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Review

Activation of extrasynaptic NMDA receptors induces LTD in rat hippocampal CA1 neurons

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ABSTRACT

In the adult rat hippocampus, activation of N-methyl-D-aspartate receptors (NMDARs) is required for the induction of certain forms of synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD). Several studies have indicated the opposing role of synaptic NMDARS (S-NMDARs) *versus* extrasynaptic NMDARs (ES-NMDARs) in CREB-dependent gene regulation and neuronal survival/death. The contribution of ES-NMDARs in synaptic plasticity, however, remains unclear. Here we investigated the contribution of ES-NMDARs on LTD induction in CA1 neurons of rat hippocampal slices. ES-NMDARs were selectively activated by theta burst stimulation (TBS) after selective blockade of S-NMDARs with pairing of 5 Hz stimulation and MK-801, an irreversible use-dependent antagonist of NMDARs. Application of TBS in naïve slices evoked a transient potentiation. In contrast, the activation of ES-NMDARs evoked a robust LTD. These results suggest the involvement of ES-NMDARs in LTD induction.

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1. Introduction

Long-term depression (LTD), as well as long-term potentiation (LTP), is a persistent activity-dependent change in synaptic efficacy which is considered to be an important mechanism for information storage in the brain. In hippocampal CA1 pyramidal neurons, N-methyl-D-aspartate receptor (NMDAR)-mediated Ca^{2+} influx plays a key role in the induction of both LTP (Herron et al., 1986; Morris et al., 1986) and LTD (Dudek and Bear, 1992; Mulkey and Malenka, 1992). On the other hand, the distribution of NMDARs in different neuronal dendritic locations, including the synaptic area (S-NMDARs) and extrasynaptic sites (ES-NMDARs) have been found and extensively studied through blockage of S-NMDARs by using MK-801, an irreversible use-dependent antagonist of NMDARs, and low frequency stimulation during the last decade (Hessler et al., 1993; Weisskopf and Nicoll, 1995; Huang and Stevens, 1997; Chavis and Westbrook, 2001; Hardingham et al., 2002; Tovar and Westbrook, 2002; Harris and Pettit, 2008; Groc et al.,

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2009; Speed and Dobrunz, 2009; Wang et al., 2011). Studies have emphasized the distinct functions of S-NMDARs and ES-NMDARs. Although it has been reported that either activation of S- or ES-NMDARs was equally capable of excitotoxicity (Sattler et al., 2000; Wroge et al., 2012), the accumulating evidence suggests that ES-NMDARs play an important role in triggering excitotoxic neuronal damage. Hardingham et al. showed in cultured neurons that activation of ES-NMDARs triggers cAMP-responsive element-binding protein (CREB) shut-off and the cell death pathway, while calcium influx through S-NMDARs induces CREB activity-dependent brain derived neurotrophic factor (BDNF) gene expression. Studies of GeneChip DNA microarray analyses showed that activation of NMDARs regulates different transcriptional responses dependent on their synaptic or extrasynaptic location (Medina, 2007). In addition, studies have implied that ES-NMDARs contribute to the induction of LTD rather than LTP: bath application of NMDA, which causes simultaneous activation of both S- and ES-NMDARs, can either attenuate LTP (Kato et al., 1999) or promote LTD induction (Lee et al., 1998; Kamal et al., 1999; Massey et al., 2004; Yang et al., 2005; Kollen et al., 2008) at different concentrations. The role of ES-NMDARs in induction of LTD by synaptic released glutamate, however, has not yet been established directly. In the current study, we examined whether selective activation of ES-NMDARs induces LTD in juvenile rat hippocampal CA1 pyramidal neurons.

2. Materials and methods

2.1. Animals

All experiments were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the *Animal Care and Experimentation Committee of Shanghai Jiaotong University*. A total of 16 healthy juvenile male Sprague-Dawley rats were provided by the Shanghai Laboratory Animal Center, Chinese Academy Sciences (application no. SYXK (Hu) 2007-0005).

2.2. Slice preparation

Hippocampal slices were prepared as described previously (Yang et al., 2010) from male Sprague-Dawley rats (4–5 week old). After being deeply anaesthetized with halothane, the brain was removed immediately and placed in an ice-cold artificial cerebrospinal fluid (ACSF) solution containing the following (mM): 119 NaCl, 2.5 KCl, 1.3 $MgSO_4$, 2.5 $CaCl_2$, 1.0 NaH_2PO_4, 26.2 $NaHCO_3$, and 11 glucose. ACSF was continuously bubbled with 95%O_2 and 5%CO_2. Transverse hippocampal slices (400 μm) were cut at 0–4 °C using a vibratome tissue slicer (Vibratome, St. Louis, MO).

2.3. Electrophysiological recording

Field EPSP recordings were performed as described previously (Lin et al., 2011). In all experiments, picrotoxin (100 μM, GABAA receptor antagonist) (Sigma–Aldrich) was included in the ACSF, and a cut was made to separate the CA3 region from the CA1 region to avoid epileptiform activity. The amplitudes of the field excitatory postsynaptic potentials (EPSPs) were calculated as the initial slope of the EPSP. Similar to the previous reports, we applied a short train of LFS (5 Hz/16 s) in the presence of MK-801 (20 μM, pretreated for 20 min) (Tocris Cookson Bristol) to selectively block synaptic NMDARs (Chen and Diamond, 2002; Clark and Cull-Candy, 2002; Hardingham et al., 2002; Tovar and Westbrook, 2002; Lozovaya et al., 2004; Scimemi et al., 2004; Harris and Pettit, 2008). After complete wash out of MK-801 for 30 min (Harris and Pettit, 2007), ES-NMDARs were activated by stimulating the presynaptic inputs with a theta-burst (TBS): a total of 180 trains were delivered at 1 Hz, each train contained 5 pulses at 100 Hz LTD values were calculated as the ratio of averaged response 50–60 min after the induction and that 20 min before the induction. Paired-pulse stimulations were given with a 200 ms interstimulus interval (ISI) with equal strength. A Multiclamp 700B amplifier (Molecular Devices) was used in all experiments, and the data were stored on a personal computer and analyzed (filtered at 3 kHz, sampled at 10 kHz) using PClamp 10 (Molecular Devices).

2.4. Statistical analysis

Data were expressed as mean ± SEM. The statistical significance was determined using the One-way ANOVAs for three groups' comparison or ANOVAs for repeated measured data, or paired *t*-test for fiber volley and PPF measurements that tested before and after the induction of LTD. A *P* value <0.05 refers to the existing differences statistically.

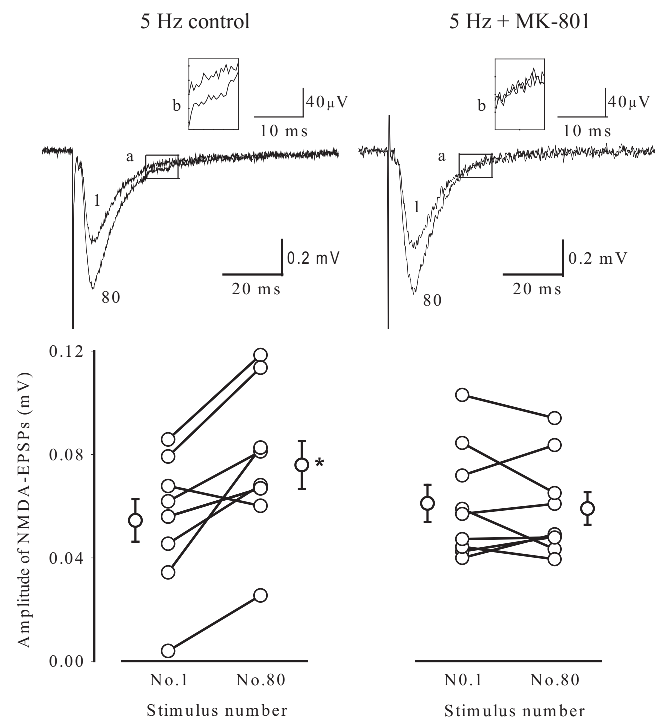

Fig. 1. Selective blockade of S-NMDARs during field potential recordings. Field EPSPs of pyramidal cells-mediated Schaffer collateral-commissural fiber activation were recorded. *Upper*, sample traces evoked by 5 Hz stimulation delivered for 16 s with or without MK-801. The amplitude of NMDA-EPSPs was calculated as the average amplitude of 30–32 ms from the onset of stimuli. Box 'a' is the part of the trace 25–35 ms from the onset of stimuli; while box 'b' is the enlarged box 'a'. *Lower*, the amplitude of NMDA-EPSPs evoked by the first stimulation was compared with that of the 80th stimulation in control slices (*left*) and MK-801 treated slices (*right*). Note that the amplitude of NMDA-EPSPs was increased in control but not in MK-801 treated slices.

3. Results

3.1. ES-NMDAR-evoked induction of LTD in hippocampal CA1 neurons

It has been demonstrated that ES-NMDARs could be activated selectively in cultured neurons by using MK-801 (Hardingham et al., 2002; Tovar and Westbrook, 2002). Since the short train of 5 Hz stimulation activates S- but few ES-NMDARs (Harris and Pettit, 2008), the co-application of MK-801 with the 5 Hz stimulation could irreversibly block S-NMDARs. Using acute slice preparations we firstly tested whether the combination of MK-801 with 5 Hz stimulation (for 16 s) could block synaptic NMDA-EPSPs measured by field potential recordings. Since the AMPA receptor-dependent component of field EPSPs almost decayed to the baseline level within 30 ms, the amplitude of the NMDAR-dependent component of field EPSPs (NMDA-EPSP) was measured as the mean amplitude of 30–32 ms after the onset of the field EPSP (Fig. 1). Our results showed that the amplitude of NMDA-EPSPs was not altered by applying the 5 Hz stimulation in the presence of MK-801 (Fig. 1, *right*, the first NMDA-EPSP, 40.6 ± 9.5 μV; the last (80th) NMDA-EPSP, 45.4 ± 14.5 μV; n = 6, paired t-test, p = 0.608), although applying 5 Hz stimulation alone in the absence of MK-801 enhanced it (Fig. 1, *left*, the first NMDA-EPSP, 53.6 ± 7.5 μV; the last (80th) NMDA-EPSP, 69.6 ± 9.6 μV; n = 9, paired t-test, p = 0.004). These results demonstrate that applying the extrasynaptic procedure blocks S-NMDARs. We washed out MK-801 with normal ACSF for 30 min, and then applied TBS to selectively activate ES-NMDARs that were not blocked by MK-801 (extrasynaptic procedure). Using this extrasynaptic procedure, we investigated whether activation

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