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BRAIN RESEARCH

Research Report

Zinc differentially acts on components of long-term potentiation at hippocampal CA1 synapses

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ARTICLE INFO

Article history:
Accepted 29 January 2010
Available online 6 February 2010

Keywords:
Zinc
Heavy metal
NMDA receptor
Antagonist
LTP
Hippocampal CA1

ABSTRACT

Long-term potentiation (LTP) at hippocampal CA1 synapses consists of N-methyl-D-aspartate (NMDA) receptor-dependent and NMDA receptor-independent forms. The action of divalent heavy metals, which are NMDA receptor antagonists, was examined focusing on the evidence that CA1 LTP induced by a 100-Hz tetanus for 1 s is abolished in the presence of 2-amino-5-phosphonovalerate (APV), a NMDA receptor antagonist. Only $ZnCl_2$ (5 μM) of heavy metals tested potentiated CA1 LTP. CA1 LTP induced by repeated 100-Hz tetanus (1 s, 6 times, 10 min interval), which reached a plateau in magnitude, was abolished in the presence of 50 μM APV. In this case, CA1 LTP after the first tetanus was potentiated in the presence of 5 μM $ZnCl_2$, whereas CA1 LTP after the last tetanus was not potentiated. These results indicate that the magnitude of NMDA receptor-dependent CA1 LTP can be positively shifted with 5 μM $ZnCl_2$ in the range of the maximum magnitude. CA1 LTP induced by a 200-Hz tetanus for 1 s was not potentiated in the presence of 5 μM $ZnCl_2$ and was partially inhibited in the presence of APV. Furthermore, CA1 LTP induced by a 200-Hz tetanus for 1 s in the presence of APV was not potentiated in the presence of 5 μM $ZnCl_2$, indicating that NMDA receptor-independent CA1 LTP is not potentiated with 5 μM $ZnCl_2$. The present study suggests that zinc differentially acts on CA1 LTP components.

1. Introduction

The hippocampus plays an important role in learning, memory and recognition of novelty. The most widely accepted mechanisms of memory formation are synaptic plasticity (Bliss and Lomo, 1973; Bliss and Collingridge, 1993). The mechanisms of plasticity at the Schaffer collateral/commissural synapses in the hippocampal CA1 region have been extensively studied in the brain (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999; Luscher et al., 2000). It is well established that long-term potentiation (LTP) at this pathway involves the synaptic activation of N-methyl-D-aspartate (NMDA) receptors (Nicoll and Malenka, 1999; Malenka and Bear, 2004). This activation plays a key role for the increase in postsynaptic Ca^{2+} concentration.

The activation of NMDA receptors, which are heterogeneous with multiple subclasses (Mayer and Armstrong, 2004), is blocked by divalent heavy metals such as zinc (IC_{50} for the low-affinity site, approximately 20 μM at −40 mV) and copper (IC_{50}, 0.27 μM) (Vlachova et al., 1996; Paoletti et al., 2009). Zinc and copper are trace metals that play essential roles in the brain function as well as brain development (Prohaska, 1987; Mathie et al., 2006). They are present at high levels in the brain, especially in the hippocampus (Hanig and Aprison, 1967;

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doi:10.1016/j.brainres.2010.01.085

Donaldson et al., 1974; Tarohda et al., 2004). A major portion of both metals serves as key components in many proteins and co-factors for the activity of many enzymes that are critical for brain function (Vallee and Falchuk, 1993). Both ions can also function as signaling molecules; zinc and copper, which are histochemically reactive as revealed by Timm's sulfide-silver staining method, are concentrated in synaptic vesicles, especially in some glutamatergic neurons (Frederickson, 1989).

It is estimated that the basal concentrations of zinc and copper in the brain extracellular space are <0.5 μM and 0.2–1.7 μM, respectively (Weiss et al., 2000; Mathie et al., 2006). Because they are co-released with neurotransmitters during neuronal excitation (Vogt et al., 2000; Hopt et al., 2003), it is possible that the extracellular concentrations of zinc and copper in the brain are changed spatially and temporally. However, the changes in their concentrations are poorly understood. The extracellular concentration of zinc in the hippocampus, which is stained at high densities by Timm's method, is estimated to be less than 1 μM, judging from the data on in vivo microdialysis experiments (Takeda et al., 2003). Although the extracellular concentration of zinc reached during LTP induction is a matter of debate, the data that zinc (5 μM) multi-functionally modulates LTP induction in the hippocampus imply that it is very low micromolar (Takeda et al., 2008, 2009a).

It is likely that other heavy metals such as manganese exist in the synaptic vesicles (Takeda 2003). Manganese can be released into the extracellular space by neuronal excitation (Takeda et al., 1998), although extracellular manganese concentration after tetanic stimulation is estimated to be much less than zinc and copper. Cadmium is believed to be unnecessary for brain function. When cadmium is transported

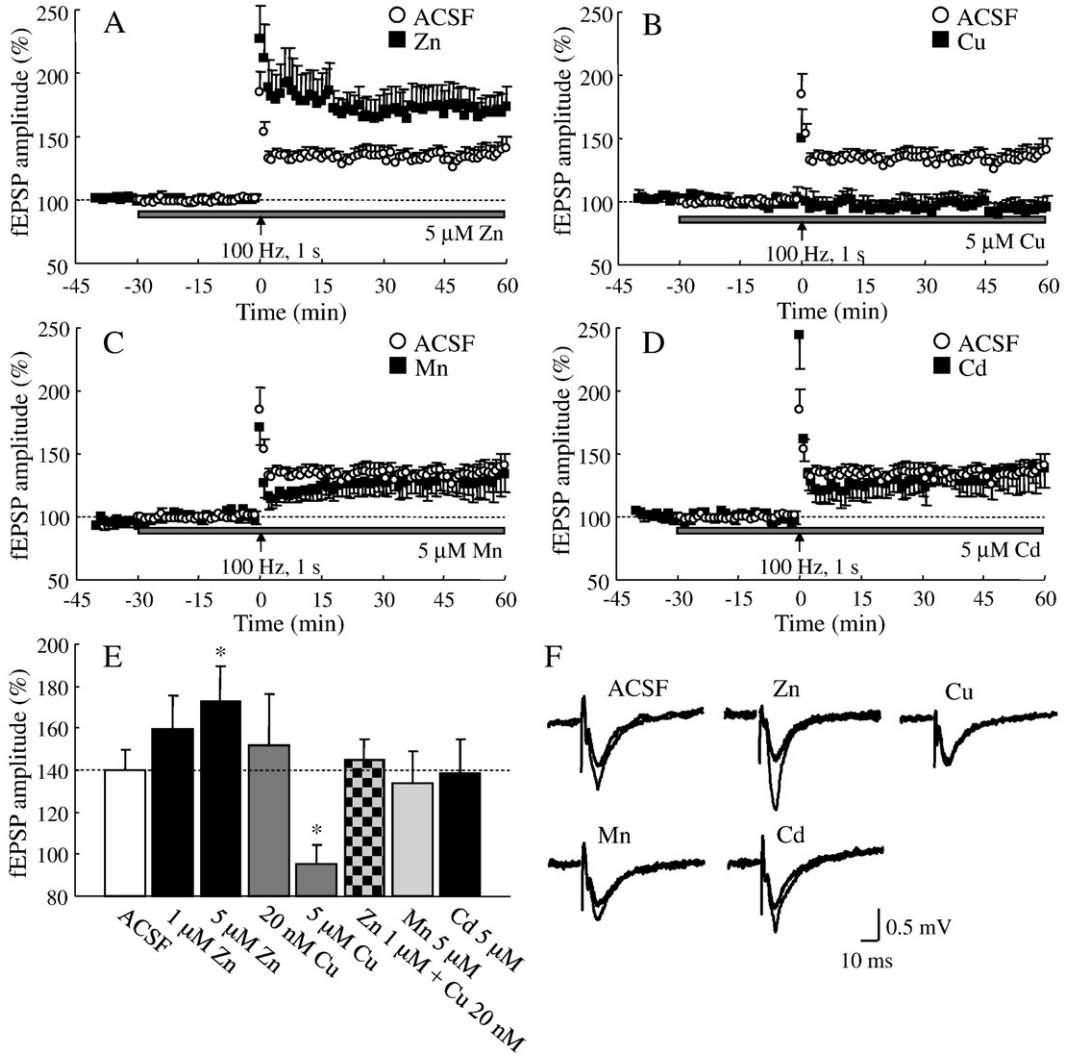

Fig. 1 – Effect of heavy metals on LTP. The hippocampal slices were perfused with ACSF for 30 min and then ACSF (10 slices), 1 μM $ZnCl_2$ in ACSF (7 slices), 5 μM $ZnCl_2$ in ACSF (8 slices, A), 20 nM $CuCl_2$ in ACSF (8 slices), 5 μM $CuCl_2$ in ACSF (6 slices, B), 1 μM $ZnCl_2$ + 20 nM $CuCl_2$ in ACSF (7 slices), 5 μM $MnCl_2$ in ACSF (6 slices, C) or 5 μM $CdCl_2$ in ACSF (6 slices, D) for 30 min, tetanized at 100 Hz for 1 s, and perfused for 60 min under the same condition. Shaded bars indicate the period of perfusion with heavy metals. Each point and line (the mean ± SEM) shows the mean of 60 s (A–D). Each bar and line (the mean ± SEM) shows fEPSPs 60 min after tetanic stimulation (E). *, $p < 0.05$, vs. ACSF. Representative fEPSP recordings at time −35 and 50 min are shown (F).