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Inhibition of associative long-term depression by activation of β-adrenergic receptors in rat hippocampal CA1 synapses

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Abstract

The aim of this study was to investigate the role of *β*-adrenergic receptors in modulating associative long-term depression (LTD) at CA1 synapses in rat hippocampal slices. Standard extracellular electrophysiological techniques were employed to record field excitatory post-synaptic potential (fEPSP) activity and to induce associative LTD. Two independent Schaffer collateral pathways were elicited in hippocampal CA1 areas. In one (weak) pathway, the stimulating intensity was adjusted to elicit small fEPSP activity (20–30% of the maximum response). In contrast, 80–90% of the maximum response was evoked in the other (strong) pathway. Associative LTD of weak pathway could be induced by paired stimulation of weak and the strong pathways, repeated 100 times at 0.167 Hz. The associative LTD of weak pathway was NMDA receptor- and phophatase 2B dependent, because bath application of 50 μM D, L-AP5 or 10 μM cypermethrin blocked its induction. Bath application of 1 μM isoproterenol inhibited associative LTD, and this effect was blocked by timolol, suggesting the involvement of *β*-adrenergic receptors. The inhibitory effect of *β*-adrenergic receptors on LTD induction was blocked in slices pretreated with inhibitors of protein kinase A and mitogen-activated protein kinase, suggesting that these signal cascades are downstream effectors following activation of *β*-adrenergic receptors. Nevertheless, bath application of timolol or cypermethrin alone did not have significant effect on associative LTD induction, suggesting neither endogenous function of *β*-adrenergic receptor nor endogenous PKA activity does have a role in associative LTD induction.

Introduction

Long-term potentiation (LTP) and depression (LTD) are use-dependent changes in synaptic efficacy, and are believed to play an important role in many complex mechanisms of neuronal networks, including learning and memory [1, 2]. Homosynaptic LTD was first described as the reverse process of LTP and was referred to as depotentiation, because the potentiation of synaptic efficacy at given synapses by tetanic stimulation is depressed to the resting condition following additional prolonged low-frequency stimulation [3, 4]. Sequential reports suggested that at normal conditions, synaptic strength could also be long-term depressed following low-frequency stimulation [5, 6]. Induction of homosynaptic LTD by low-frequency stimulation is NMDA receptor-dependent, and it is now generally believed that dephosphorylation of functional AMPA receptors by phosphatase 2B (calcineurin) after activation of NMDA receptors is involved in the expression of LTD [7].

Recently, it was demonstrated that associative LTD could also be induced if stimulation of the pre-synaptic fibers occurs simultaneously in conjunction with post-synaptic spiking preceded by

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20–100 ms at many CNS synapses [8, 9]. Furthermore, reversing the sequence of pre- and post-synaptic activities has been reported to result in potentiation of synaptic strength. These associatively induced LTP and LTD are collectively referred to as spike-timing-dependent plasticity [10, 11]. The phenomenon of STDP has been described in many CNS synapses and its significant role in experience- or use-dependent remodeling of neuronal circuits has been explored in many sensory systems [9, 12], the molecular mechanisms underlying its induction and expression however require further study. In a recent study, we reported that at hippocampal CA1 synapses, associative LTP could be induced in a weak Schaffer collateral input after it was paired with a separate strong input, with the weak preceding the strong input by 3–10 ms [13]. Induction of this form of associative LTP was NMDA receptor-dependent and involved activation of protein kinase A (PKA)-mitogen-activated protein (MAPK)/ERK kinase, and was modulated by β-adrenergic receptors. In this study, we tested if a pairing protocol similar to that used in our previous report but having a reversed sequence of weak–strong input stimuli could induce associative LTD and investigated the possible role of β-adrenergic receptors.

Materials and methods

The use of animals in this study was in accordance with the guidelines of the local ethical committee for animal research. Consistence with our previous studies, Sprague–Dawley rats aged 25–40 days was used [13]. Animals were anesthetized with halothane and decapitated. The brains were quickly removed and placed in ice-cold artificial cerebral spinal fluid (ACSF) containing (mM): 119 NaCl, 2.5 KCl, 26.2 $NaHCO_3$, 1 NaH_2PO_4, 1.3 $MgSO_4$, 2.5 $CaCl_2$, and 11 glucose (the pH were adjusted to 7.4 by gassing with 5% CO_2/95% O_2). Transverse hippocampal slices (450 μm thick) were cut with a vibrating tissue slicer (Campden Instruments, Loughborough, UK), and transferred to an interface-type holding chamber at room temperature (25–27 °C). For extracellular field potential recording, slices were transferred to an immersion-type recording chamber, perfused with ACSF containing 0.1 mM picrotoxin. The perfusion rate was controlled at 2 ml/min. To prevent epileptiform discharge of pyramidal neurons, a surgical cut was made at the border between CA1 and CA3 areas. A glass pipette filled with 3 M NaCl was positioned in the stratum radiatum of the CAl area to record field excitatory post-synaptic potentials (fEPSPs). On each side of recording pipette, two bipolar stainless steel electrodes (FHC, Bowdoinham, ME) were placed at the stratum radiatum near the recording pipette to elicit two separate Schaffer collateral branches. In one pathway, the intensity of stimulation was adjusted to elicit fEPSP activity that was about 20–30% of that at which population spikes after fEPSP began to appear. This pathway will be referred to as the ''weak'' pathway. For the other pathway, the stimulating intensity was adjusted so 80–90% of the maximal response elicited. This pathway is referred as the strong pathway hereafter. A period of stable baseline fEPSP activity of the weak pathway was elicited every 30 s for at least 10 min. Associative LTD of the weak pathway was then induced by pairing the weak pathway with the strong pathway for 10 min at 6-s intervals. During the pairing protocol, the delivery of strong stimulation preceded weak stimulation by 40–150 ms. Baseline fEPSP activity of the weak pathway was again elicited every 30 s for an additional 30 min. Different durations of pairing protocol were employed in the same animal to comparison the induction of associative LTD. All signals were filtered at 2 kHz by a low-pass Bessel filter provided by the amplifier (Axopatch-1D) and digitized at 5 kHz using a CED micro 1401 interface running Signal software provided by CED (Cambridge Electronic Design, Cambridge, UK). All drugs were bath applied. They were purchased from Sigma (St. Louis, MO), except for APV, timolol, KT5720, PD98059, and U0126 that were from Tocris-Cookson (Bristol, UK). The initial slopes of the fEPSP were measured for data analysis. Synaptic responses were normalized to average values measured over a baseline period. The average size of the slope of fEPSPs, recorded at between 25 and 30 min after the pairing protocol, was used for statistical comparisons. All data are presented as the mean ± standard error, and were statistically compared by non-parametric Mann–Whitney test. The criterion for significance was $p < 0.05$.

Results

Associative LTD induced at hippocampal CA1 synapses

After a 10-min period of baseline recording, associative LTD of the weak pathway could be induced by pairing it with strong stimulation, with the latter preceding the former by 40 ms during the pairing protocol (LTD = 69.8% ± 5.3%, $n = 6$, $p < 0.01$) (Figure 1A). The pairing protocol in which the strong pathway precedes the weak pathway was maintained for all subsequent experiments shown. LTD of the weak pathway could also be induced by the pairing protocol with the pairing interval increased up to 100 ms (70.5% ± 5.7%, $n = 6$, $p < 0.01$) (Figure 1B). When the pairing intervals were increased to 150 ms, no LTD was found (98.1% ± 7.1%, $n = 6$, $p = 0.2$) (Figure 1C). Figure 1D summarizes all results showing the relationship between the pairing protocol and corresponding changes in synaptic efficacy. As can be seen, associative LTD could be successfully induced at the weak pathway if the interval between the strong and weak pathways was less than 100 ms during pairing.

Associative LTD induced by the present pairing protocols are heterosynaptic and NMDA receptor/calcineurine but not endogenous β-adrenergic receptor/PKA-dependent

In order to avoid the heterosynaptic facilitation, we further test the independence of inputs activated by two stimulatory electrodes. As shown in Figure 2A, fEPSPs evoked by weak stimulus shows no significance from that evoked in condition, when the weak stimulus was preceded by strong stimulus by 50 ms; this result suggests the absence of heterosynaptic facilitation, confirming that the two inputs evoked in this study are

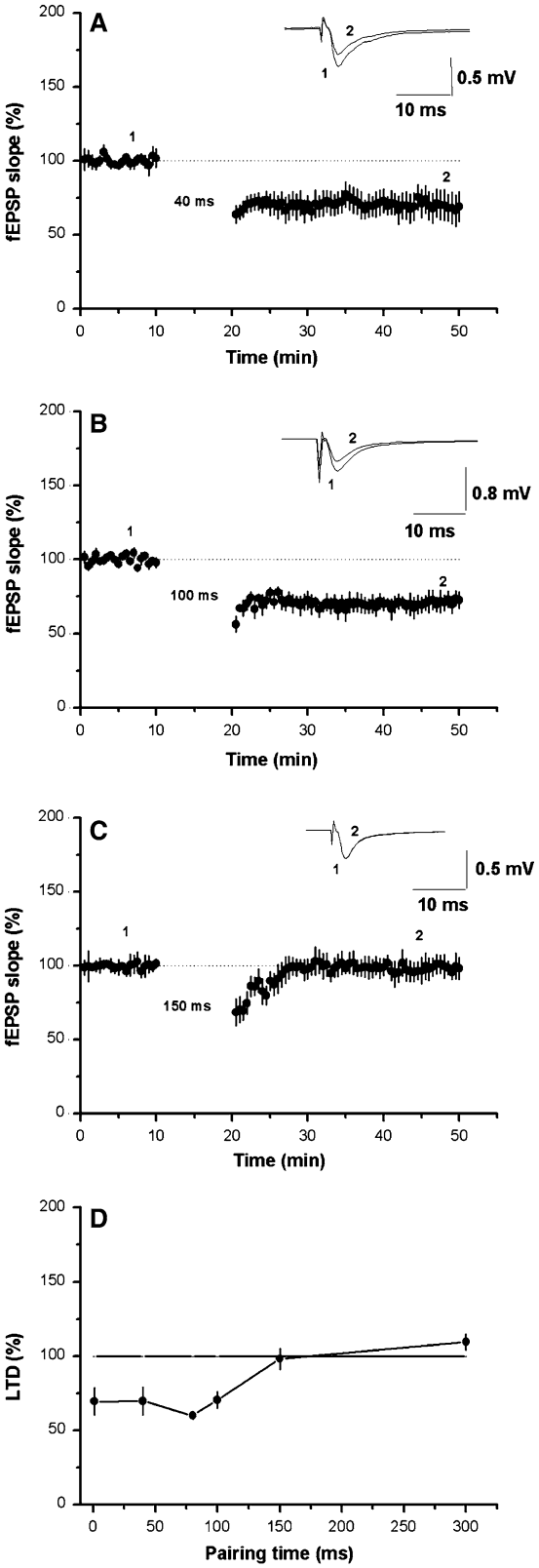

Figure 1. Associative LTD induced at CA1 synapses. (A) ▶ Associative LTD was induced at the weak pathway with the present pairing protocol. (B) LTD could also be induced by the pairing protocol with a 100-ms delay. (C) No LTD could be induced when the delay interval was increased to 150 ms. Inserts in (A), (B), and (C) are superimpositions of data tracts averaged over 10 sweeps recorded immediately before and 25 min after the pairing protocol. (D) Summarized results show relationship between change of synaptic efficacy and different delay interval during pairing.

independent. Because the strong input elicited about 80% of the maximum synaptic response, it may have overlapped some fibers that were also recruited by weak stimulation. Therefore, LTD induced in Figure 1 could be homosynaptic rather than associative. This possibility was ruled out based on the following observations. First, we found no significant change in synaptic efficacy caused by the pairing protocol during which the strong (Figure 2A) (LTD = 98.4% ± 4.7% of baseline, $n = 6$; $p = 0.5$) or weak stimulation (Figure 2B) (LTD = 101.1% ± 7.9% of baseline,

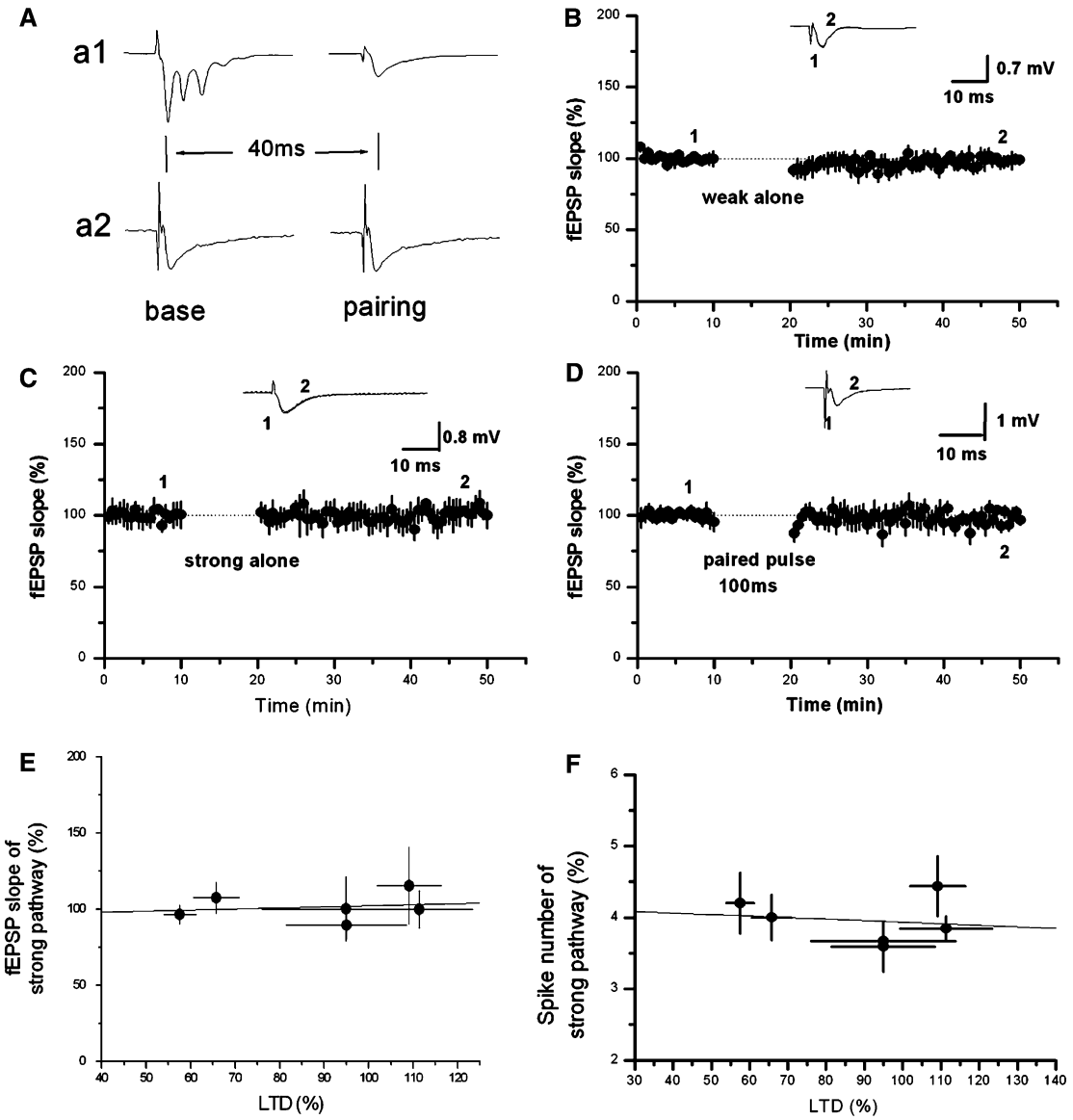

Figure 2. Associative LTD induced by the present pairing protocol is not homosynaptic. (A) The delay interval between the strong and weak pathways was 40 ms, with the strong preceding the weak one during pairing (a1). There were not significant change in waveform in the weak pathway by using 50 ms interval paired pulse suggest that the absence of heterosynaptic facilitation between the two inputs (a2). (B & C) No LTD could be induced when only weak (B) or strong (C) pathways were stimulated during the pairing protocols. (D) Paired pulses (interval = 100 ms) delivered to the weak pathway resulting in no LTD. Inserts are superimpositions of raw data tracts averaged over 10 sweeps recorded immediately before and 25 min after the pairing protocol. (E & F) There was neither relationship between the magnitude of LTD and the fEPSP slope of the strong pathway (E) nor between the magnitude of LTD and the number of spikes of the strong pathway (F).

$n = 6$; $p = 0.7$) was turned off. Second, 100 paired pulses (interval = 100 ms) delivered to the weak pathway repeated at 6-s intervals resulted in no LTD (Figure 2C) (LTD = 97.4% ± 4.7% of baseline, $n = 6$; $p = 0.7$). Third, we found neither relationship between the magnitude of LTD and the fEPSP slope of the strong pathway (Figure 2D) ($r = 0.17$; $p = 0.73$) nor between the magnitude of LTD and the number of spikes of the strong pathway (Figure 2E) ($r = -0.15$; $p = 0.78$).

Because paired pulses of 100-ms intervals delivered to the weak pathway resulted in no LTD and could reliably induce associative LTD, this protocol was adopted in the following experiments. Induction of associative LTD was completely blocked by bath application of 50 μM D, L-AP5 (101.5% ± 3.8%, $n = 7$; $p = 0.7$) (Figure 3A), suggesting that associative LTD induced in the present study was NMDA receptor dependent. In slices with 10 μM cypermethrine in ACSF, no LTD was observed (98.5% ± 5.2%, $n = 6$; $p = 0.8$) (Figure 3B). Furthermore, LTD could be induced either in 50 μM timolol (69.8% ± 3.9%, $n = 6$, $p < 0.01$) (Figure 4A) or 10 μM H89 treated slices (71.2% ± 4.3%, $n = 6$, $p < 0.01$) (Figure 4B). The above results suggest that associative LTD induced herein was NMDA receptor- and phosphatase 2B-dependent, and endogenous activity of β-adrenergic receptor and PKA play no role in associative LTD induction.

Inhibition of associative LTD by activation of β-adrenergic receptors is PKA-MAPK/ERK pathway-dependent

We next investigated the effect of β-adrenergic receptors on associative LTD, and the possible

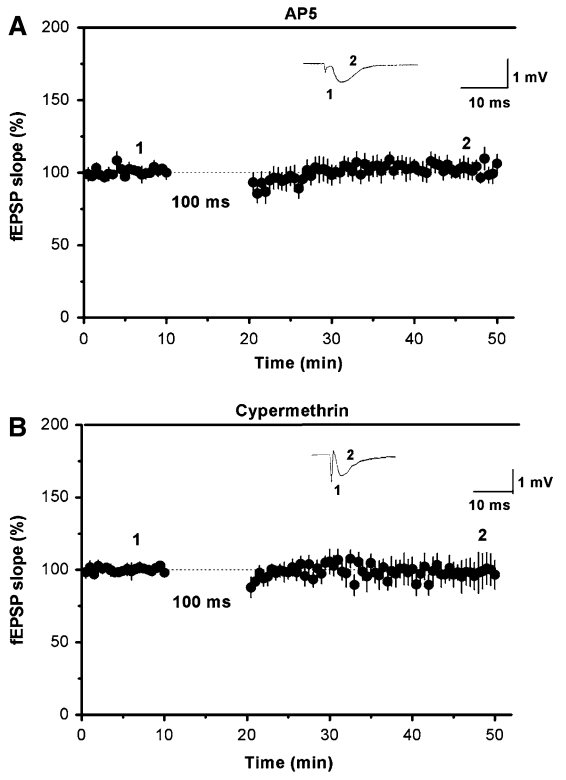

Figure 3. Associative LTD induced by the present pairing protocols was NMDA- receptor/calcineurine-dependent. (A) LTD was blocked by application of 50 μM D, L-AP5 in the ACSF to block NMDA receptors. (B) LTD was also blocked by the calcineurine blocker, cypermethrin. Inserts are superimpositions of raw data tracts averaged over 10 sweeps recorded immediately before and 25 min after the pairing protocol.

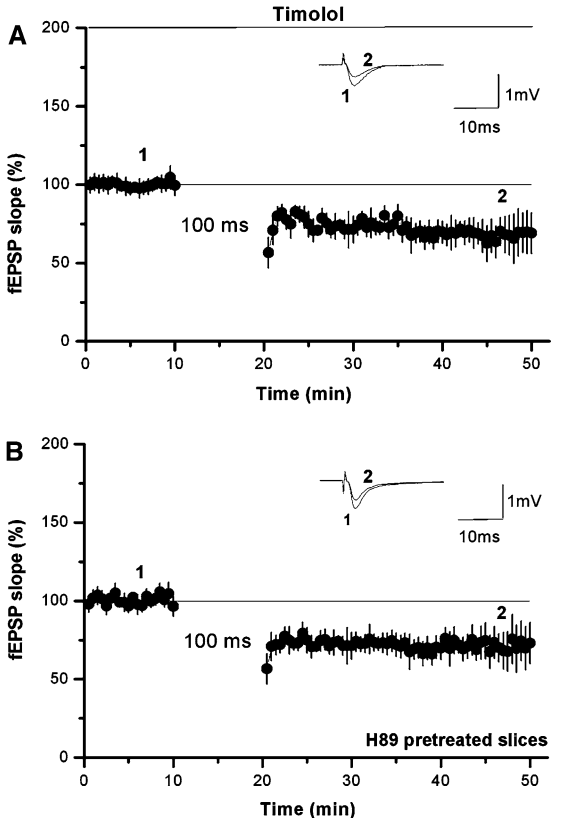

Figure 4. Associative LTD induced by the present pairing protocols was β-adrenergic receptors and PKA independent. (A) LTD was not blocked by β-adrenergic receptor blocker timolol. (B) LTD was not blocked in H89 treated slice. Inserts are superimpositions of raw data tracts averaged over 10 sweeps recorded immediately before and 25 min after the pairing protocol.

downstream signal cascade following activation of β-adrenergic receptors. Induction of associative LTD was remarkably inhibited by the bath application of 1 μM isoproterenol(Iso) (LTD = 98.8% ± 6.9%, $n = 6$; $p = 0.01$) (Figure 5A). This inhibitory effect of isoproterenol on associative LTD was blocked by including 50 μM timolol, a β-adrenergic receptor antagonist, in the ACSF, suggesting that the effect of Iso occurred via activation of β-adrenergic receptors (LTD = 70.8% ± 7.6%, $n = 6$; $p = 0.02$) (Figure 5B). The activation of β-adrenergic receptors being able to activate the G_s-protein, then increase c-AMP in cytoplasm, and finally activate protein kinase A (PKA). We therefore tested the effect of pretreatment of slices with H-89, the membrane-permeable blocker of PKA, on LTD inhibited by

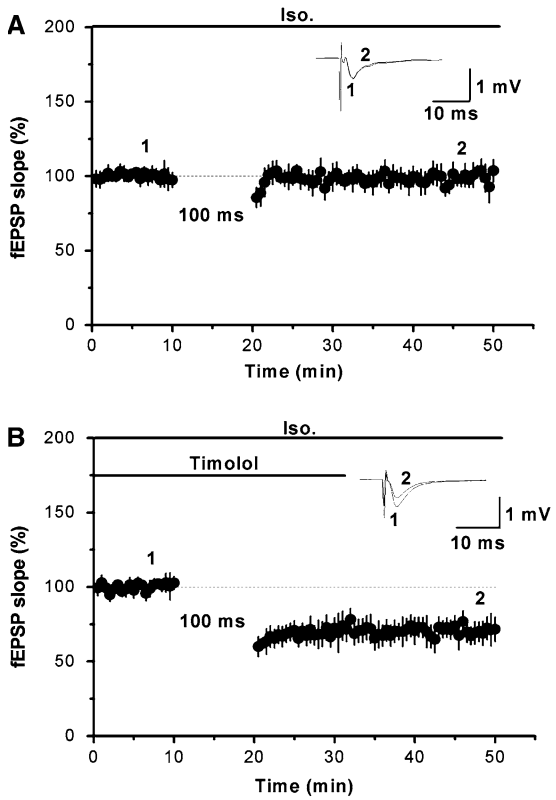

Figure 5. Inhibition of associative LTD by activation of β-adrenergic receptors. (A) Application of 1 μM isoproterenol (Iso) inhibited induction of associative LTD. (B) Application of the β-adrenergic receptor antagonist, timolol, blocked the inhibition effect of Iso, suggesting that it exerts its function via activation of β-adrenergic receptors. Inserts are superimpositions of raw data tracts averaged over 10 sweeps recorded immediately before and 25 min after the pairing protocol.

β-adrenergic receptors. As can be seen, the inhibitory effect of Iso on LTD induced by a pairing protocol of 100 ms was blocked in slices that were preincubated with 1 μM H-89 at 35 °C for at least 2 h (Figure 6A) (LTP = 69.5% ± 7.4%, $n = 7$, $p = 0.009$). Regarding modulation of synaptic plasticity at CA1 as well as other CNS synapses, recent studies have suggested that the mitogen-activated protein kinase (MAPK) is the downstream protein kinase of PKA [13]. We therefore tested the effect of MAPK on the inhibition of Iso in associative LTD with a broad-spectrum MAPK blocker (PD98059) and an ERK kinase-specific blocker (U0126). Slices were pretreated with 50 μM PD98059 or 50 μM U0126 at 35 °C for at least 2 h. The inhibitory effect of Iso on LTD was also blocked in slices that were pretreated with PD98059 (LTD = 71.1% ± 6.4%, $n = 6$; $p = 0.003$) (Figure 6B), as well as in slices pretreated with U0126 (LTD = 70.7% ± 3.9%, $n = 6$; $p = 0.007$) (Figure 6C). The above results suggest that inhibition of associative LTD by Iso was blocked by PKA-MAP/ERK kinase pathways.

Discussion

In this study, we demonstrate that associative LTD can be induced at a weak Schaffer collateral input after it is repeated paired with an independent strong input. For associative LTD to successfully be induced stimulation by the strong input has to precede the weak input and the timing window for the strong-weak stimulation has to be within 100 ms. Induction of associative LTD is NMDA receptor-dependent and requires activation of calcineurine. Activation of β-adrenergic receptors with isoproterenol inhibited associative LTD, and PKA and MAP/ERK kinase comprise the signaling pathway downstream of β-adrenergic receptor activation.

We previously reported that associative LTP can be induced by a pairing protocol in hippocampal CA1 and lateral perforant pathway [13, 14]. We have also demonstrated that results obtained with the extracellular recording technique are compatible with those obtained with the whole-cell recording technique, in which LTP of the weak pathway is induced by pairing it with post-synaptic spiking. We therefore concluded that

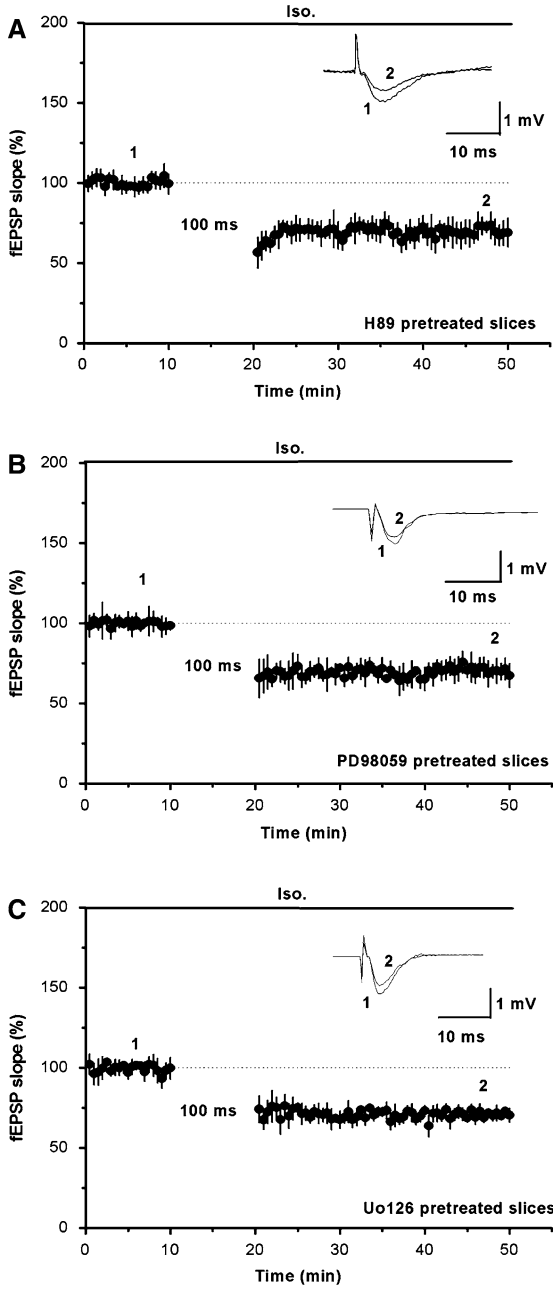

Figure 6. Inhibition of associative LTD by β-adrenergic receptors via PKA-MAPK/ERK cascades. (A) Associative LTD induced by the pairing protocol plus application of Iso was blocked if slices were pretreated with H89. (B & C) The inhibitory role of Iso on LTD was also blocked in slices pretreated with PD98059 (B), as well as in slices pretreated with U0126 (C). The above data demonstrate that the inhibition effect of β-adrenergic receptors occurs via PKA-MAPK/ERK cascades. Inserts are superimpositions of raw data tracts averaged over 10 sweeps recorded immediately before and 25 min after the pairing protocol.

the synaptic plasticity of the weak pathway induced in this study and in our previous study can be attributed to its interaction with post-synaptic spiking triggered by strong stimulation during the pairing protocol, and that it is analogous with spike-timing-dependent plasticity as previously reported [8, 14]. Associative LTD induced by the pairing of pre- and post-synaptic activities has been reported for many CNS synapses [15, 16]. The timing window required for induction of associative LTP/LTD has been well described for synapses in hippocampal cultures [8, 17] and slices of the rat barrel cortex [9, 18]. A timing window for conjunction pre-synaptic activation with post-synaptic spiking of 20 ms is required for induction of associative LTP, and a symmetrical [8, 14] or a longer timing window for conjunction post-synaptic spiking with pre-synaptic activation is required for associative LTD induction. Our results showing that a delay window of 100 ms is required for associative LTD induction at hippocampal CA1 synapses is consistent with previous results on other CNS synapses.

It is well known that the induction of NMDA-dependent form of LTD dependent largely on the age in rats [19, 20]; the incident of success in LTD induction declines when the animals is becoming mature. In the present study, however, the rate of success in associative LTD induction is high and is independent on age of animals (P20–P40 days) used in the present study. In consistent with results of the present study of CA1 synapses, our recent study [14], in which P20–P40 animals were also used, showed that associative LTD at later peforant paths on granules cells of dentate gyrus could be induced by paired pre- and post-synaptic stimulation. One possibility for accounting of this discrepancy could be that the paired pre- and post-synaptic stimulation, in which the membrane potential is depolarized by back propagating action potential, is more efficient to activate NMDA receptors than is the low frequency stimulation, therefore promoting the rate of success in LTD induction in mature animals.

At least two distinct forms of homosynaptic LTDs have been reported at CA1 synapses in the hippocampus of juvenile rats [21, 22]. In addition to NMDA receptor-dependent homosynaptic LTD induced by prolonged low-frequency stimulation, superfusion of slices with DHPG, an

agonist of group I metabotropic glutamate receptors, can induce a persistent decrease in synaptic efficacy after DHPG has been washed out [23]. This DHPG-induced LTD can also be induced by electrical stimulation using 900-paired pulses (50 ms) given at 1 Hz [4]. These facts raise the possibility that LTD induced here could be homosynaptic and analogous to DHPG-LTD, if the Schaffer collateral fibers recruited by strong stimulation overlap those involved in weak stimulation. We could not rule out this possibility for LTD induced by the pairing protocol with a pairing interval of less than 50 ms. We therefore remained focused on LTD induced by the pairing protocol with an interval of 80–100 ms, as the above mentioned possibility is less likely because paired-pulses with 100 ms interval given at 0.17 Hz induced no significant change in synaptic efficacy (see Figure 2C). In addition, induction of associative LTD in this study was NMDA receptor-dependent, further supporting the associative LTD induced here not being correlated with DHPG-LTD.

Prolonged low-frequency stimulation using single pulses, e.g., 900 pulses given at 1 Hz, can induce NMDA receptor-dependent LTD. Induction of this form of homosynaptic of LTD requires activation of phosphatase 2B, which causes dephosphorylation of AMPA receptors and leads to expression of LTD [7]. In a recent study, we have demonstrated that induction of associative LTD by paired- pre- and post-synaptic stimulation shares common molecular mechanism with induction homosynaptic LTP; namely it also involves in activation of phosphatase 2B [14]. The activity of phosphatase 2B is inactivated by inhibitor I [24, 25], which is subject to regulation by PKA. It is therefore possible that the depressant effect of β-adrenergic receptor activation on LTD induction might through the regulation of inhibitor-I by PKA and its downstream effectors, such as MAPK/ERK kinase, following activation of β-adrenergic receptor. We and others reported that β-adrenergic receptors have a promoting effect on homosynaptic LTP induction [26, 27], and these effects involved activation of the G protein-cAMP- PKA signal pathway [27]. In a recent study, we reported that associative LTP can be induced by conjunction pre-synaptic activation with post-synaptic activity at CA1 synapses, and that activation of β-adrenergic receptors can enhance associative LTP induction by increasing the timing window for the pairing of pre- and post-synaptic activities. In addition to activation of PKA, MAPK/ERK kinase is also involved following activation of β-adrenergic receptors [27]. Those results together with the present findings suggest a similar role of β-adrenergic receptors in modulating homosynaptic and associative synaptic plasticity, although the underlying physiological significance may differ between them.

In our previous study using an animal model, in which the endogenous noradrenergic system is depleted by 6-hydorxy-dopamine, we found that the induction of homosynaptic LTP was impaired, while induction of homosynaptic LTD was unaffected at CA1 synapses [27]. We proposed that noradrenergic fibers would only recruited by high frequency stimulation for LTP induction but not by the low frequency stimulation used for LTD induction; accordingly endogenous noradrenaline only play role in LTP but not LTD induction. Since the pre-synaptic stimulation is given at low frequency as well for induction of associative LTP, the above argument is supported by the fact that endogenous indeed does not plays any role in associative LTP induction [13]. In consistent with this idea, we found endogenous activity of β-adrenergic receptor and PKA activity are not involved in associative LTD induction here. In forebrain, including hippocampus, the principal source of noradrenergic innervations is from locus coeruleus (LC) [28]. On the increasing activity of LC neurons, timing window for the spike timing based synaptic plasticity would be changed, including the increase in window for LTP induction [13] and the closing of window for LTD induction. This mechanism might provide cellular substrate for the role of β-adrenergic receptor in modulating cortical plasticity.

In conclusion, the present results suggest that the induction of associative LTD is NMDA receptor- and calcineurine-dependent and may be inhibited by activation of β-adrenergic receptors via the PKA-MAPK/ERK kinase signal cascade.

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