Norepinephrine enables the induction of associative long-term potentiation at thalamo-amygdala synapses

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Emotional arousal, linked to a surge of norepinephrine (NE) in the amygdala, leads to creation of stronger and longer-lasting memories. However, little is known about the synaptic mechanisms of such modulatory NE influences. Long-term potentiation (LTP) in auditory inputs to the lateral nucleus of the amygdala was recently linked to the acquisition of fear memory. Therefore we explored whether LTP induction at thalamo-amygdala projections, conveying the acoustic conditioned stimulus information to the amygdala during fear conditioning, is under adrenergic control. Using whole-cell recordings from amygdala slices, we show that NE suppresses GABAergic inhibition of projection neurons in the lateral amygdala and enables the induction of LTP at thalamo-amygdala synapses under conditions of intact $GABA_A$ receptor-mediated inhibition. Our data indicate that the NE effects on the efficacy of inhibition could result from a decrease in excitability of local circuit interneurons, without direct effects of NE on release machinery of the GABA-containing vesicles or the size of single-quanta postsynaptic $GABA_A$ receptor-mediated responses. Thus, adrenergic modulation of local interneurons may contribute to the formation of fear memory by gating LTP in the conditioned stimulus pathways.

GABA | synaptic plasticity

Memory enhancements for emotionally charged events are thought to be associated with the release of norepinephrine in the amygdala (1, 2), which is also a key brain structure in another cognitive process, emotional learning (3). Strong emotional memories could be established through fear conditioning, a form of associative learning, which results from assigning of predictive properties to an initially neutral conditioned stimulus (CS) after its pairing with an aversive unconditioned stimulus during behavioral training (3–5). Previous studies provide evidence for the correlative link between long-term potentiation in the CS pathways conveying auditory information to the lateral amygdala (LA) and fear learning (6–10). A recent work has confirmed and extended these earlier findings by showing that synaptic enhancements at the cortico-amygdala synapses could be observed in slices from conditioned animals for at least 10 days after fear conditioning (11). The persistent facilitation of synaptic transmission in cortico-amygdala pathway is accompanied by occlusion of long-term potentiation (LTP) induced by electrical stimulation in slices (8). Although further studies will be needed to establish unequivocally the link between LTP and behavior, these findings indicate that behaviorally induced plasticity in the neural circuits of fear learning may use LTP mechanisms. Whereas the LA receives noradrenergic projections from the locus coeruleus (12), it remains unknown whether norepinephrine release in the amygdala, associated with the acquisition of fear memory, may contribute to fear behavior by affecting the mechanisms of synaptic plasticity in afferent inputs that deliver the CS information to the LA.

During fear conditioning, acoustic signals, constituting the CS, may be transmitted to the LA via direct projections from the medial geniculate nucleus and the posterior intralaminar nucleus of the auditory thalamus and also via projections originating in the auditory cortex (3). Consistent with the role of learning-induced synaptic enhancements in thalamo-amygdala pathway in the encoding of the CS information, a recent study has demonstrated that auditory fear conditioning is associated with postsynaptic trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors into thalamo-amygdala synapses (13). Thus, we asked whether the mechanisms of LTP in thalamo-amygdala pathway are under modulatory control of the noradrenergic inputs, and, if so, how such modulation might be achieved.

Here we report that norepinephrine (NE) suppresses tonic and feed-forward GABAergic inhibition of projection neurons in the LA and gates spike timing-dependent LTP at thalamo-amygdala synapses. These findings support the notion that adrenergic projections to the LA may affect fear conditioning by controlling the ability of synapses in the CS pathways to undergo LTP potentially needed for retention of fear memory.

Results

Adrenergic Gating of LTP in Thalamo-Amygdala Pathway Under Conditions of Intact GABAergic Inhibition. To explore the role of NE in regulation of synaptic plasticity in thalamic input to the LA, we obtained whole-cell recordings of excitatory postsynaptic potentials (EPSPs) from LA pyramidal neurons in brain slices. The EPSPs were elicited by stimulation of the internal capsule that contains axonal fibers originating in the auditory thalamus (3, 14) (Fig. 1*A*, stimulation electrode $S_{thalamic}$). We found that repeated pairing of EPSPs with action potentials (APs), directly triggered in the recorded neuron by depolarizing current injections, in the presence of the $GABA_A$ receptor antagonist picrotoxin (PTX; 50 μM) resulted in significant LTP of the thalamo-amygdala EPSP (Fig. 1 *B* and *D*; $n = 8$, t test, $P < 0.01$ versus baseline amplitude). Under these conditions, bath-applied NE (10 μm) had no effect on LTP induced in thalamic input with the same EPSP-AP pairing protocol ($n = 8$, $P = 0.47$ versus control LTP).

In agreement with previous observations (15, 16), the EPSP-AP pairing-induced LTP could not be observed at thalamo-amygdala synapses if $GABA_A$ receptor-mediated inhibition was not blocked (no PTX in the bath solution) with the EPSP remaining at 100 ± 8% (Fig. 1 *C* and *D*; $n = 9$, t test, $P = 0.9$ versus baseline) of its initial value. Conversely, LTP-inducing stimulation in the presence of 10 μM NE in the bath solution under conditions of intact inhibition led to potentiation of the EPSP amplitude to 165 ± 17% ($n = 10$) (t test, $P < 0.005$ compared with the "no NE" group). The effect of NE on the induction of LTP was not mediated by its action on NMDA receptors, because NE did not alter either the peak amplitude of

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Abbreviations: AP, action potential; CS, conditioned stimulus; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential; LA, amygdala; LTP, long-term potentiation; mIPSC, miniature inhibitory postsynaptic current; NE, norepinephrine; PTX, picrotoxin; sIPSC, spontaneous inhibitory postsynaptic current.

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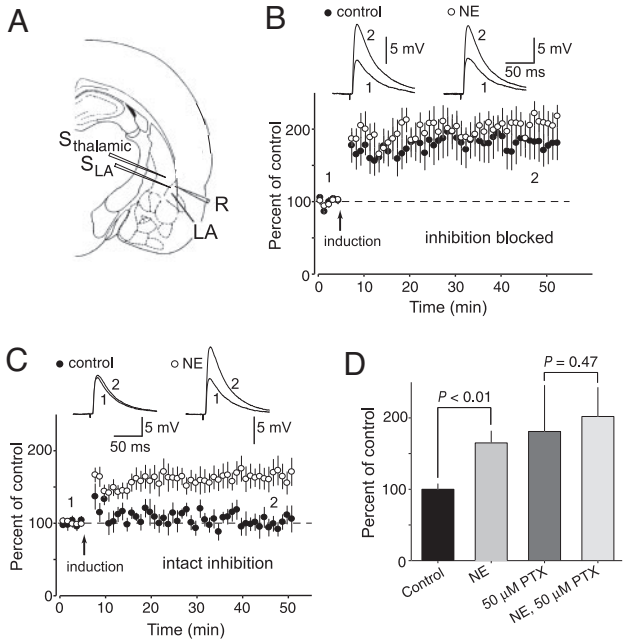

Fig. 1. Norepinephrine gates LTP at thalamo-amygdala synapses under conditions of intact $GABA_A$ receptor-mediated inhibition. (*A*) Schematic representation of a brain slice containing the LA that shows the position of the recording (R) and stimulation (S) pipettes. (*B*) EPSP-AP pairing-induced LTP of the thalamo-amygdala EPSP in the presence of PTX (50 μM) without NE (filled circles; $n = 8$; mean ± SEM) or with 10 μM NE (open circles; $n = 8$ neurons) in the bath solution. Traces are averages of three EPSPs obtained from individual experiments before (1) and after (2) LTP induction (arrow). (*C*) Summary graphs of LTP experiments in thalamo-amygdala pathway under conditions of intact inhibition without NE (filled circles; $n = 9$) or with 10 μM NE (open circles; $n = 10$) in the bath solution. Traces are averages of three EPSPs obtained before (1) and after (2) LTP induction. During LTP experiments, NE was applied throughout the recording period. (*D*) Summary of LTP experiments at the thalamo-amygdala pathway (mean ± SEM).

the isolated NMDAR excitatory postsynaptic currents (EPSCs) ($n = 10$, t test, $P = 0.22$) or their voltage dependence (Fig. 2 *A* and *B*). These results imply that NE might enable the induction of LTP in thalamic input to the LA by affecting inhibitory GABAergic neurotransmission.

Direct Effects of NE on Synaptic and Neuronal Functions in the LA. The facilitatory effect of NE on the induction of LTP in thalamic input could be mediated, in part, by its action on basal synaptic transmission in the LA. Therefore, we investigated the effects of bath-applied NE on EPSCs evoked in LA principal neurons under voltage-clamp conditions by stimulation of the internal capsule at a holding potential of −70 mV. The addition of 10 μM NE to the external solution did not result in significant changes in the peak EPSC amplitude (Fig. 2 *C* and *F*; $n = 6$, t test, $P = 0.28$). This observation is surprising because it has been demonstrated previously that NE, acting on specific adrenoreceptor subtypes, could either inhibit or facilitate glutamatergic synaptic transmission in lateral or basal nuclei of the amygdala (17–20). In agreement with previous studies, we found that activation of β-adrenoreceptors by 10 μM NE in the presence of the α_2-adrenoreceptor antagonist yohimbine (20 μM) led to potentiation of the thalamo-amygdala EPSC to 149 ± 10% of its initial value (Fig. 2 *D* and *F*; $n = 7$, paired t test, $P < 0.01$). The potentiating effect of NE on glutamatergic EPSCs in thalamic input was specifically linked to the β-adrenoreceptor activation, because it was reversed by the β-adrenoreceptor antagonist propranolol (10 μM) (Fig. 2*D*). Thus, the EPSC amplitude 10 min after beginning of propranolol application has returned to 127 ± 9% of its initial value. When β-adrenoreceptors were blocked by propranolol, bath-applied NE reduced the amplitude of the EPSC to 67 ± 6% of the predrug baseline (Fig. 2 *E* and *F*; $n = 4$, paired t test, $P < 0.02$). Consistent with the role of α_2-adrenoreceptors in depression of the thalamo-amygdala EPSC observed under these conditions, the effect of NE was partially reversed by the α_2-receptor antagonist yohimbine: the EPSC amplitude has returned to 86 ± 3% of its initial value (Fig. 2*E*). The oppositely directed synaptic modifications, induced by simultaneous activation of different adrenoreceptor subtypes by NE, appear to compensate for each other, thus resulting in unchanged overall synaptic efficacy in thalamic input to the LA. Thus, the effect of NE on the induction of early LTP in thalamo-amygdala pathway could not be attributed to direct effects of NE on baseline glutamatergic neurotransmission.

It has been demonstrated that NE inhibits the slow afterhyperpolarization that follows trains of action potentials and thus facilitates spike firing in LA neurons (21). In agreement with these reports, we found that application of 10 μM NE had significant effect on the firing properties of LA neurons. In our experiments, the number of spikes triggered by depolarizing current injections of gradually increasing intensity under current-clamp conditions was increased in the presence of NE (Fig. 2 *G* and *H*; $n = 8$; paired t test, $P < 0.02$). This observation indicates that NE may increase neuronal excitability in the LA, thus facilitating spike firing in response to potentiated synaptic inputs and increasing the probability that incoming signals will be transmitted from the LA to other components of the neural circuitry implicated in fear conditioning.

NE Gates LTP in Thalamic Input Through Suppression of $GABA_A$ Receptor-Mediated Inhibition. Consistent with the role of NE in modulation of inhibition, NE application reduced the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) recorded in the LA neurons in the absence of Tetrodotoxin (TTX) (baseline frequency: 3.62 ± 0.67 Hz; NE: 2.02 ± 0.34 Hz, $n = 16$, paired t test, $P < 0.02$) (Fig. 3 *A–C*), but not in the presence of TTX when miniature inhibitory postsynaptic currents (mIPSCs) were recorded (baseline frequency: 0.88 ± 0.21 Hz; NE: 0.93 ± 0.07 Hz, $n = 4$, paired t test, $P = 0.86$) (Fig. 3*C*), without any effect on the amplitude of either sIPSCs (baseline amplitude: 48.8 ± 6.1 pA; NE: 50.9 ± 6.9 pA, paired t test, $P = 0.77$) or mIPSCs (baseline amplitude: 28.0 ± 4.9 pA; NE: 28.8 ± 4.3 pA, paired t test, $P = 0.91$). In the experiments using direct recordings from interneurons in the LA, identified by their morphology and nonaccommodating firing properties (16) (Fig. 3*D*), NE application induced an outward (hyperpolarizing) current under voltage-clamp conditions in 9 of 16 cells tested (Fig. 3*E*; mean current amplitude was 17.6 ± 3.4 pA), with no change seen in 6 cells and a small inward current in 1 cell. The latter possibly reflects pharmacological heterogeneity of adrenoreceptor subtypes expressed by different subgroups of LA interneurons. We found also that NE had no effect on evoked monosynaptic $GABA_A$ receptor-mediated synaptic currents in projection neurons induced by direct stimulation of interneurons in the LA (Fig. 1 *A*, stimulation electrode S_{LA}; Fig. 3*F*; $n = 4$, paired t test, $P = 0.9$ versus pre-NE baseline). Taken together, these findings indicate that NE may suppress tonic inhibition of LA neurons by hampering AP firing in local circuit interneurons but does not influence the machinery of GABA release by interneurons or sensitivity of $GABA_A$ receptors expressed by principal neurons to GABA.

The decreased interneuronal excitability could lead to suppression of both feedforward and feedback inhibition of principal neurons in the LA, affecting the induction of LTP at thalamo-amygdala synapses. We explored this possibility by assaying the effects of NE on the EPSP/inhibitory postsynaptic

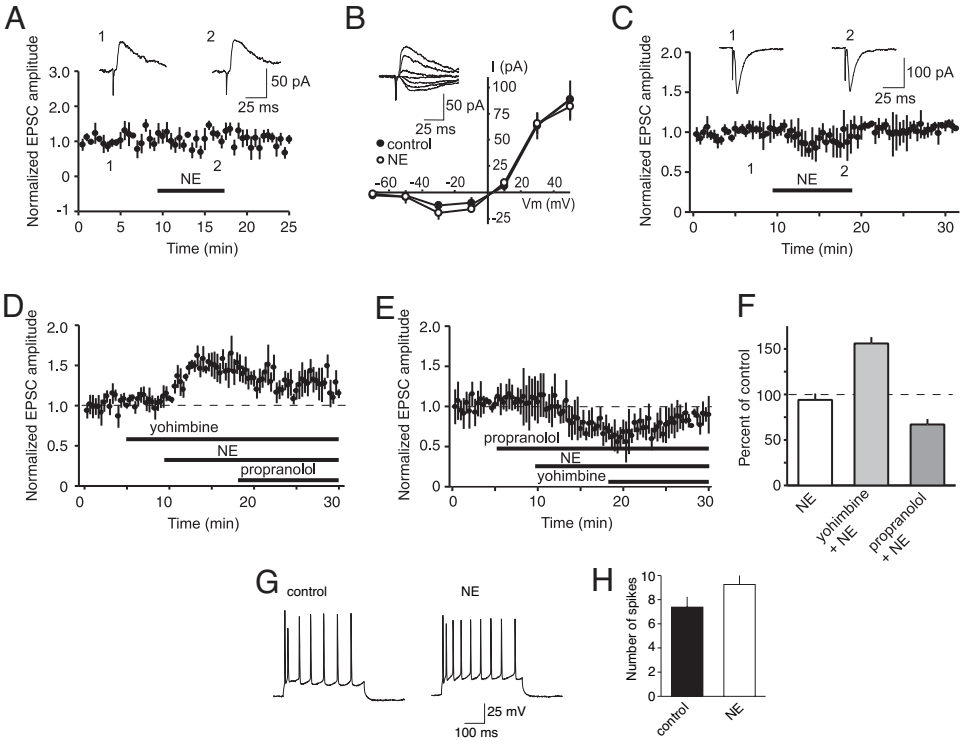

Fig. 2. NE has no direct effect on baseline glutamatergic synaptic transmission in thalamo-amygdala pathway. (*A*) Values of amplitude of the NMDA receptor-mediated EPSCs (normalized by the pre-NE baseline) are plotted as a function of time (mean ± SEM; $n = 10$ neurons). Solid bar shows the duration of 10 μM NE application. Traces (top) show NMDAR EPSCs recorded before (1) and during (2) NE application. Synaptic currents were recorded in the presence of the AMPAR antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (20 μM) and PTX (50 μM) at a holding potential of +30 mV. (*B*) Current-voltage plot of the NMDA receptor EPSCs. Synaptic currents (*Inset*) were recorded in the presence of 6-cyano-7-nitroquinoxaline-2,3-dione and PTX at holding potentials of −70 mV to +50 mV under baseline conditions (filled symbols) and ≈15 min after switching to the NE-containing solution (open symbols; $n = 6$ neurons). Traces are averages of three EPSCs recorded at each holding potential. (*C*) The AMPAR-mediated thalamo-amygdala EPSCs were recorded from pyramidal neurons at a holding potential of −70 mV ($n = 6$ neurons). Solid bar shows the duration of 10 μM NE application. Traces (top) are averages of three EPSCs recorded before (1) and during (2) NE application. (*D*) Application of NE induced potentiation of the thalamo-amygdala EPSC when α_2-adrenoreceptors were blocked by yohimbine (20 μM; $n = 5$). This potentiation was reversed by 10 μM propranolol. (*E*) NE application produced depression of the EPSC when β-adrenoreceptors were blocked by propranolol (10 μM; $n = 4$). Yohimbine partially blocked this potentiation. (*F*) Summary plot of the effects of NE on glutamatergic EPSCs in thalamic input to the LA. Error bars indicate SEM. (*G*) Responses of LA neurons to prolonged current injections (500 ms, 200 pA) recorded before (control) and during NE application. (*H*) Summary plots of the experiments as in *G* ($n = 8$; mean ± SEM).

potential (IPSP) sequences evoked by stimulation of thalamo-amygdala pathway (15, 16). Bath-applied NE significantly reduced the peak amplitude of disynaptic GABAergic IPSPs (Fig. 4 *A* and *B*; $P < 0.01$), with no effect on the peak EPSP amplitude ($P = 0.19$). This NE-induced suppression of GABAergic inhibition was sufficient to enable the induction of LTP in thalamo-amygdala pathway. Thus we found that in the presence of a low concentration of PTX (1 μM), which decreases the IPSP amplitude to the level comparable with that induced by NE (22), the EPSP-AP pairing protocol now resulted in potentiation of the thalamo-amygdala EPSP to 168 ± 41% ($n = 4$) (Fig. 4*C*; $P < 0.01$ versus pre-LTP baseline; $P < 0.01$ versus the EPSP amplitude when the LTP protocol was delivered without PTX in the bath solution). This strengthens the notion that NE may permit the induction of early LTP in thalamic input to the LA by decreasing GABAergic inhibition of projection neurons by local circuit interneurons.

Discussion

Our present results show that NE gates LTP in a thalamo-amygdala pathway under physiological conditions of intact inhibition by decreasing excitability of local circuit interneurons and facilitates neuronal spike firing in the LA without detectable effects on basal glutamatergic synaptic transmission. The weakening of inhibitory drive to LA neurons would facilitate activation of postsynaptic NMDA receptors (16), thus making thalamo-amygdala synapses susceptible to LTP induced by a tight temporal association between the stimulus-evoked EPSPs and postsynaptic APs. It is possible, however, that some unidentified additional mechanisms also could contribute to the effects of NE on the induction of early LTP at thalamo-amygdala synapses. Further work will be needed to provide behavioral evidence that gating of LTP in thalamic input by NE contributes to fear conditioning. These findings are consistent with the results of recent experiments, using single-unit recordings in anesthetized rats, which demonstrated that activation of the locus coeruleus, supplying NE to different regions of the brain, may reduce activity of physiologically identified feedforward inhibitory interneurons (23). Perhaps consequentially, emotional arousal induced by a single inescapable footshock led to lasting increases in spontaneous firing rates of projection neurons in the basolateral amygdala of freely moving animals (24). Direct electrical stimulation of the locus coeruleus in anesthetized rats was shown to produce a variety of changes in single-unit responses in the basolateral amygdala (25), ranging from a decrease in the firing rate (observed in ≈50% of the recorded cells) to increased firing, with some cells showing no response to the stimulation. However, the types of recorded cells (neurons versus interneurons), which could respond differently to NE, were not identified in this recent work.

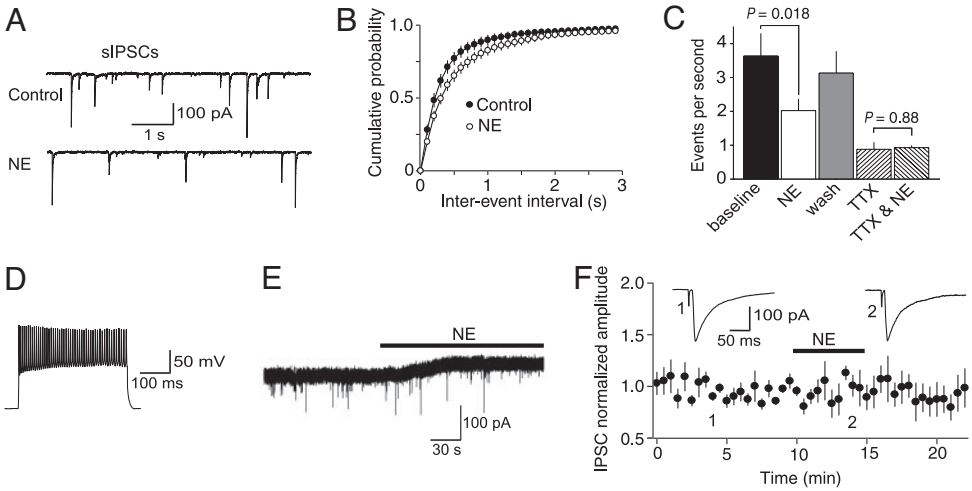

Fig. 3. NE suppresses GABAergic inhibition of neurons in the LA by decreasing excitability of local circuit interneurons. (*A*) Representative sIPSPs in the LA neuron at a holding potential of −70 mV recorded with or without 10 μM NE in the bath solution. (*B*) Cumulative interevent interval histograms of sIPSCs recorded under baseline conditions (filled symbols) and after NE was applied (open symbols) ($n = 16$). (*C*) Summary plots of sIPSC and mIPSC (recorded in the presence of 1 μM Tetrodotoxin (TTX; $n = 4$) data (mean ± SEM). (*D*) Recording from interneuron that showed the nonaccommodating firing pattern in response to depolarizing current injection. (*E*) An outward current in the LA interneuron recorded under whole-cell conditions at a holding potential of −70 mV in the presence of 10 μM NE in the bath solution. (*F*) NE does not depress monosynaptic $GABA_AR$ IPSCs in the LA. The IPSCs were recorded from pyramidal neurons at a holding potential of −70 mV ($n = 4$ cells). Stimulation pipette was placed within the LA. Traces (top) are averages of three IPSCs recorded before (1) and during (2) NE application. Synaptic currents were recorded in the presence of 20 μM 6-cyano-7-nitroquinoxaline-2,3-dione.

Activity-dependent regulation of GABAergic neurotransmission appears to provide a general mechanism that may control the induction of LTP in afferent inputs to the LA and fear conditioning. Thus, it has been shown that the magnitude of early LTP at synapses in the pathways delivering the CS information to the LA is determined by the strength of $GABA_A$ receptor-mediated inhibition of projection neurons and that both the inhibitory inputs and LTP could be modulated by dopamine (15), gastrin-releasing peptide (9), or synaptically released Zn^{2+} (22). Our finding that NE did not produce increases in tonic inhibition of neurons in the LA, which contrasts with a previous report (20) where activation of the α_{1A} adrenoreceptor was associated with the increased frequency of the spontaneous $GABA_AR$-mediated synaptic events, supports the notion that differences in the available NE receptor subtypes and their expression density in specific nuclei of the amygdala may determine the resulting electrophysiological phenotype (25).

Previous studies have repeatedly demonstrated that the adrenergic system may play a crucial role in enhanced consolidation of emotional memory (reviewed in ref. 2). It has become almost common knowledge that release of NE in the amygdala during either behavioral training or real-life events may trigger molecular and cellular processes needed for the formation of long-term memory for fear. This notion has been challenged recently in a study of fear conditioning in genetically modified mice lacking both norepinephrine and epinephrine due to the ablation of the dopamine β-hydroxylase gene (26). Cued fear conditioning, produced in this study by the single-trial training paradigm, was not affected in knockout mice when tested 1 day after training. It is possible, however, that compensatory modifications in the brains of dopamine β-hydroxylase knockout mice (26), e.g., changes in GABAergic inhibition of projection neurons in the basolateral amygdala, could explain unchanged long-term fear memory in the absence of NE. In another study, using neuropharmacological approaches, consolidation of auditory fear memory in rats was not affected by posttraining inactivation of β-adrenoreceptors by the specific antagonist, propranolol, bilaterally injected in the lateral and basal nuclei of the amygdala (27). However, as mentioned in the latter work, it is not clear whether the administered dose of propranolol was

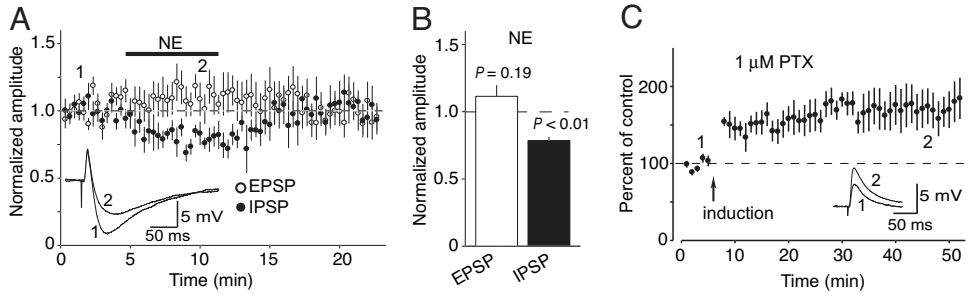

Fig. 4. NE-induced suppression of feedforward GABAergic inhibition is sufficient to gate LTP in thalamic input to the LA. (*A*) Effects of NE on biphasic synaptic responses evoked by stimulation of thalamo-amygdala pathway. The EPSP/IPSP sequences were recorded in the LA neuron under current-clamp conditions at −55 mV. (*Inset*) The averages of three responses recorded under baseline conditions (1) and during NE application (2). (*B*) Summary plot of the effects of NE on glutamatergic EPSPs and GABAergic IPSPs in thalamic input to the LA. The average amplitudes of synaptic responses recorded over the final 3 min of NE application were normalized by their baseline values ($n = 8$). (*C*) EPSP-AP pairing-induced LTP in thalamo-amygdala pathway in the presence of 1 μM PTX ($n = 4$). Traces show EPSPs recorded before (1) and after (2) the pairing procedure. Error bars indicate SEM.

sufficient to prevent activation of β-adrenoreceptors by endogenously released NE. These findings, although arguing against an essential function of NE in consolidation of fear memory, do not exclude a role for NE in the mechanisms of short-term memory of auditory fear conditioning. Consistent with the notion that endogenously released NE may be required for the acquisition of fear memory, it was demonstrated earlier that pretraining manipulations of the adrenergic activity in the amygdala impair auditory fear conditioning (28). Another interesting possibility is that the NE-mediated modulation of inhibition in the BLA could also play a role in fear extinction (29).

In summary, NE released in the amygdala may serve a permissive role in the induction of associative LTP in afferent inputs to the LA, thus potentially contributing to the mechanisms of emotional memory, as exemplified by memory for fear.

Materials and Methods

Amygdala slices (250–300 μm) were prepared from 3- to 5-week-old Sprague–Dawley rats with a vibratome. Slices were continuously superfused in solution containing 119 mM NaCl, 2.5 mM KCl, 2.5 mM $CaCl_2$, 1 mM $MgSO_4$, 1.25 mM NaH_2PO_4, 26 mM $NaHCO_3$, and 10 mM glucose and equilibrated with 95% O_2 and 5% CO_2 (pH 7.3–7.4) at room temperature (22–24°C). Whole-cell recordings were obtained from either projection neurons or interneurons in the dorsolateral division of the LA under visual guidance (DIC/infrared optics) with an EPC-10 amplifier and Pulse v8.65 software (HEKA Elektronik, Lambrecht/Pfalz, Germany) (16). In all current-clamp experiments, the patch electrodes (4–6 MΩ resistance) contained 120 mM K-gluconate, 5 mM NaCl, 1 mM $MgCl_2$, 0.2 mM EGTA, 10 mM Hepes, 2 mM MgATP, 0.2 mM NaGTP (adjusted to pH 7.2 with KOH). To record spontaneous and evoked IPSCs, 120 mM KCl was used instead of K-gluconate. To examine the effects of NE on evoked NMDAR EPSCs, cesium methane-sulfonate was substituted for potassium in the pipette solution. NMDAR EPSCs were recorded in the presence of the AMPA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (20 μM) and picrotoxin (50 μM). Synaptic responses were evoked by current pulses applied through a fine tipped ($\approx$5 μm) concentric stimulating electrode consisting of a patch pipette that was coated with silver paint (9, 16). The stimulating pipette was positioned in the internal capsule to activate the thalamic input to the LA (Fig. 1 *A*). To evoke monosynaptic $GABA_AR$ IPSCs, the stimulation electrode was placed within the LA. LTP was induced by pairing of 80 presynaptic stimuli, delivered at 2 Hz to the fibers in the internal capsule, with APs that were evoked in a postsynaptic cell with a 4- to 6-ms delay from the onset of each EPSP. APs were induced by short depolarizing current injections through the recording electrode. Summary LTP graphs were obtained by normalizing data in 60-s epochs to the mean value of the baseline EPSP. The sIPSCs and mIPSCs were analyzed with the Mini Analysis Program v6 (Synaptosoft, Inc., Decatur, GA).

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