Noradrenergic ‘Tone’ Determines Dichotomous Control of Cortical Spike-Timing-Dependent Plasticity

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Norepinephrine (NE) is widely distributed throughout the brain. It modulates intrinsic currents, as well as amplitude and frequency of synaptic transmission affecting the ‘signal-to-noise ratio’ of sensory responses. In the visual cortex, \(\alpha\)- and \(\beta\)-adrenergic receptors (AR) gate opposing effects on long-term plasticity of excitatory transmission. Whether and how NE recruits these plastic mechanisms is not clear. Here, we show that NE modulates glutamatergic inputs with different efficacies for \(\alpha\)- and \(\beta\)-AR. As a consequence, the priming of synapses with different NE concentrations produces dose-dependent competing effects that determine the temporal window of spike-timing dependent plasticity (STDP). While a low NE concentration leads to long-term depression (LTD) over broad positive and negative delays, a high NE concentration results in bidirectional STDP restricted to very narrow intervals. These results indicate that the local availability of NE, released during emotional arousal, determines the compound modulatory effect and the output of STDP.

The locus coeruleus (LC) is a widespread projection system that supplies norepinephrine (NE) to the entire central nervous system (CNS)\textsuperscript{1}. NE is released both tonically and phasically from axonal varicosities in the efferent circuits targeted by the LC, and directly supports arousal-related brain states and behavior\textsuperscript{2,3}. In cortical neurons, NE has been proposed to enhance the ‘signal-to-noise ratio’ and to change receptive field properties by potentiating strong synaptic responses and reducing weak ones, or alternatively, by ‘gating’ otherwise subthreshold synaptic inputs\textsuperscript{4}.

Studies \textit{in vitro} have shown that NE modulates intrinsic cellular excitability\textsuperscript{5} and synaptic transmission\textsuperscript{6,7} in the cortex. However, NE exerts complex excitatory and inhibitory effects and many contradicting results have been reported. It is possible that the distinct actions attributed to NE are in fact mediated by different effective concentrations of NE activating specific adrenergic receptor subtypes in target circuits. Indeed, the three main adrenergic receptor (AR) subtypes (\(\alpha_1\), \(\alpha_2\) and \(\beta\)) produce distinct synaptic actions via metabotropic G-proteins linked to different signal transduction cascades\textsuperscript{7}. For example, in the cerebral cortex, \(\alpha_1\)-AR and \(\beta\)-AR suppress and enhance evoked excitatory synaptic responses, respectively\textsuperscript{8}, while \(\alpha_2\)-AR modulate inhibitory transmission\textsuperscript{8}. In addition, AR-mediated signaling strongly controls long-term plasticity, since \(\alpha_1\)-AR agonists selectively enable LTD and suppress LTP, while \(\beta\)-AR agonists enable LTP and suppress LTD\textsuperscript{9-11}. Thus, \(\alpha_1\)- and \(\beta\)-AR mediate opposing acute and long-term plastic effects. Since endogenous NE binds to all AR subtypes, the question arises as to how these opposing and mutually suppressive plastic mechanisms are evoked by NE and how they interact.

Here we show that pyramidal cells in layer II/III (LII/III PyrCs) of the mouse visual cortex are sensitive to both \(\alpha_1\)- and \(\beta\)-AR agonists, and that exogenous NE produces opposing modulatory effects on excitatory transmission via these receptors when applied in the presence of the appropriate antagonists. Most importantly, these neuromodulatory effects occur with different efficacies for \(\alpha_1\)- and \(\beta\)-AR. Hence, different concentrations of NE lead to strong competing modulatory interactions that determine the output of spike-timing dependent plasticity (STDP)\textsuperscript{12}. Our results demonstrate that the plastic effects of NE are dose-dependent and receptor-specific, and provide a basis for understanding integrative functions of NE in cortical plasticity at the cellular and network level.

Results
Isolation of excitatory responses by intracellular blockade of chloride channels. In acute slices, extracellular electrical stimulation evokes overlapping excitatory and inhibitory responses in normal aCSF. Thus, to determine
the direct effects of norepinephrine (NE) on excitatory transmission, postsynaptic inhibitory conductances must first be removed. GABA_A receptors (GABA_ARs) can be blocked by extracellular perfusion of antagonists, although this generally induces hyperexcitability and affects the entire network. To circumvent this problem, we blocked GABA_ARs in single recorded neurons by adding 1 mM picrotoxin to the intracellular solution (+[PiTxi]), and assessed the efficacy of this effect in the presence of ionotropic glutamate receptor antagonists by monitoring inhibitory postsynaptic currents (IPSCs) at −30 mV (Fig. 1A, C). The blockade of GABA_ARs was very quick and evident just after breaking the seal, indicating rapid diffusion of [PiTxi] (Fig. 1C). Twenty minutes after breaking the seal, the IPSCs were 6.4 ± 2.9% of those observed in control solution (−[PiTxi]: 188.3 ± 36.2 pA; n = 11; +[PiTxi]: 12.1 ± 5.4 pA; n = 10; interlaced conditions) and they were fully blocked by extracellular perfusion of 100 μM PiTx (+[PiTxic]; Fig. 1C). No major changes in input resistance or resting membrane potential were observed in the presence of [PiTxi] (−[PiTxi]: Rm = 550.2 ± 101.8 MΩ; +[PiTxi]; Rm = 561.6 ± 139.2 MΩ; F1,18 = 1.285, P = 0.26; −[PiTxi]; RMP = −73.1 ± 1.0 mV; +[PiTxi]: RMP = −72.6 ± 0.9 mV; F1,18 = 0.079, P = 0.78; internal solution with QX-314)28. Thus, adding 1 mM PiTx to the internal solution blocked GABA ARs channels and eliminated the evoked IPSCs at all membrane potentials tested (Fig. 1C, D), as well as the miniature IPSCs (mIPSCs)29. Finally, we confirmed that translaminar inhibition (i.e. LIV→LII/III; Fig. 1E) was blocked in the recording configuration used to study EPSCs, as described below.

**Figure 1** | Isolation of excitatory responses by intracellular chloride channel blockade. (A) Recordings were obtained from LII/III pyramidal cells (PyrCs) in the monocular portion of the primary visual cortex (V1M). (B) Sample biocytin-filled PyrC stained with streptavidin Alexa Fluor 564, and an amplified image of a dendrite with spines (upper right inset; scalebar 10 μm). A regular spiking pattern is shown in the inset lower right (scalebars: 500 ms and 50 mV). Labeled cells were not used for experiments. (C) IPSCs evoked by fixed extracellular stimulation (~100 μA) in LII/III (~100–300 μm away from the recorded cell) in the presence of GluR antagonists. Responses were acquired immediately after breaking the seal with internal solutions with or without picrotoxin (+[PiTxi], filled circles; −[PiTxi], open circles). IPSCs were eliminated by extracellular perfusion of 100 μM PiTx ([PiTxi], gray box and bold sample traces). (D) The I–V plot shows average peak IPSCs ± [PiTxi], collected ≥ 10 min after breaking the seal. Apparent GABA reversal potential (EGABA) is in agreement with theoretical Cl− equilibrium potential from the Nernst equation (−[PiTxi]: EGABA = −59.5 ± 3.1 mV, n = 11). Sample traces on the right. (E) Sample LIV→LII/III synaptic currents at −80 mV in control aCSF with [PiTxi], evoked in presence (bold traces) or the absence (thin traces) of GluR antagonists; no remaining currents were observed at Vh = −30 mV (data not illustrated). Sample responses represent the average of 5 traces. Number of experiments in parentheses.

**NE exhibits different efficacies in modulating excitatory responses through alpha and beta adrenergic receptors.** In cortical PyrCs, pharmacological activation of α1- or β-adrenergic receptors (AR) depresses or potentiates synaptic excitation, respectively29,30. However, it remains unclear whether these two receptor subtypes are co-expressed and co-activated by NE. To improve our measurements and ensure that the effects observed are due to the exogenous NE, we first eliminated the possible influence of the endogenous NE system by disrupting the monoamine vesicular transporter with reserpine (see methods). In this condition, we investigated whether NE bidirectionally modulates EPSCs by activating α1-AR or β-AR, incubating the slices with specific antagonists to block the contribution of either receptor: the α1-AR was blocked with prazosin (Prz, 1 μM) and the β-AR with propranolol (Prop, 1 μM).

NE (8.75 μM) was applied to the bath solution for 20 min and the net effect was measured by averaging the EPSC amplitude over the last 10 min. In the presence of Prz, NE increased EPSC amplitude to 140.6 ± 16.2% of the control levels (n = 6, P < 0.05), whereas in the presence of Prop, NE decreased the EPSC amplitude to 75.2 ± 5.7% of the control levels (n = 6, P < 0.05). Both effects exhibited similar kinetics (Prz: t1/2 = 8.7 ± 1.4 min; Prop: t1/2 = 7.9 ± 0.8 min; P = 0.62). No changes in EPSCs (Prz + Prop: 97.9 ± 5.5%, n = 14, P = 0.42), nor in Rm or holding currents, were observed when the slices were treated with both antagonists (Fig. 2A), suggesting that α2-AR do not modulate EPSCs at these synapses. Moreover, no change in the paired-pulse ratio (PPR = EPSC2/EPSC1) 1.285, P = 0.079; internal solution with QX-314)28. Thus, adding 1 mM PiTx to the internal solution blocked GABA ARs channels and eliminated the evoked IPSCs at all membrane potentials tested (Fig. 1C, D), as well as the miniature IPSCs (mIPSCs)29. Finally, we confirmed that translaminar inhibition (i.e. LIV→LII/III; Fig. 1E) was blocked in the recording configuration used to study EPSCs, as described below.
PPR and the effects were fully reversed within 20 min of washing out the specific agonists (Iso, Prz, 1 μM) and decreased EPSCs in propranolol (Prop, 1 μM), yet it had no effect in Prz + Prop (no change in holding current; data not illustrated). Similar kinetics for both effects. No change in Rin or PPR were detected (scalebars: 20 MΩ, 200 MΩ, 2). (B) EPSC amplitudes augmented with isoproterenol (Iso, 10 μM, 10 min) and after washout, it decreased with methoxamine (Mtx, 5 μM, 10 min). Both effects were reversible. (CD) NE-concentration-response curves for EPSCs in the presence of prazosin (Prz, upper panels) or propranolol (Prop, lower panels). The ordinate in (D) indicates the change in EPSC amplitude averaged over the last 10 min of NE application. Lines are generalized logistic functions. (E) Reversible effects of [NE]high and [NE]low (0.33 μM NE) in control aCSF. Number of experiments in parentheses.

Figure 2 | Norepinephrine modulates excitatory responses via α1- and β-ARs. (A) Norepinephrine ([NE]high = 8.75 μM NE) potentiated EPSCs in prazosin (Prz, 1 μM) and decreased EPSCs in propranolol (Prop, 1 μM), yet it had no effect in Prz + Prop (no change in holding current; data not illustrated). Similar kinetics for both effects. No change in Rin or PPR were detected (scalebars: 20 MΩ, 200 MΩ, 2). (B) EPSC amplitudes augmented with isoproterenol (Iso, 10 μM, 10 min) and after washout, it decreased with methoxamine (Mtx, 5 μM, 10 min). Both effects were reversible. (CD) NE-concentration-response curves for EPSCs in the presence of prazosin (Prz, upper panels) or propranolol (Prop, lower panels). The ordinate in (D) indicates the change in EPSC amplitude averaged over the last 10 min of NE application. Lines are generalized logistic functions. (E) Reversible effects of [NE]high and [NE]low (0.33 μM NE) in control aCSF. Number of experiments in parentheses.

The NE concentration determines the compound modulation of spike-timing-dependent plasticity in the mouse visual cortex. Neuromodulatory receptors have been implicated in modulating
the efficacy of spike-timing-dependent plasticity (STDP) in brain slices\(^7\). One would expect that the plastic effect of a single neuromodulator receptor subtype should increase with agonist concentration. But, does NE leads to interactions between the plastic effects of \(\alpha_1\)- and \(\beta\)-AR affecting the outcome of STDP? We investigated whether the different concentrations of NE, \([\text{NE}]_{\text{high}}\) and \([\text{NE}]_{\text{low}}\) influenced STDP plasticity. After recording at least 10 min of baseline EPSCs, NE was applied for 10 min and the STDP-protocol was delivered at the end of the drug application (see methods). In control aCSF, although inhibition was blocked intracellularly, we observed no lasting changes in EPSCs when the postsynaptic burst preceded presynaptic activation (negative delay of \(\Delta t = -10.4 \pm 0.5\) ms: 103.1 \(\pm 6.4\)%, \(n = 13, P = 0.11\); Fig. 3A, empty circles) or vice versa (positive delay of \(\Delta t = +7.1 \pm 0.2\) ms: 102.7 \(\pm 6.6\)%, \(n = 11, P = 0.13\); Fig. 3B empty circles), consistent with previous observations\(^6\). However, priming synapses with \([\text{NE}]_{\text{high}}\) led to timing-dependent long-term depression (t-LTD) for pairings with a negative delay (NE 8.75 \(\mu\)M at \(\Delta t = -9.8 \pm 0.2\) ms: 70.5 \(\pm 6.8\)%, \(n = 7, P < 0.05\); Fig. 3A, black circles) and long-term potentiation (t-LTP) for a positive delay (NE 8.75 \(\mu\)M at \(\Delta t = 6.5 \pm 0.3\) ms: 126.6 \(\pm 4.6\)%, \(n = 11, P < 0.05\); Fig. 3B, black circles). Notably, larger negative or positive intervals produced no persistent changes with \([\text{NE}]_{\text{high}}\). NE 8.75 \(\mu\)M at \(\Delta t = -19.1 \pm 0.6\) ms: 96.9 \(\pm 7.6\)%, \(n = 9, P = 0.63\); \(\Delta t = 17.4 \pm 0.4\) ms: 105.5 \(\pm 4.4\)%, \(n = 8, P = 0.15\); Fig. 3C, D, black circles). By contrast, when pairings were combined with \([\text{NE}]_{\text{low}}\), t-LTD was observed both at negative and positive delays (NE 0.33 \(\mu\)M at \(\Delta t = -18.75 \pm 0.6\) ms: 74.3 \(\pm 5.4\)%, \(n = 8, P < 0.05\); \(\Delta t = -9.4 \pm 0.4\) ms: 70.5 \(\pm 12.0\)%, \(n = 8, P < 0.05\); \(\Delta t = 6.4 \pm 0.5\) ms: 71.9 \(\pm 4.3\)%, \(n = 8, P < 0.05\); \(\Delta t = 16.5 \pm 0.4\) ms: 81.2 \(\pm 5.1\)%, \(n = 11, P < 0.05\); Fig. 3A–D, grey circles). This indicates that NE concentration determines the output of STDP.

Neither application of NE nor induction of associative plasticity affected the average PPR or \(R_n\) (Fig. 3A, B) and no lasting changes were induced when NE was applied in conjunction with either presynaptic activation alone (NE 8.75 \(\mu\)M: 99.2 \(\pm 5.4\)%, \(n = 10\), paired t-test, \(P = 0.63\); NE 0.33 \(\mu\)M: 101.8 \(\pm 6.3\)%, \(n = 6, P = 0.39\); data not illustrated) or with postsynaptic firing alone (NE 8.75 \(\mu\)M: 98.4 \(\pm 3.6\)%, \(n = 10, P = 0.84\); NE 0.33 \(\mu\)M: 95.8 \(\pm 2.8\)%, \(n = 10, P = 0.11\); data not illustrated). Interestingly, we could not induce STDP when priming was attempted with single postsynaptic spikes instead of bursts (NE 8.75 \(\mu\)M at \(\Delta t = 7.4 \pm 0.5\) ms: 94.2 \(\pm 8.2\)%, \(n = 6, P = 0.45\); data not illustrated). Thus, in our recording conditions, NE permitted the induction of STDP only when pre-synaptic and robust postsynaptic activity were combined.

We explored the priming effects of NE on STDP also at several larger delays (Fig. 3E, F). We found that \([\text{NE}]_{\text{low}}\) enabled t-LTD over a wide range of negative (\(\Delta t \leq -20\) ms) and positive (\(\Delta t \leq +50\) ms) delays (Fig. 3E), whereas \([\text{NE}]_{\text{high}}\) enabled t-LTD only at a short negative delay (\(\Delta t = -9.8 \pm 0.2\) ms) and t-LTP for a short positive delay (\(\Delta t = +6.5 \pm 0.3\) ms; Fig. 3F). We conclude that the output of
STDP is not rigid, as [NE]_low was associated with a broad t-LTD-only STDP-window, while [NE]_high led to bidirectional STDP, restricted to very narrow time intervals. Through a dichotomous action by activating α1- and β-AR, the noradrenergic ‘tone’ increased the temporal contrast of STDP.

NE mediates competing modulation of t-LTP and t-LTD. Our results suggest that NE generates a compound neuromodulatory effect that determines the outcome of STDP. The question arises as to whether NE induces opposing long-term neuromodulatory effects through α1-AR and β-AR. We reasoned that if compound plastic effects by NE are mediated by co-activation of these two receptors, then pharmacological blockade of one receptor subtype should unmask the plastic effects mediated by NE acting on the competing receptor. Accordingly, in the presence of the α1-AR blocker prazosin, [NE]_high led to t-LTP with STDP pairings at a negative delay (Prz + NE: 8.75 μM at Δt = −11.36 ± 0.3 ms: 120.5 ± 8.3%, n = 11, P < 0.05; NE 7.5 μM at Δt = −9.8 ± 0.2 ms: 70.5 ± 6.8%, n = 7, P < 0.05; Fig. 4A), while in the presence of the β-AR blocker propranolol, [NE]_high led to t-LTD at a positive delay (Prop + NE 8.75 μM at Δt = 7.9 ± 1.0 ms: 80.4 ± 6.4%, n = 11, P < 0.05; NE 8.75 μM at Δt = 6.5 ± 0.3 ms: 126.6 ± 4.6%, n = 11, P < 0.05; Fig. 4B). Thus, the gating of STDP by NE depends upon competing processes that are mediated by α1-AR and β-AR, which control LTD and LTP, respectively.

Discussion

We have investigated the role of NE in the acute and long-term modulation of excitatory transmission in LII/III PyrCs from the mouse visual cortex. The rate of AR activation depends on the concentration of NE and its affinity for these receptors, which differs for α1- and β-AR. Using increasing concentrations of NE in the presence of α1- or β-AR antagonists, we determined the EC50 values for the modulation of EPSCs by NE acting through α1- and β-AR in LII/III PyrCs. Remarkably, these values differed more than 20-fold. Opposing NE modulation of EPSCs was mediated by α1- and β-AR, and it was abolished in the presence of antagonists for both receptors. Hence, the neuromodulatory actions of NE on these synapses appear to be predominantly mediated through α1- and β-AR, and not through α2-AR. Furthermore, LII/III PyrCs were co-sensitive to sequential application of selective α1- and β-AR agonists, demonstrating the co-expression of these receptors in the recorded cells. Acute modulation of EPSCs was fully reversible and did not affect paired-pulse ratios, in contrast to what is observed for IPSCs. Unlike the arbitrary ratios of AR activation achieved with specific agonists, the use of NE enables a specific profile of activation of α1- and β-AR. Based on the EC50 values, we selected two NE concentrations: one that targeted α1-AR ([NE]low) and depressed EPSCs and one that co-activated α1- and β-AR ([NE]high). Co-activation was reflected as a reduced EPSC potentiation by [NE]high compared to that obtained in the presence of the α1-AR antagonist prazosin.

Recent in vitro studies have shown that Gα-coupled receptors (e.g., β-AR) directly promote LTP and suppress LTD while Gβγ-coupled receptors (e.g., α1-AR) promote LTD and suppress LTP19–21. This prompted us to investigate the effects of different NE concentrations on the induction of STDP19–21. We found that NE, without the participation of additional neuromodulatory systems, was necessary and sufficient to gate bidirectional STDP with an appropriate induction protocol. Moreover, [NE]low enabled a t-LTD-only window at broad positive and negative delays, while [NE]high enabled bidirectional STDP (t-LTP/t-LTD) with very narrow timing intervals. Interestingly, a similar t-LTD-only STDP window occurs by activation of muscarinic cholinergic receptor M1 (Gq-coupled) and a broad bidirectional STDP window is obtained by co-activation of M1 and β-AR20. One possibility to explain this low temporal contrast of STDP is that the co-activation of Gq- and Gβγ-coupled receptors could reduce their mutually suppressive (plastic) effects, or they may even cancel out, although not in a simple linear manner20. However, the results we obtained here are more consistent with a mutual suppression scenario, because [NE]high led to a sharp STDP window, restricted to small intervals, and with a reduction in the gain for t-LTD compared to that obtained with [NE]low. If one adopts this view, this would indicate that the suppressive effect of β-AR was absent with [NE]low, as these receptors are not activated at this concentration, but became robust with [NE]high thereby strongly reducing t-LTD and sharpening the STDP window. Moreover, the experiments displayed in Fig. 4 indicate that once suppression was removed by blockade of either α1- or β-AR, the gating effect of the unblocked receptor operated in the opposite direction. We propose that the suppressive plastic properties of α1- and β-AR do not disappear during co-activation but remain robust. By co-activating α1- and β-AR, the NE concentration controls mutual suppression, increasing the temporal contrast of the STDP window. Therefore, NE not only enables STDP but also regulates the size of the ‘STDP gate’.

The temporal windows for STDP produced with [NE]low and [NE]high are in contrast with ‘canonical’ STDP which is temporally asymmetric and has a broader region for t-LTD than for t-LTP19–21. The symmetry (and anti-symmetry) observed in our STDP windows may reflect the isolation from the effects of endogenous catecholamines, although it may also depend on other factors21. The broadened t-LTD window that we observed with [NE]low favors a generalized build-up of synaptic depression and could contribute to the stabilization of postsynaptic firing rates under conditions of excessive excitatory drive21.

We have shown that pharmacological activation of α1-ARs primes visual cortical neurons to produce a form of visual experience-induced LTD in vivo24, with relevant behavioral consequences25. This form of α1-AR LTD is expressed at ascending excitatory inputs carrying visual information to layer II/III and correlates with a selective and orientation-specific decrease in visual discrimination performance of sinusoidal drifting gratings at high spatial frequencies. Thus, at least a fraction of ARs participates in allowing visual

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**Figure 4 | Norepinephrine exerts competing modulatory actions for STDP.** In normal aCSF, pairings at −10 ms with [NE]high led to LTD (black circles, A) while pairings at +10 ms led to LTP (black circles, B) (same data as in Fig. 3). If slices were incubated in prazosin (+Prz), pairings at −10 ms led to LTP (white squares, A), whereas in propranolol (+Prop), pairings at +10 ms lead to LTD (white squares, B). No significant changes in Rm, Rmp or PPR (scalebars: 20 ΩM, 200 ΩM, 2). Similar modulatory actions to those observed in cells from Fig. 2A (repeated measures two-factor ANOVA, [NE]high in Prop: F1,150 = 0.2, P = 0.65; [NE]high in Prz: F1,180 = 3.5, P = 0.08). Delivery of the STDP protocol is depicted by black arrows. Number of experiments in parentheses.
Electrophysiological experiments.

Coronal slices of the visual cortex (350 μm) from postnatal day 29 (P29) were used in the present study. Mice were housed in groups of up to 10 per cage (type III, 825 cm²; Ehret, Emmendingen, Germany) with ad libitum access to food and water. To study slice preparations in the absence of endogenous NE, catecholamine pools were depleted by incubating the monoamine vesicular transporter with reserpine (5 mg/kg; in 10% 1,2 propanediol) for 60 min. It is tempting to speculate that the ‘tones’ of NE during wakefulness and sleep participate in reorganizing cortical synaptic weights in a spike-timing dependent manner. The higher NE levels present during wakefulness and non-REM sleep stages could promote bidirectional plasticity of active sensory inputs, while the lower NE levels found during REM sleep may favor the generalized build-up of synaptic depression of active synapses. Action potential driven quantal release of NE from central neurons occurs by exocytosis of vesicles with intravesicular concentration of ~0.4–1 M NE which might well support conditions with synaptic NE concentrations in the micromolar range (i.e. such as NE-/high). Moreover, a mechanism for gating generalized LTD during sleep is attractive, as it could contribute to increase in the ‘signal-to-noise ratio’ of relevant memories, remove spurious associations and contribute to synaptic homeostasis.

In contrast, the higher NE levels during emotional arousal could facilitate the formation of new memories. The present results contribute to our understanding of how NE interacts with divergent AR signaling cascades to support generalized weakening and restrictive strengthening of cortical synapses.

Methods

Animals.

A total of 133 wild-type male C57BL/6 mice (Charles River; Sulzfeld, Germany) were used in the present study. Mice were housed in groups of up to 10 per cage (type III, 825 cm²; Ehret, Emmendingen, Germany) with ad libitum access to food and water. To study slice preparations in the absence of endogenous NE, catecholamine pools were depleted by incubating the monoamine vesicular transporter with reserpine (5 mg/kg; in 10% 1,2 propanediol) for 60 min. It is tempting to speculate that the ‘tones’ of NE during wakefulness and sleep participate in reorganizing cortical synaptic weights in a spike-timing dependent manner. The higher NE levels present during wakefulness and non-REM sleep stages could promote bidirectional plasticity of active sensory inputs, while the lower NE levels found during REM sleep may favor the generalized build-up of synaptic depression of active synapses. Action potential driven quantal release of NE from central neurons occurs by exocytosis of vesicles with intravesicular concentration of ~0.4–1 M NE which might well support conditions with synaptic NE concentrations in the micromolar range (i.e. such as NE-/high). Moreover, a mechanism for gating generalized LTD during sleep is attractive, as it could contribute to increase in the ‘signal-to-noise ratio’ of relevant memories, remove spurious associations and contribute to synaptic homeostasis.

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Author contributions
M.T. designed the study and planned the experiments. H.S. and M.T. performed experiments and analyzed data. All authors wrote and reviewed the manuscript.

Additional information
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