulin-sensitive adenyl cyclase I. This enzyme exists abundantly in mossy fiber boutons. All giant boutons of mossy fibers contain zinc in the presynaptic vesicles. Zinc is released from mossy fiber boutons by tetanic stimulation (10-100 Hz), which induces the mossy fiber LTP. However, the role of zinc in mossy fiber LTP is poorly understood.

On the basis of the postulation that exogenous zinc enhances the action of zinc released from mossy fibers, mossy fiber LTP after tetanic stimulation (100 Hz, 1 s) was checked in the presence of exogenous zinc at low micromolar concentrations. Mossy fiber LTP was significantly attenuated in the presence of 5-30 μM $ZnCl_2$ and the amplitude of fEPSP 60 min after tetanic stimulation was decreased to almost the basal level. Mossy fiber LTP was also attenuated in the presence of 5 μM $ZnCl_2$ 5 min after tetanic stimulation. The present study is the first to demonstrate that low micromolar concentrations of zinc attenuate mossy fiber LTP. When mossy fiber LTP was induced in the presence of CaEDTA and ZnAF-2 DA, a membrane-impermeable and a membrane-permeable zinc chelator, respectively, extracellular and intracellular chelation of zinc enhanced a transient post-tetanic potentiation (PTP) without altering LTP. It is likely that zinc released by tetanic stimulation is immediately taken up into the mossy fibers and attenuates mossy fiber PTP. These results suggest that attenuation of PTP rather than LTP at mossy fiber synapses is a more physiological role for endogenous zinc. Targeting molecules of zinc in mossy fiber LTP seem to be different between during and after LTP induction because of the differential synaptic activity between them.