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Long-term depression in rat CA1-subicular synapses depends on the G-protein coupled mACh receptors

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Abstract

The subiculum, which is the primary target of CA1 pyramidal neurons and sending efferent fibres to many brain regions, serves as a hippocampal interface in the neural information processes between hippocampal formation and neocortex. Long-term depression (LTD) is extensively studied in the hippocampus, but not at the CA1-subicular synaptic transmission. Using whole-cell EPSC recordings in the brain slices of young rats, we demonstrated that the pairing protocols of low frequency stimulation (LFS) at 3 Hz and postsynaptic depolarization of −50 mV elicited a reliable LTD in the subiculum. The LTD did not cause the changes of the paired-pulse ratio of EPSC. Furthermore, it did not depend on either NMDA receptors or voltage-gated calcium channels (VGCCs). Bath application of the G-protein coupled muscarinic acetylcholine receptors (mAChRs) antagonists, atropine or scopolamine, blocked the LTD, suggesting that mAChRs are involved in the LTD. It was also completely blocked by either the Ca^{2+} chelator BAPTA or the G-protein inhibitor GDP-β-S in the intracellular solution. This type of LTD in the subiculum may play a particular role in the neural information processing between the hippocampus and neocortex.

Keywords: Long-term depression (LTD); Subiculum; Muscarinic receptor; G-protein; Calcium

1. Introduction

The hippocampus has a time-limited role in the permanent storage of memory (Reed and Squire, 1998; Manns et al., 2003), but eventually memories are stored in the neocortex and depend on the interactions between the hippocampus and its sub-adjacent areas or neocortex (Bontempi et al., 1999; Fries et al., 2003). The subiculum is the primary target of CA1 pyramidal neurons and projects to many brain regions. Growing evidence shows that the subiculum plays a crucial role in many functions such as memory processing and reinstatement of drug seeking (Gabrieli et al., 1997; Small et al., 2000; Vorel et al., 2001; Zeineh et al., 2003). It has been suggested that the subiculum may serve as a hippocampal interface in the neural information processing between hippocampal formation and neocortex (Amaral et al., 1991; O'Mara et al., 2001).

Activity-dependent forms of synaptic plasticity, such as LTD and long-term potentiation (LTP), are believed to underlie the mechanisms of learning and memory (Malenka, 1994; Bear and Abraham, 1996; Martin et al., 2000). The synaptic plasticity in the subiculum may involve in the transition from immediate memory to permanent memory. Previous studies have demonstrated that the CA1-subicular synapses express an NMDA receptor-independent form of LTP in mice slices (Kokaia, 2000), but LFS fails to induce

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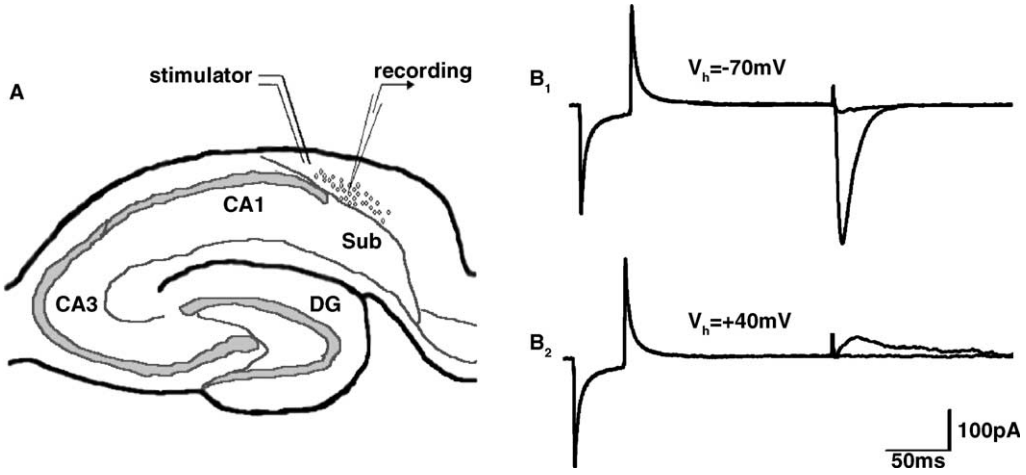

Fig. 1. Synaptic responses elicited by S.O. stimulation in the subiculum. (A) A patch-clamp recording pipette was placed in the proximal-dorsal subiculum in response to electrical stimulations of the CA1-subiculum border in stratum oriens of the coronary sectioned hippocampal slices. (B_1) The AMPA receptors-mediated EPSC recorded at a holding potential of −70 mV before and after CNQX (10 μM) bath application. (B_2) the NMDA receptors-mediated EPSC recorded at a holding potential of +40 mV before and after APV (50 μM) bath application. Each trace was the average of 5 responses.

LTD in anaesthetized adult rats (Anderson et al., 2000). To our knowledge, the subicular LTD and the underlying mechanisms remain unknown.

mAChRs are well known to be involved in learning and memory. The subiculum is a primary site of degeneration in Alzheimer's diseases (Hyman et al., 1984; Davies et al., 1988; Richards et al., 2003) that may involve cholinergic hypofunction (Levey, 1996; Pesavento et al., 2002). Among the converging afferents from CA1 area and other sources, the inputs from the medial septum and diagonal bands of Broca provide the subiculum with dense acetylcholine (Ach) (Lewis and Shute, 1967). LFS in the stratum oriens of the hippocampal CA1 area may trigger the release of acetylcholine (Araque et al., 2002; Brunner and Misgeld, 1994; Cole and Nicoll, 1983; Kaufer et al., 1998). Since the activation of mAChRs facilitates the induction of LTP in the hippocampus (Fujii et al., 2003; Natsume and Kometani, 1997; Shimoshige et al., 1997) and LTD in the perhinal cortex (Massey et al., 2001); while the inactivation of mAChRs blocks LTD induction in the perhinal cortex (Warburton et al., 2003), we have hypothesized that the mAChRs modulate the subicular LTD. In the present study, we successfully elicited the subicular LTD by using the pairing protocols of low frequency stimulation (LFS) at 3 Hz and postsynaptic depolarization of −50 mV in the brain slices of young rats and found that the LTD was the G-protein coupled mAChRs dependent.

2. Materials and methods

2.1. Slice preparation

The experimental protocols were approved by Department of Biology of The Chinese Academy of Sciences, PR China. The slice preparation and electrophysiological protocols were similar to those described previously (Sun et al., 2005; Wu et al., 1998). 14–21 days old Wistar rats (inbred strain, Animal House Center, Kunming General Hospital, Kunming) were decapitated and the brain was quickly removed and immersed in ice-cold artificial cerebral

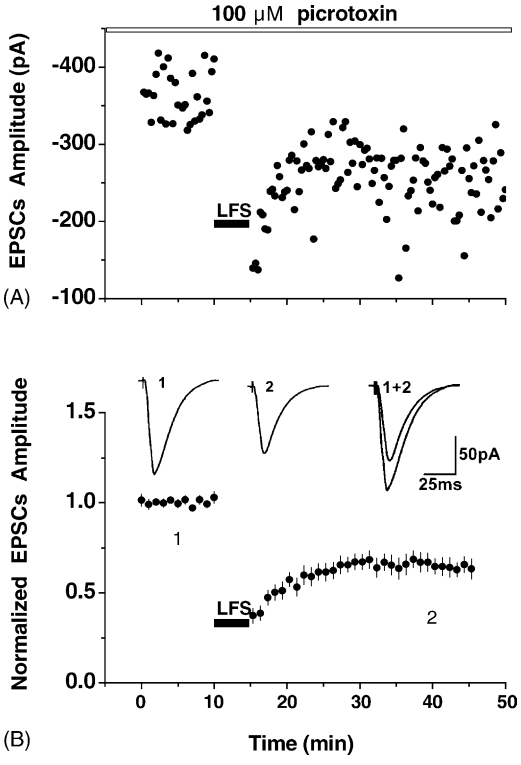

Fig. 2. Pairing protocol elicited long-term depression in the subiculum. (A) Pairing protocol, LFS at 3 Hz and holding the postsynaptic cell at −50 mV, induced long-term depression in the presence of picrotoxin (100 μM). (B) Summarized graph indicated that this type of LTD was reliable ($n = 12$, $p < 0.05$). (Insets) Representative traces of EPSC (average of 5 responses) at the time indicated by numbers.

spinal fluid (ACSF) in vibroslicer chamber. Hippocampal slices (400 μm thick) were cut coronally and then transferred into a submersion-type incubation chamber containing 300 ml ACSF heated to 35 ± 1 °C for 1 h recovery. During incubation, slices were placed on nylon mesh and both sides of the slices were perfused by oxygenated ACSF. The ACSF contained (in mM): NaCl 118, KCl 4.75, $NaHCO_3$ 25, KH_2PO_4 1.19, $CaCl_2$ 2.50, $MgSO_4$ 1.19, and D-glucose 11 and was continuously bubbled with the gas mixture of 95% O_2 and 5% CO_2. Then, the slice was gently transferred into a recording chamber, and held submerged between two nylon nets and maintained at room temperature (22–25 °C). The recording chamber consisted of a circular well of low volume (1–2 ml) and was perfused with ACSF at a flow rate of 4–5 ml/min. A buffer groove enchased with platinum wires was located between recording chamber and vacuum pipette to allow for the most rapid flow while minimizing cell movement.

2.2. Electrophysiology

The recording chamber was placed on the stage of an upright Nikon microscope (600-FN; Nikon, Japan) equipped with a 10× objective and a 10× ocular. Although the pyramidal neurons in the subiculum are divided into 'regular spiking' (RS) and 'bursting' neurons, there are no detectable differences in the characteristics of morphology, synaptic responses, and LTP induction (Kokaia, 2000; O'Mara et al., 2001). The microscope was used to identify the subicular neurons and then EPSC were recorded by using blind-patch approach in the cells in response to electrical stimulation of the stratum oriens. Cells were voltage clamped at −70 mV, and experiments were begun only after the access resistance had stabilized. The input and series resistance in post-synaptic pyramidal cells were monitored using voltage steps (−5 mV, 10 ms) at 30 s interval throughout experimental periods. Series resistance ranged from 10 to 30 MΩ. The data from experiments was accepted for analysis only in cases that the postsynaptic currents did not vary beyond 20% of the average values over the control periods and the input resistance (100–300 MΩ) remained constant throughout the experiment, and that the initial EPSC amplitude was larger than 100 pA. EPSC were judged as monosynaptic transmission by which the latencies of EPSC from the onset of stimulation were constant with different stimulus intensities in a cell and were usually 2–4 ms. Stimulating electrode was made by gluing together a pair of twisted Teflon-coated 90% platinum/10% iridium wires (50 μm inner diameter, 75 μm outer diameter), and patch pipette was pulled from borosilicate glass tubing (1.5 mm outer diameter, 0.84 mm

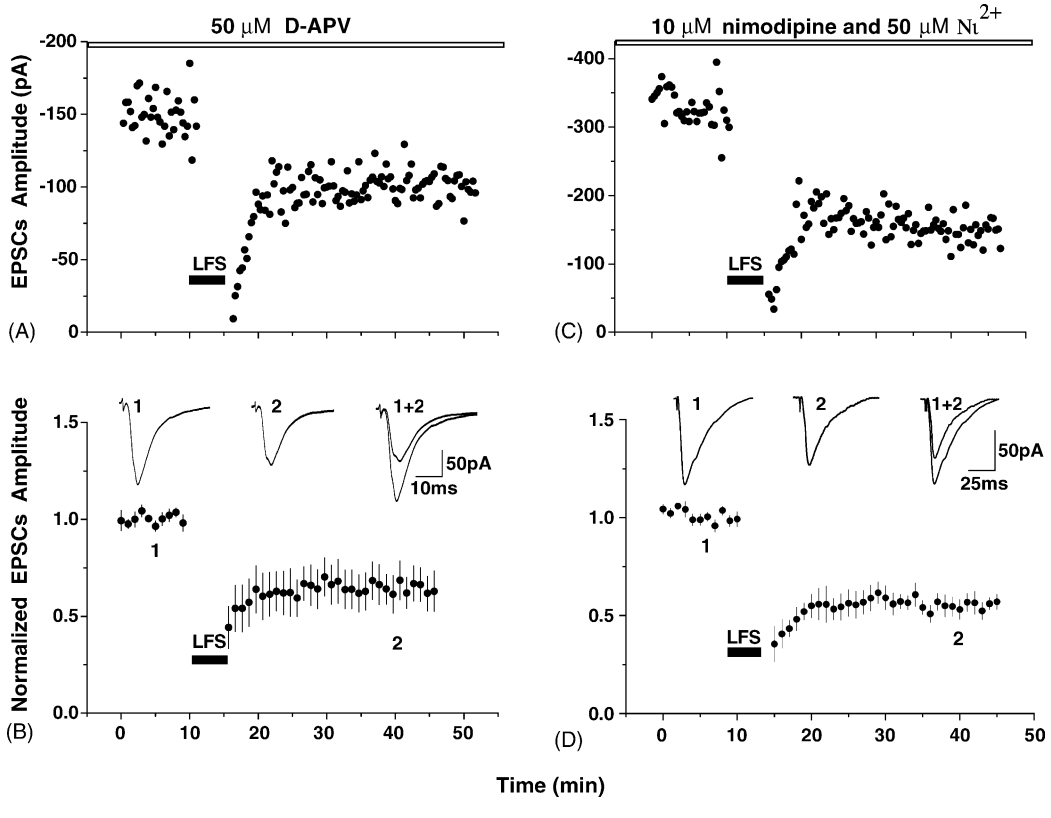

Fig. 3. Subicular LTD was not dependent on NMDA receptors and L- and T-type Ca^{2+} channels. (A) The NMDA receptor antagonist D-APV (50 μM) failed to block the pairing protocol-induced LTD. (B) The summarized graph indicated the LTD was not dependent on NMDA receptors ($n = 6$, $p < 0.05$). (C) The cocktail of the L-type Ca^{2+} channel antagonist nimodipine (10 μM) and T-type Ca^{2+} channel antagonist Ni^{2+} (50 μM) failed to block the pairing protocol-induced LTD. (D) The summarized graph indicated the LTD was not dependent on voltage-dependent Ca^{2+} channels ($n = 7$, $p < 0.05$). (Insets) Representative traces of EPSC (average of 5 responses) at the time indicated by numbers.

inner diameter) (World Precision Instruments Inc., USA) with a Brown-Flaming micropipette puller (P-87; Sutter Instruments Company, USA).

Whole-cell recording was obtained by using electrode (3–6 MΩ) containing (in mM): potassium gluconate 130, KCl 10, $CaCl_2$ 1, NaCl 6, HEPES 20, EGTA 10, Mg-ATP 3, Na-GTP 0.5, and QX-314 5, pH 7.2 (321 mOsm). Experiments with the rapid Ca^{2+} chelator BAPTA used a similar solution and protocol described previously (Xu et al., 2005; Crepel and Ben Ari, 1996). The intracellular solution contains (in mM): potassium gluconate 120, NaCl 6, HEPES 10, EGTA 10, Mg-ATP 3, Na-GTP 0.5, and BAPTA-Cs_4 10, pH 7.2. To block G-protein, Na-GTP was replaced by GDP-β-S (2 mM) in the regular intracellular solution. Electrical stimuli (0.1 ms in duration) were delivered at a frequency of 0.05 Hz to obtain baseline (10 min) that were approximately half-maximal response. Long-term depression (LTD) in whole cell recording was induced by low-frequency stimulation (LFS; 900 pulses, 3 Hz) with the same stimulation intensity used for baseline recordings combined with depolarizing the postsynaptic neuron to −50 mV (Sun et al., 2005). The whole-EPSC recordings were made in the presence of 100 μM picrotoxin to block the $GABA_A$ receptor-mediated currents. For most experiments, drugs (unless otherwise noted, Sigma, St. Louis, MO) were added directly to the ACSF. To block the L-and T-type Ca^{2+} channels, nimodipine and $NiCl_2$ (China National Medicine Group ShangHai Chemical Reagent Company) were added directly to the ACSF. Because the nimodipine and scopolamine are light sensitive, the experiments were performed in near-darkness conditions.

2.3. Data analysis and statistics

Recordings were made by using an Axopatch 200B amplifier; and signals were filtered at 5 kHz and digitised at 20 kHz and stored on computer. LTD was measured 20–30 min after LFS. All cells tested were included in the average, regardless of whether or not they exhibited robust LTD. All values are reported as mean ± S.E.M., n being the number of slice. Student's two-tailed paired t-test was used for statistical comparison. Significance level was set at $p < 0.05$.

3. Results

3.1. Subicular LTD was elicited by the pairing protocol of low frequency stimulation and postsynaptic depolarization

Stimulating the stratum oriens evoked monosynaptic transmissions of the whole-cell EPSC in the subicular neurons. It was depended on AMPA/kaniate receptors (Fig. 1B_1), because bath application of the AMPA/kaniate receptors antagonist CNQX (10 μM) completely blocked the EPSC (Fig. 1B_1, membrane potential was held at −70 mV). When the cell was depolarized to +40 mV, the same stimulation evoked EPSCs that were blocked by bath application of APV (50 μM) (Fig. 1B_2). Subicular neurons were voltage clamped at −70 mV and 10 min baseline EPSC was recorded. Then, low frequency stimulation (LFS; 3 Hz, 900 pulses) was delivered to the stratum oriens combined with depolarization of the postsynaptic neurons to −50 mV. This pairing protocol induced a robust long-term depression (LTD) in the brain slices of young rats ($n = 12$; 65.3 ± 4.6% of baseline EPSC amplitude 20 min after LFS, $p < 0.05$ compared with baseline; Fig. 2A and B).

3.2. Subicular LTD was not dependent on NMDA receptors and L- and T-type Ca^{2+} channels

NMDA receptors are necessary for LTD induction at many synapses (Mulkey and Malenka, 1992; Dudek and Bear, 1992; Kirkwood et al., 1993; Kirkwood and Bear, 1994; Wang and Gean, 1999; Thomas et al., 2000). We first examined whether the subicular LTD was dependent on NMDA receptors. The slices were perfused with the NMDA receptor antagonist D-APV (50 μM) for 30 min. The pairing protocol still induced a reliable LTD (Fig. 3A and B; 65.1 ± 8.8% of baseline; $n = 6$; $p < 0.05$). This result suggests that the subicular LTD is not dependent on NMDA receptors.

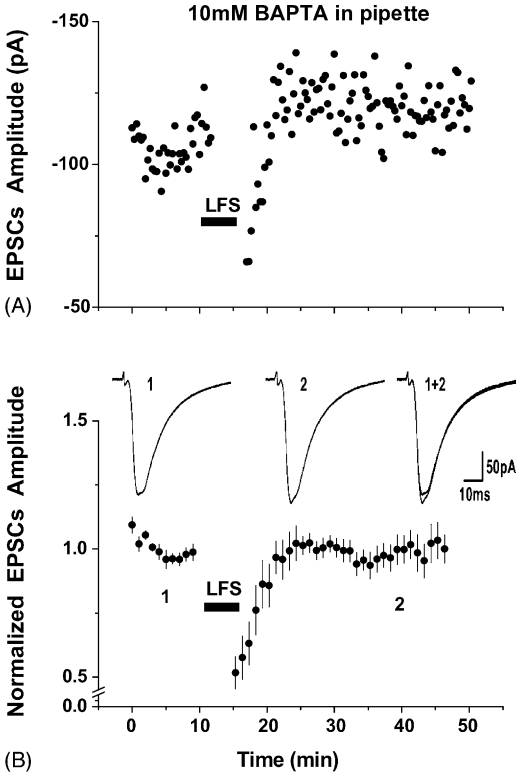

Fig. 4. Elevation of postsynaptic intracellular Ca^{2+} was required for the induction of subicular LTD. (A) The rapid Ca^{2+} chelator BAPTA (10 mM) in the recording pipette completely prevented the LTD induction. (B) The summarized graph indicated that this type of LTD was dependent on the elevation of intracellular Ca^{2+} ($n = 8$, $p > 0.05$). (Insets) Representative traces of EPSC (average of 5 responses) at the time indicated by numbers.

Since previous evidence has shown that LTD induction is depended on the L-type voltage-gated calcium channels (Bolshakov and Siegelbaum, 1994; Christie et al., 1997), or T-type Ca^{2+} channels (Oliet et al., 1997), we examined whether L- and T-type Ca^{2+} channels might involve in the induction of subicular LTD. The selective L-type Ca^{2+} channel antagonist nimodipine (10 μM) and T-type Ca^{2+} channel antagonist Ni^{2+}(50 μM) were perfused to bath solution. The same pairing protocol induced a robust LTD ($n = 7$; $46.1 \pm 2.2\%$ of baseline EPSC amplitude 20 min after LFS; $p < 0.05$ compared with baseline; Fig. 3C and D). The subicular LTD in nimodipine and Ni^{2+}-treated slices and APV-treated slices may be involved different mechanisms in both pre- and post-synaptic neurons. However, these results indicate that the activation of L- and T-type Ca^{2+} channels or NMDA receptors is not the necessary condition for the induction of subicular LTD.

3.3. Subicular LTD was dependent on the elevation of intracellular Ca^{2+} concentration

It is generally agreed that the rise of postsynaptic intracellular Ca^{2+} concentration plays critical roles in the induction of LTP/LTD. Thus, even through the subicular LTD was not dependent on NMDA receptors and voltage-gated calcium channels (VGCCs), chelating the intracellular Ca^{2+} may be able to block this type of LTD. We loaded the subicular neurons with rapid Ca^{2+} chelator BAPTA (10 mM) in the intracellular solution for 30 min before LTD induction. As expected, this regimen blocked the induction of subicular LTD ($n = 8$; $97.9 \pm 5.0\%$ of baseline EPSC amplitude 20 min after LFS; $p > 0.05$ compared to baseline; Fig. 4A and B). This was not due to the longer time after rupture the membrane because the pairing protocol induced a robust LTD after 30 min baseline recordings ($n = 6$; $54.8 \pm 3.4\%$ of baseline EPSC amplitude $p < 0.05$ compared with baseline, supplemental Fig. 1).

3.4. The mACh receptors antagonists blocked the subicular LTD induction

Since mACh receptors play important roles in the functions of subiculum (Levey, 1996; Pesavento et al., 2002), we examined whether the mACh antagonists influenced the LTD. Scopolamine (30 μM), a broad spectrum antagonist of mACh receptors, was bath applied after a 10 min stable baseline recording. Scopolamine did not affect basal synaptic transmission, but it blocked LTD induction ($n = 12$; $93.7 \pm 9.3\%$ of baseline EPSC amplitude; $p > 0.05$ compared to baseline; Fig. 5C and D).

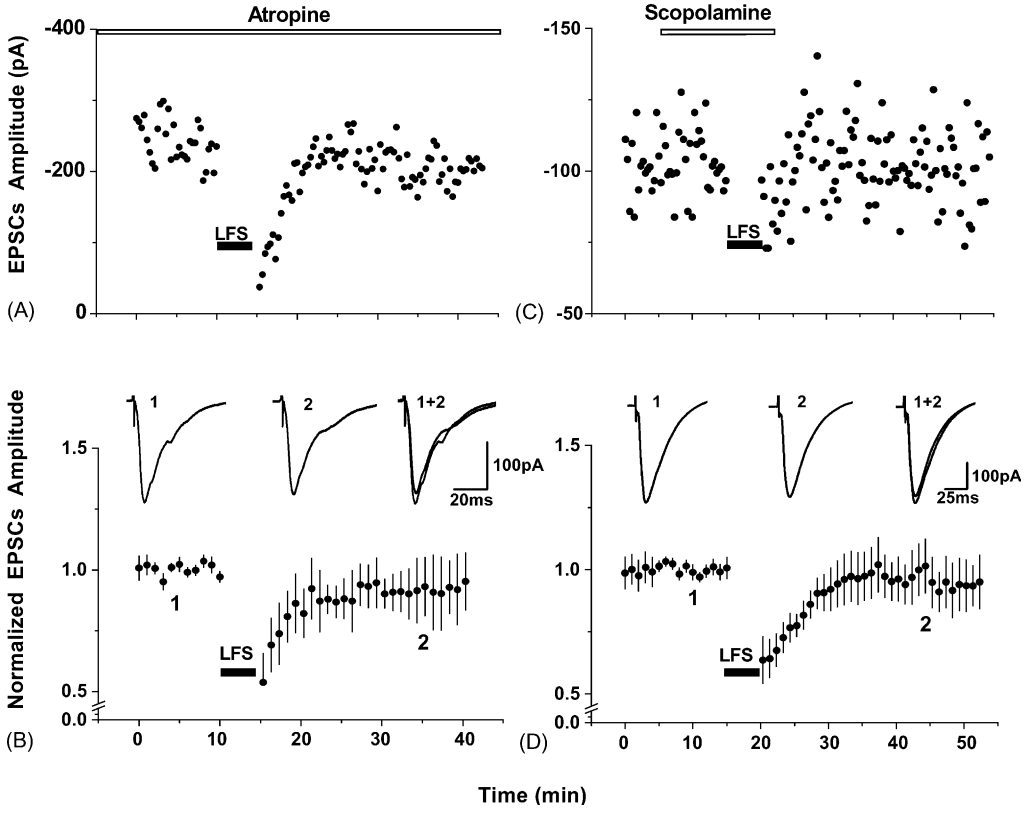

Fig. 5. The mAChRs antagonists blocked the induction of subicular LTD. (A) Bath application of the mAChRs antagonist atropine (50 μM) blocked the pairing protocol-induced LTD. (B) The summarized graph indicated that this type of LTD may be dependent on the mAChRs ($n = 9$, $p > 0.05$ compared with baseline). (C) The mAChRs antagonist scopolamine (30 μM) had no effect on basal synaptic transmission, but it blocked the LTD induction. (D) The summarized graph indicated that this type of LTD may be dependent on the mAChRs ($n = 12$, $p > 0.05$ compared with baseline). (Insets) Representative traces of EPSC (average of 5 responses) at the time indicated by numbers.

Similarly, bath application of the mACh antagonist atropine (50 μM) largely impaired the LTD ($n = 9$; 90.3 ± 10.2% of baseline EPSC amplitude; $p > 0.05$ compared with baseline; Fig. 5A and B). This evidence provided a possibility that the subicular LTD might depend on the mACh receptors.

3.5. Subicular LTD was dependent on postsynaptic G-protein activation

Since the activation of mACh will trigger the G-protein signaling pathway, we examined whether postsynaptic G-protein was necessary for the subicular LTD. We replaced GTP in the intracellular solution with GDP-β-S (2 mM), which was a non-hydrolyzable GTP-analog. The pairing protocol 20 min after rupture the membrane failed to induce LTD ($n = 10$; 101.2 ± 5.1% of baseline EPSC amplitude; $p > 0.05$ compared with baseline; Fig. 6A and B). These results suggested that the G-protein coupled-mACh receptors played a significant role in the induction of subicular LTD.

3.6. Subicular LTD did not alter the paired-pulse facilitation

The paired-pulse EPSC ratios may provide an measurement of the changes in presynaptic release probability (Manabe et al., 1993). Although the subicular neurons exhibited the paired-pulse facilitation with an interstimulus interval of 50 ms during the baseline period, we did not find any changes in the paired-pulse ratio ($n = 10$; 107 ± 6.3% of baseline ratios; $p > 0.05$ compared to baseline; Fig. 7, p2/p1,) 20 min after LTD induction ($n = 10$; 70.4 ± 6.4% of baseline EPSC amplitude; $p < 0.05$ compared to baseline, Fig. 7, p1).

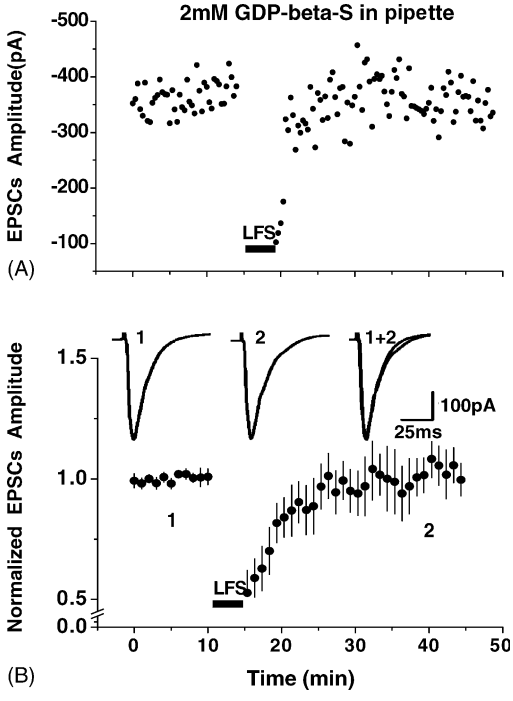

Fig. 6. G-protein was required for the subicular LTD. (A) The non-hydrolyzable GTP-analog GDP-β-S (2 mM) was loaded in the recording pipette. The regimen completely prevented the pairing protocol-induced LTD. (B) The summarized graph indicated that the LTD was dependent on the activation of G-protein ($n = 10$, $p > 0.05$ compared with baseline). (Insets) Representative traces of EPSC (average of 5 responses) at the time indicated by numbers.

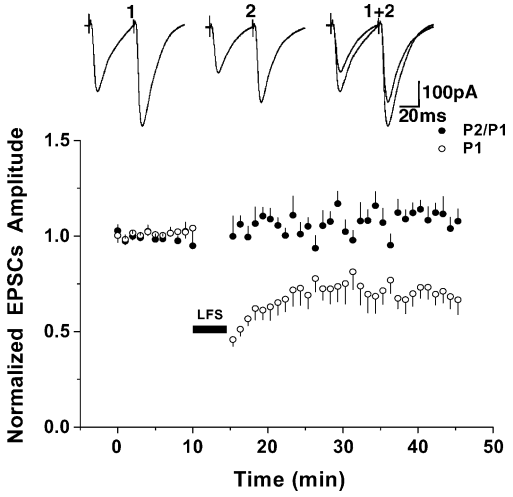

Fig. 7. The paired pulse ratios remained unchanged after the subicular LTD induction The EPSCs were evoked by paired-pulse stimulation (50 ms inter-stimulus interval). The normalized amplitude of the first EPSC (P1, open circle) and paired-pulse ratio (P2/P1, filled circle) was plotted against time. The paired pulse ratio did not change significantly after the LTD induction. (Insets) Representative traces of EPSC (average of 5 responses) at the time indicated by numbers.

4. Discussion

In the present study we demonstrated that the subicular LTD was not dependent on NMDA receptors, L- and T-type Ca^{2+} channels, but it depended on the rise of intracellular Ca^{2+} and the G-protein coupled mAChRs. Since the subiculum receives the major afferents from the CA1 area of the hippocampus and sends out efferents to many brain regions, the LTD may play important roles in the neural information processing.

4.1. The property of subicular LTD

Previous study showed that, in the CA1-subicular excitatory synapses, high frequency stimulation induced NMDA receptor-independent form of LTP (Kokaia, 2000), but LFS failed to induce LTD in the anaesthetized adult rats (Anderson et al., 2000). In the present study, we used the pairing protocol to induce a robust LTD in the brain slice of young rats. The discrepancy may be due to the difference in experimental preparations in vivo and in vitro. However, other factors cannot be excluded. For example, previous study in the CA1 area has shown that LTD is reliably induced in young but not adult rats (Kemp et al., 2000).

It is not known why the subicular LTD induction needs the Ca^{2+} sources via G-protein coupled-mACh receptors but not

NMDA receptors or the voltage gated Ca^{2+} channels. Maybe, the G-protein coupled-mACh receptors are sufficient to supply the rise of intracellular Ca^{2+} in the subicular LTD induction so that it dose not need the additional sources, consistent with the previous findings in perhinal cortex (Anagnostaras et al., 2003; Massey et al., 2001). The mAChRs are the G-protein-coupled receptors and can be divided into five subtypes (M1-M5): M1, M3 and M5 coupled to the phospholipase C pathway and hence inositoltrisphosphate (IP3) and diacylglycerol (DAG); M2 and M4 receptors negatively coupled to adenylyl cyclase. It is possible that the activation of M1, 3 and 5 receptors contributes to the subicular LTD, because IP3 and DAG is able to trigger calcium release from intracellular stores and activates protein kinase C, respectively (Bashir, 2003). Thus, it is reasonable that the subicular LTD is modulated by the mAChRs and abolished by GDP-β-S, a blocker of G-protein coupled signal transduction.

4.2. Physiological significance of LTD in the subiculum

The subiculum receives the major output of the hippocampal formation and projects to many cortical and subcortical regions, including the prefrontal cortex, septal complex, perirhinal cortex, and nucleus accumbens (O'Mara et al., 2001). The subicular LTD described here may modulate the outgoing information, primarily from the distal part of CA1 area to the subcortical regions (Cao et al., 2004). The significance of subicular LTD may be interpreted by a complex network model of the hippocampal functions in learning and memory, in which the cholinergic signal functions as a switch between inflow (encoding or write-in) and outflow (recall or write-out) of the hippocampus (Hasselmo, 1999). The present finding that the subicular LTD is dependent on the G-protein coupled mAChRs is consistent with a recent report that the M_1 acetylcholine receptor is involved in memory processes through the interaction between cortex and hippocampus (Anagnostaras et al., 2003). In the subiculum, the NMDA-independent LTP in the previous findings (Kokaia, 2000) and the G-protein coupled mAChRs-dependent LTD in the present findings may endow the hippocampus to integrate neural information with many brain regions (Douglas, 1967).

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neures.2005.04.002.

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