

# Role of the Noradrenergic System in Synaptic Plasticity in the Hippocampus

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## Summary

The cortical noradrenergic (NAergic) system, which originates from the locus coeruleus (LC) located in the pons, plays an important role in cortical plasticity and many other brain functions. In rats in which the NAergic system has been eliminated by 6-hydroxydopamine during the neonatal period, induction of long-term potentiation (LTP) at CA1 synapses in the hippocampus is impaired, whereas induction of long-term depression is unaffected. Bath application of norepinephrine, a  $\beta$ -adrenergic receptor agonist, or activators of effector molecules downstream of the  $\beta$ -adrenergic receptor restores LTP. Similarly, activation of  $\beta$ -adrenergic receptors enhances associative LTP induced by paired stimuli to two independent synaptic inputs on the same postsynaptic neuron. The time window within which LTP can be induced by paired stimuli is increased by  $\beta$ -adrenergic receptor activation, but the magnitude of LTP is not affected. The signaling molecules involved in enhancement of the homosynaptic and associative LTP following  $\beta$ -adrenergic receptor activation are the same and include protein kinase A and mitogen-activated protein kinases. These experimental results suggest that a simultaneous increase in the activity of LC neurons during induction protocols may have a permissive role in the induction of homosynaptic and associative LTP in the hippocampus.

**Key words** LTP, LTD,  $\beta$ -Adrenergic, 6-Hydroxydopamine, Locus coeruleus

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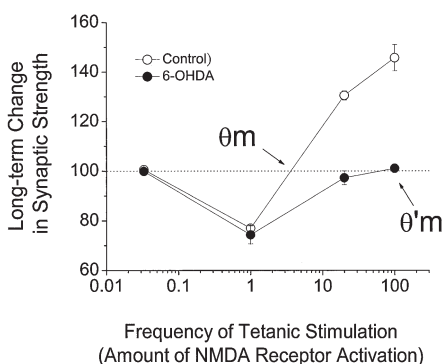
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## Introduction

Long-term potentiation (LTP) and long-term depression (LTD) are use-dependent changes in synaptic efficacy that are generally accepted as the cellular substrate for memory storage in the brain [1, 2]. They have attracted much attention during the past few decades, and the mechanisms involved in their induction and expression have been well characterized [2–4]. Activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors is required for induction of both LTP and LTD. The voltage-dependent nature of the NMDA receptor makes it an ideal detector for the total postsynaptic response produced by a population of activated synapses. These active synapses are potentiated when the total postsynaptic response they produce exceeds a critical value, referred to as the modification threshold ( $\theta_m$ ), and are depressed if the total response is greater than zero but less than  $\theta_m$  [5, 6].

This idea of regulation of synaptic strength is called the BCM theory, named after the three scientists, Bienenstock, Cooper, and Murp, who proposed it [5]. An example of BCM modification for synaptic efficacy (or BCM curve) at the CA1 synapse is shown in Fig. 1. According to this theory, a total postsynaptic response greater than  $\theta_m$  activates large numbers of NMDA receptors, which leads to LTP by the activation of protein kinases, which phosphorylate AMPA receptors. In contrast, a total postsynaptic response greater than zero but less than  $\theta_m$  activates fewer NMDA receptors, which leads to LTD because of the activation of phosphatases and the subsequent dephosphorylation of AMPA receptors [4, 7].

Norepinephrine (NE), one of the most important neuronal modulators in the brain, is involved in the regulation of many brain functions, including the wake/



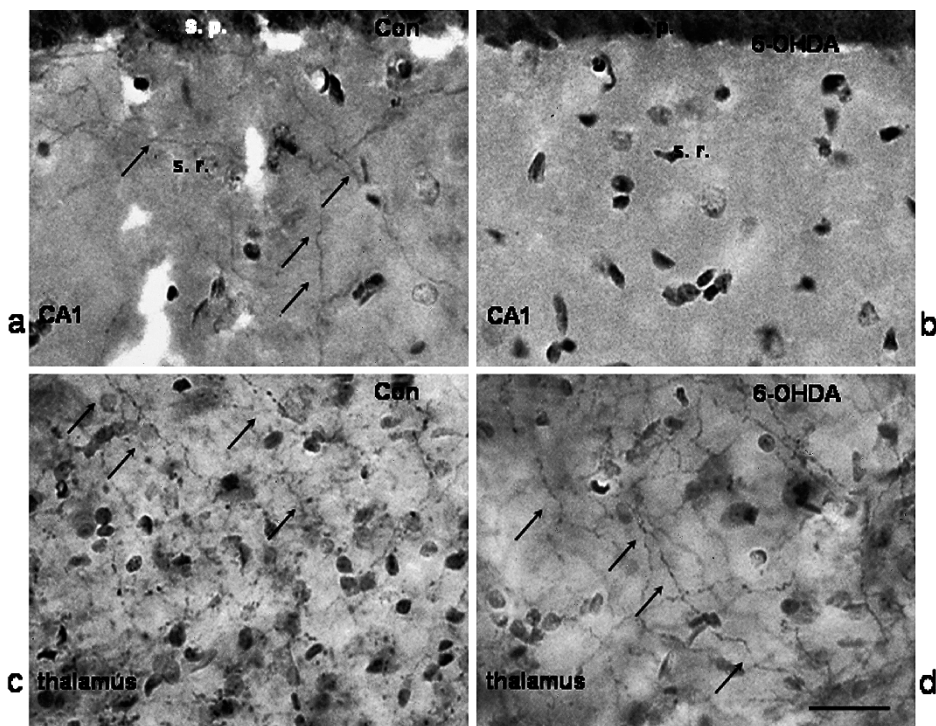
**Fig. 1.** Effect of norepinephrine (NE) on the BCM curve. The BCM curve shows the relation between the frequency of tetanic stimulation [or the amount of *N*-methyl-D-aspartate (NMDA) receptor activation by tetanic stimulation] and the resultant long-term change in synaptic strength in control slices (*open circles*). The *arrow* indicates the modification threshold ( $\theta_m$ ). Note the right shift of  $\theta_m$  in the control slices to  $\theta'_m$  in the 6-hydroxydopamine (6-OHDA)-treated slices (*filled circles*), suggesting that NE depletion impairs long-term potentiation (LTP) but has no effect on long-term depression (LTD) induction. (From Yang et al. [12], with permission)

sleep cycle [8], memory storage [9], synaptic/cortical plasticity [10–12], autonomic functions [13], and pain modulation [14]. In the neocortex and hippocampus, NE fibers mainly originate from the locus coeruleus (LC), located in the pons. In vitro studies have suggested that NE, acting on  $\beta$ -adrenergic receptors, has a significant effect on synaptic plasticity at CA1 synapses [10, 12, 15, 16] and mossy fiber synapses [17]. In this chapter, we first discuss the permissive role of NE in modulating synaptic plasticity based on previous studies, followed by some interesting issues that need to be examined further.

## Role of the Noradrenergic System in Homosynaptic Plasticity

At hippocampal CA1 synapses, bath application of 10  $\mu$ M NE during the delivery of conditioned stimulation to induce a long-term change in synaptic strength results in a left shift of  $\theta_m$  in the BCM curve. That is, application of NE does not have any effect on the magnitude of LTP induced by high-frequency stimulation at 50 or 100 Hz but blocks induction of LTD by low-frequency stimulation (1 Hz) and enhances the effect of 10-Hz stimulation—which alone does not result in any significant change in synaptic strength in control conditions—to induce LTP [15]. Similar observations have been made at mossy fiber synapses on CA3 pyramidal neurons [17, 18]. An in vivo study also showed that induction of LTP by mild tetanus stimulation is impaired in animals in which endogenous catecholamine was depleted by injecting 6-hydroxyl dopamine (6-OHDA), but LTP can still be induced by strong tetanus [19]. These observations therefore suggest that the cortical noradrenergic (NAergic) system might have a permissive role in modulating LTP induction in the hippocampus.

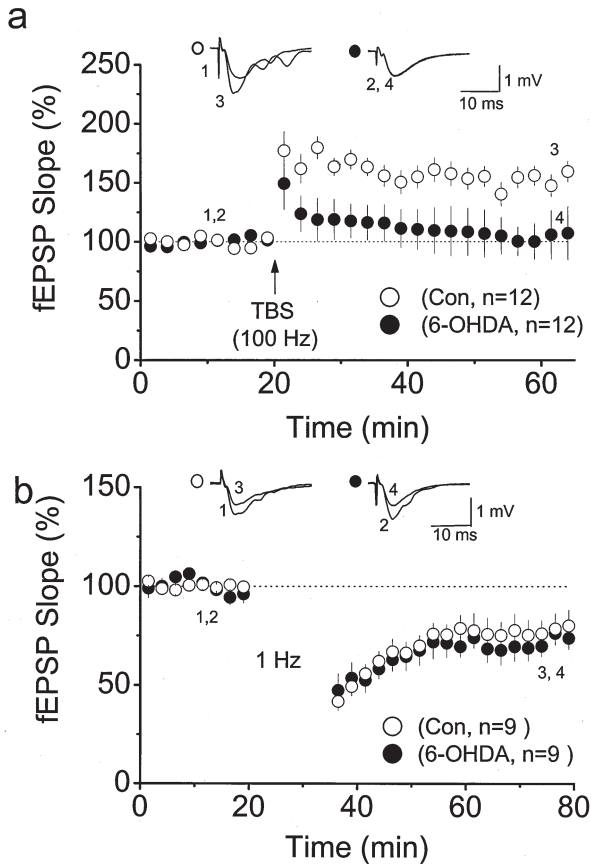
Nevertheless, a critical question remains: How do conditioned stimuli for LTP induction activate the NAergic pathway to enhance LTP induction? A high density of NAergic fibers is found in the stratum radiatum of the CA1 region (Fig. 2) and the stratum lucidum of the CA3 region [20, 21]. The overlapping distribution of NAergic and glutamatergic fibers of the Shaffer collateral branches provides an opportunity for simultaneous activation of glutamatergic and NAergic fibers during tetanus. Consistent with this argument, studies in which electrophysiological and neurochemical data were simultaneously recorded in the hippocampus in vivo showed that the local NE concentration can rise to several times the basal value during tetanus for LTP induction [22, 23]. Another potential approach to addressing this question is to examine synaptic plasticity in hippocampal slices from animals in which endogenous NAergic fibers in the hippocampus have been depleted. The treatment of neonatal rats with 6-OHDA might provide a model meeting this requirement, as it results in a persistent loss of catecholaminergic fibers in the cerebral cortex but not in subcortical areas (Fig. 2) [24]. Using hippocampal slices from 6-OHDA-treated rats, we found that the LTP induced by theta burst stimulation decays within 15 min (Fig. 3A,C), whereas the LTD induced by 900 pulses at 1 Hz is not affected (Fig. 3B,C) [12]. Taking these results together, it reveals a right



**Fig. 2.** Animal model in which endogenous NE is depleted by 6-OHDA. Dopamine- $\beta$ -hydroxylase (DBH) immunohistochemistry performed in the stratum radiatum (*s.r.*) of the hippocampal CA1 area in control (*Con*) (a) and in 6-OHDA-treated animals (b). Thalamus area in the same section in the control animal (c) and the 6-OHDA-treated animal (d). Note the DBH-immunoreactive fibers (indicated by *arrows*) in all photographs except b. *s.p.*, stratum pyramidale. Bars 50  $\mu$ m. (From Yang et al. [12], with permission)

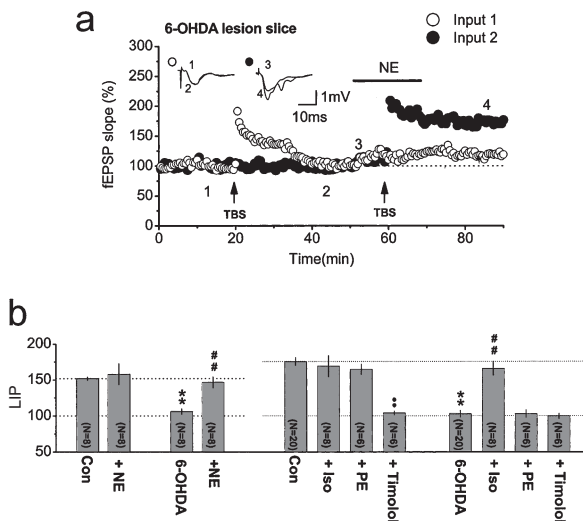
shift of  $\theta_m$  in the BCM curve that is consistent with the effect of perfusion slices with 10  $\mu$ M NE [15]. Interestingly, a similar observation has been reported at mossy fiber synapses, where the LTP induced by mild tetanus decays within 15 min when  $\beta$ -adrenergic receptors are blocked by timolol [17]. Bath application of NE restores the expression of LTP to normal and blocks LTD induction (Fig. 3A,B) in slices from 6-OHDA-treated animals but has no effect on the magnitude of LTP in slices from control animals (Fig. 3C) [12]. These observations suggest that NAergic fibers are recruited to enhance LTP induction in normal hippocampal slices, whereas a higher tetanus intensity is required for LTP induction in slices lacking NAergic innervation. Similar conclusions were drawn in a recent study that examined the expression of LTP in several strains of mice with various levels of endogenous NE [16].

The enhancement of LTP and blockage of LTD by NE in the hippocampus appears to occur through the activation of  $\beta$ -adrenergic receptors [12, 15–17]. In



**Fig. 3.** LTP and LTD in slices from 6-OHDA-lesioned animals. **a** LTP at CA1 synapses induced in slices of control (*open circles*) and 6-OHDA-treated (*filled circles*) rats using theta burst stimulation (TBS), which consists of 10 bursts at 5 Hz with each burst consisting of four pulses at 100 Hz. **b** LTD induced by 900 pulses at 1 Hz stimulation. Note the rapid decay in the LTP, but not the LTD, induced in slices from 6-OHDA-treated rats. (From Yang et al. [12], with permission)

control slices, the effect of NE on the BCM curve is blocked by timolol, a selective  $\beta$ -adrenergic receptor antagonist, but not by phentolamine, a selective  $\alpha$ -adrenergic receptor [15]. Similarly, isoproterenol, a selective  $\beta$ -adrenergic receptor agonist, but not phenylephrine, a selective  $\alpha$ -adrenergic receptor agonist, restores LTP to normal in slices from 6-OHDA-treated animals (Fig. 4) [12] and from mice with low endogenous NE levels [16]. Interestingly, the blockage of depotentiation (low frequency-induced LTD after LTP induction) at CA1 synapses requires the activation of both  $\alpha$ - and  $\beta$ -adrenergic receptors [15], suggesting that the mechanisms underlying LTD induction and depotentiation are different [25].

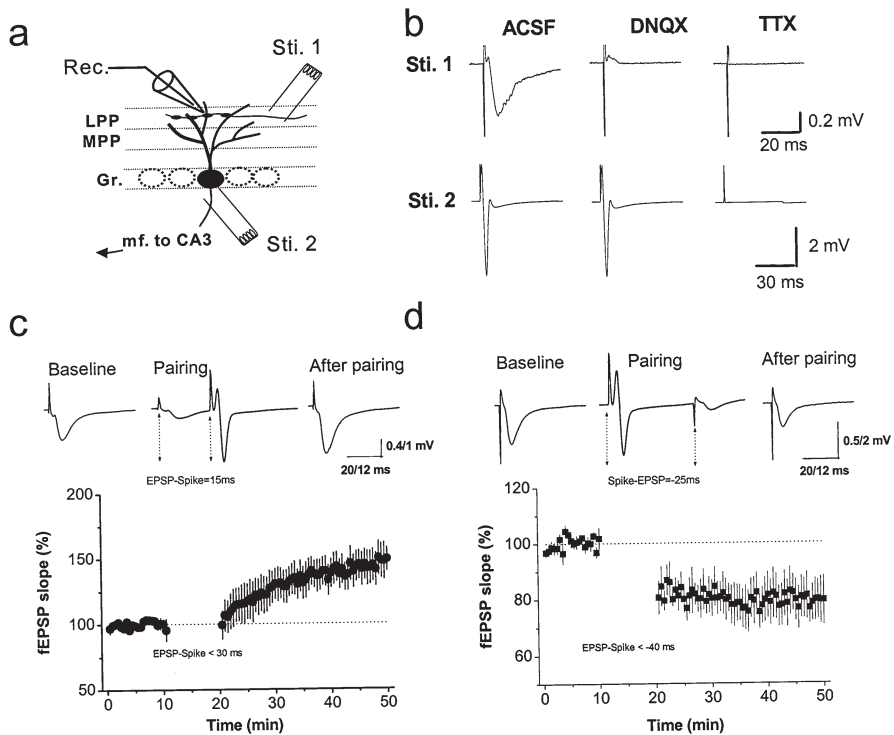


**Fig. 4.** Activation of  $\beta$ -adrenergic, but not  $\alpha$ -adrenergic, receptors restores LTP in slices from 6-OHDA-treated rats. **a** A typical experiment on a slice from a 6-OHDA-treated rat in which two independent Schaffer collateral branches were stimulated. Theta burst stimulation (TBS) was applied to one of the two inputs (input 1) to induce LTP in normal conditions; 40 min later, TBS was applied to the other input (input 2) to induce LTP with simultaneous application of NE during delivery of TBS. The resultant LTPs are compared. **b** Summarized results show that application of NE restores LTP in slices from 6-OHDA-treated rats and the summarized results of pharmacological experiments. Note that in slices from control rats LTP induction is not affected by isoproterenol (*Iso*), a  $\beta$ -adrenergic receptor agonist, or phenylephrine (*PE*), an  $\alpha$ -adrenergic receptor agonist; it is blocked by timolol, a  $\beta$ -adrenergic receptor antagonist. Also note in slices from 6-OHDA-treated rats LTP is restored by application of *Iso* but not *PE*, and this effect is prevented when the  $\beta$ -adrenergic receptor is blocked by timolol. (From Yang et al. [12], with permission)

## Role of the NAergic System in Associative Plasticity

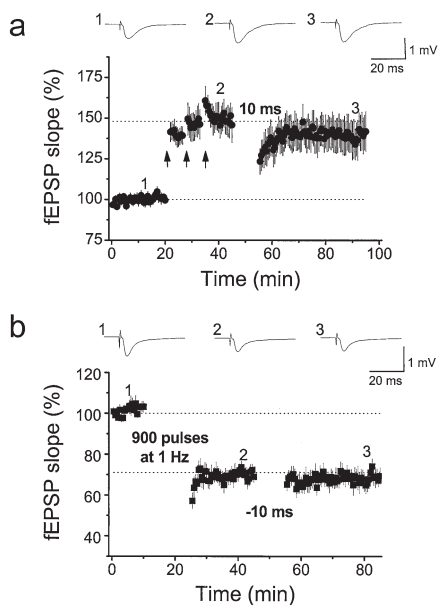
A significant weakness in suggesting a physiological role of the conventional LTP and LTD induced by tetanus or prolonged low-frequency stimulation has been the question of whether these stimulating paradigms realistically resemble any physiological function in the brain. Recently, it was demonstrated that LTP/LTD-like changes in synaptic strength can also be induced by the simultaneous spiking of a pair of pre- and postsynaptic neurons within a precise time window, so-called spike timing-dependent plasticity (STDP) [26–28]. Obviously, this form of synaptic plasticity fits very well with the Hebbian learning rules that: (1) neurons that fire in synchrony become wired together (i.e., when the presynaptic axon is active and the postsynaptic neuron simultaneously is strongly activated, the synapse formed by the presynaptic axon is strengthened); and (2) neurons that fire out of synchrony lose their link (see also Chapter 25 in [29]). It is now generally accepted that STDP provides a more genuine cellular model for experience-driven change in brain function or the Hebbian learning rules than does conventional LTP/LTD [26–28, 30, 31].

STDP is bidirectional; that is, synaptic efficacy can be either potentiated or depressed by paired pre- and postsynaptic spiking, depending on both the timing interval and the temporal order of the pre- and postsynaptic spiking. Generally speaking, to induce STDP, the timing interval between paired pre- and postsynaptic spiking has to be less than ~25 ms, whereas a significantly wider time window (up to ~100 ms) has been suggested for LTD induction [32, 33]. As for the temporal order of pre- and postsynaptic spiking, repeated paired pre/postsynaptic spiking results in LTP if presynaptic stimulation precedes postsynaptic stimulation, whereas it results in LTD if the temporal order of pre/postsynaptic spiking is reversed (Fig. 5).



**Fig. 5.** Spike-timing-dependent plasticity (STDP) at a synapse of the lateral perforant path on a granule cell in the dentate gyrus. **a** The arrangement of the recording electrode (*Rec.*) and stimulating electrodes (*Sti. 1*, *Sti. 2*). **b** Evoked neuronal activity by *Sti. 1* is field EPSP (*fEPSP*) activity, as it is completely blocked by the AMPA receptor antagonist DNQX. The activity evoked by *Sti. 2* is the field somatic spike (fSS), as it is insensitive to DNQX, but is completely blocked by tetrodotoxin (*TTX*). **c** LTP induction by paired *fEPSP*–*fSS* stimulation. The *upper traces* show baseline *fEPSP* activity (*left*), *fEPSP* and *fSS* during pairing (*middle*), and *fEPSP* activity after pairing (*right*) for one experiment. Note the potentiation of *fEPSP* activity after paired *fEPSP*–*fSS* stimulation with  $\Delta t = 15$  ms. The *lower plot* shows the summarized results for nine experiments, in which the  $\Delta t$  for the paired *fEPSP*–*fSS* stimulation was  $< 30$  ms. **d** LTD induction by paired *fSS*–*fEPSP* stimulation. Note the depression of *fEPSP* activity (compare the left and right *insets*) after paired *fSS*–*fEPSP* stimulation with  $\Delta t = -25$  ms (see middle *inset*). The lower plot shows the summarized results for eight experiments, in which  $\Delta t$  for the paired *fEPSP*–*fSS* stimulation was  $< -40$  ms. (From Lin et al. [25], with permission)

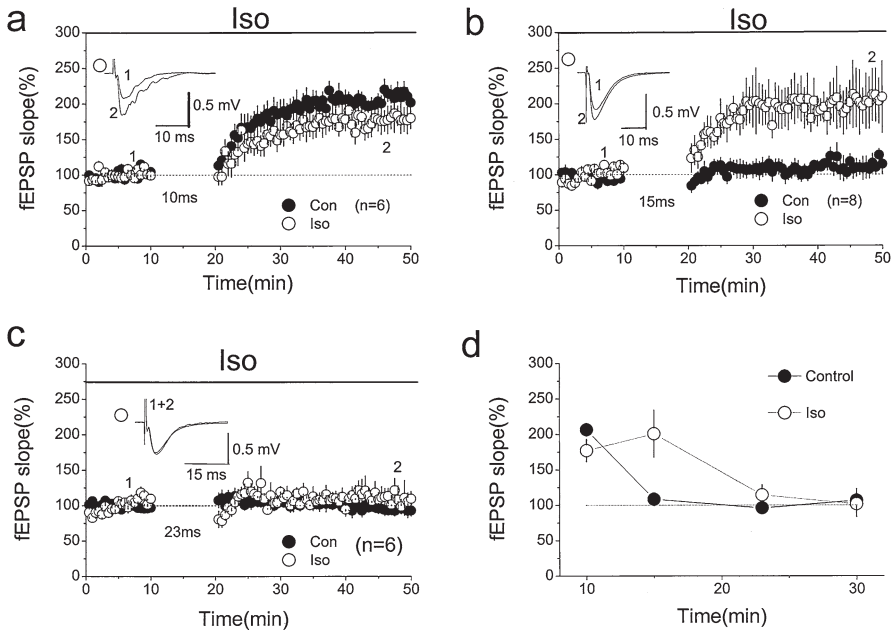




**Fig. 6.** Induction of STDP is occluded by saturated homosynaptic LTP/LTD. **a** Homosynaptic LTP induced by three trains of 100 pulses at 100 Hz (intertrain interval 30 s), repeated three times at intervals of 5 min (*arrows*); following this homosynaptic LTP, induction of LTP by paired stimulation with an interval of 10 ms is occluded. **b** LTD induced by stimulation with 900 pulses at 1 Hz; following this homosynaptic LTD, induction of LTD by paired stimulation with an interval of -10 ms is again occluded. (From Lin et al. [25], with permission)

STDP-like LTP and LTD both require activation of NMDA receptors [10, 32, 33]. Again, the voltage-dependent nature of the NMDA receptor makes it an ideal detector for the correlated pre- and postsynaptic spiking activity. Depolarization of the membrane potential by the action potential back-propagated along dendrites of postsynaptic neurons removes magnesium, which blocks the pore site of the NMDA receptor in the resting condition and allows the NMDA receptor to be activated by glutamate released presynaptically during the paired pre- and postsynaptic spiking. We have recently characterized the cellular mechanisms underlying induction of STDP at a synapse of the lateral perforant pathway on a granule cell in the dentate gyrus (Fig. 5). We found that the signaling molecules involved in STDP induction are similar to those involved in conventional LTP and LTD because the saturated synaptic potentiation or depression caused by, respectively, tetanus or low-frequency stimulation, occludes the induction of STDP (Fig. 6) [25]. Similar to the homosynaptic plasticity discussed above, STDP is also subject to modification by the NAergic system. We have reported that by acting at  $\beta$ -adrenergic receptors NE enhances STDP by increasing the time window of the pre/postsynaptic activation required for LTP induction without changing the magnitude of LTP (Fig. 7) [10].



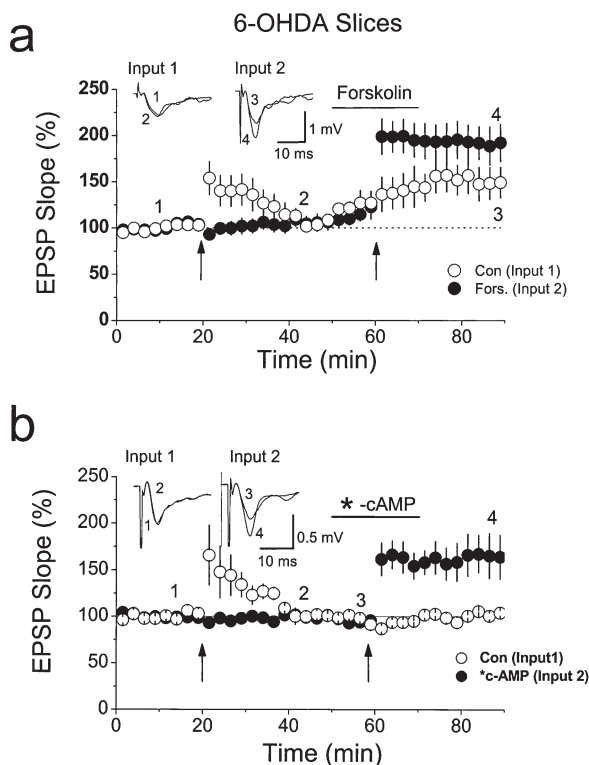


**Fig. 7.** Enhancement of STDP by activation of  $\beta$ -adrenergic receptors. **a** Application of  $1\ \mu\text{M}$  isoproterenol (*Iso*) has no significant effect on the magnitude of LTP induced using the pairing protocol with a 10-ms interval. **b** Application of *Iso* enhances LTP induction using the pairing protocol with a 15-ms interval, which does not induce LTP under control conditions. **c** Application of *Iso* has no significant effect when the interval is increased to 23 ms. **d** Summarized results for **a–c** and those using a 30-ms interval. In all of the plots, the *open circles* are results in the presence of *Iso* and the *filled circles* results from control experiments (*Con*). Note that there is no significant difference in the LTP induced in control and *Iso* experiments, except for that using a 15-ms interval. (From Lin et al. [10], with permission)

### Molecular Signaling Cascades Activated to Enhance LTP

Activation of  $\beta$ -adrenergic receptors is known to increase the cytoplasmic concentration of cyclic adenosine monophosphate (cAMP), which in turn activates cAMP-dependent protein kinase A (PKA). This signaling pathway seems to act in parallel with the signaling pathway involved in LTP induction, which requires activation of calcium/calmodulin-dependent protein kinase II (CaMKII) by calcium influx through activated NMDA receptors during tetanus [4]. However, several studies have suggested that an increase in cAMP levels in postsynaptic neurons is required for LTP induction under control conditions [34–36]. Consistent with these observations, we found that bath application of activators of Gs protein or adenylyl cyclase (AC) also restored LTP in slices from 6-OHDA-treated animals (Fig. 8) [12]. The type I and VIII ACs, which are present at high amounts in neurons, are good candidate proteins for linking these two pathways. Unlike other AC subtypes, which

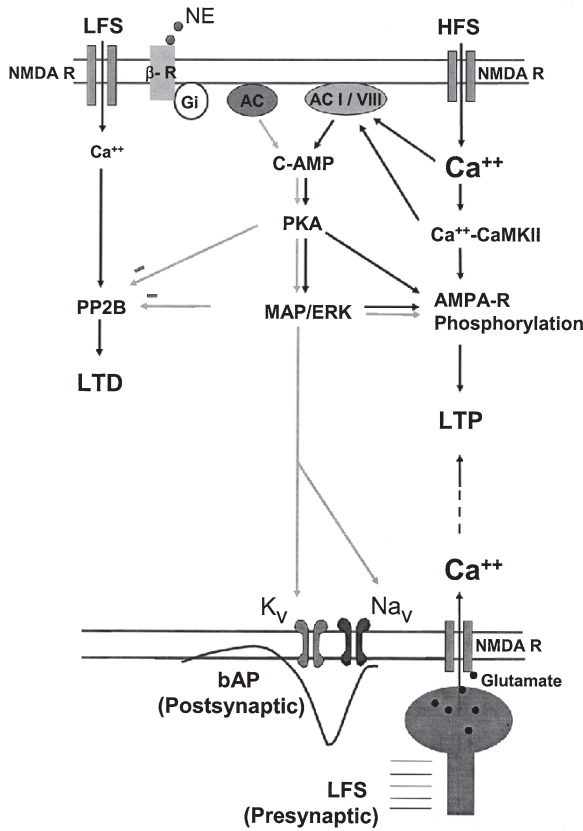
**Fig. 8.** Membrane-permeating cyclic adenosine monophosphate (*cAMP*) and protein kinase A (PKA) activators restore LTP in slices from 6-OHDA-treated rats. **a** LTP induction is restored by application of the membrane-permeating *cAMP* activator, forskolin, at Input 2. **b** Similar effect of the PKA activators 8-bromo-*cAMP* ( $n = 4$ ) and dibutyryl-*cAMP* ( $n = 4$ ) is also observed. The results of these two PKA activators are pooled. (From Yang et al. [12], with permission)



require an external signal for their activation, types I and VIII can be directly activated by CaMKII intracellularly and contribute to the *cAMP* increase in the cytoplasm [37]. Thus, the *cAMP* increase required for LTP induction might occur via activation of type I or VIII ACs by CaMKII [38, 39]. In hippocampal slices taken from type VIII AC knockout mice, induction of LTP is impaired, demonstrating the involvement of this protein in LTP induction [40].

It is likely that the permissive effect of the  $\beta$ -adrenergic receptor on homosynaptic LTP induction might be through the activation of other types of ACs downstream of the Gs proteins activated by  $\beta$ -adrenergic receptors, which in turn cause a sufficiently large increase in cytoplasmic *cAMP* for LTP induction. Therefore, cooperative activation of other types ACs by  $\beta$ -adrenergic receptors with activation of types I and VIII by NMDA receptor signaling leads to LTP induction. This could also explain why, in hippocampal slices that lack NAergic fiber innervation, strong tetanus is required for LTP induction, as more type I or VIII ACs must be activated to produce enough *cAMP* for LTP induction.

At hippocampal CA1 synapses, the expression of LTP is due to enhancement of AMPA receptor function, either by phosphorylation of existing AMPA receptors at synaptic sites or by recruitment of new AMPA receptors to the synaptic activation zone [41]. In addition to being directly involved in modulation of AMPA



**Fig. 9.** Signaling cascades involved in the enhancing effect of  $\beta$ -adrenergic receptors ( $\beta$ -R) on synaptic plasticity at CA1 synapses. *Top right* High-frequency stimulation (HFS) activates many NMDA receptors (NMDA R) and causes a large amount of calcium influx and activation of CaMKII. The activated CaMKII either phosphorylates the AMPA receptor (AMPA-R) itself, leading to LTP, or increases cytoplasmic levels of cAMP by stimulating type I or VIII ACs (AC I/VIII), which activate PKA or the more downstream effectors MAP/ERK to cause phosphorylation of AMPA receptors and LTP induction (black arrows). *Middle* Activation of  $\beta$ -adrenergic receptors increases cytoplasmic levels of cAMP to enhance LTP induction, either by stimulating type I/VIII ACs or other types of AC (gray arrows). Activation of  $\beta$ -adrenergic receptors also inhibits phosphatase 2B (PP2B) and prevents induction of LTD by low-frequency stimulation (LFS) (bottom). As regards STDP, paired pre-/postsynaptic spiking causes activation of many NMDA receptors and leads to LTP as homosynaptic LTP. In addition, the activated PKA–MAP/ERK signaling pathway also modulates voltage-dependent potassium ( $K_v$ ) and sodium ( $Na_v$ ) channels function to shape the back-propagating action potential (bAP), which in turn changes the time window for LTP induction

receptor function, the signaling molecules activated following  $\beta$ -adrenergic receptor activation must also target other ion channels or receptors to enhance the associative form of LTP or STDP. This is because  $\beta$ -adrenergic receptor activation does not affect the magnitude of LTP but increases the time window of the pre/postsynaptic activation required for LTP induction (Fig. 9) [10]. For example, one possible candidate molecule is the  $K_v4.3$  channel, which is responsible for a transient (or

A-type) potassium current reported to play an important role in controlling back-propagation of the action potential along dendrites in pyramidal neurons in the hippocampus [42]. Kv4.3 channel function is also subject to regulation by activation of  $\beta$ -adrenergic receptors through the phosphorylation of the Kv4.3 channels by PKA [42]. As a result, the time window of the pre/postsynaptic activation required for LTP induction is changed because of the changed properties of the back-propagated postsynaptic spike. Another possibility is that  $\beta$ -adrenergic receptors are located on the presynaptic terminals, and their activation results in a change in the profile of glutamate release presynaptically, which in turn changes the time window of pre/postsynaptic activation.

According to the BCM theory, during prolonged low-frequency stimulation fewer NMDA receptors are activated, there is less calcium influx into the postsynaptic cytoplasm, and phosphatase 2B (or calcineurin) is activated, rather than CaMKII, causing dephosphorylation of existing AMPA receptors and resulting in LTD [4]. Activation of the  $\beta$ -adrenergic receptor–cAMP–PKA pathway activates inhibitor I, which inhibits calcineurin (phosphatase 2B) and blocks LTD [4, 43, 44]. Interestingly, LTD induction is not affected in slices from 6-OHDA-treated animals [12], suggesting that NAergic fibers are not recruited during low-frequency stimulation, which may be due to their higher threshold for activation. Consistent with this argument, we found that STDP induction is also not affected [10], as presynaptic stimulation is given at low frequency during its induction.

## Other Considerations

If recruitment of NAergic fibers occurs only during tetanus stimulation, which does not resemble any physiological condition in the neuronal circuit, how is the NAergic system activated to modulate induction of homosynaptic plasticity and STDP under physiological conditions? Neuronal activity of LC neurons undergoes certain rhythms, which are closely related to the wake/sleep cycle of animals. They fire at highest frequency when animals are active waking, less when animals are quiet waking, and even less when animals are in non-rapid eye movement (REM) sleep and REM sleep [45, 46]. Thus, synaptic plasticity would be enhanced if an increase in synaptic activity in hippocampal circuit occurred simultaneously with an increase in the spiking rate of LC neurons; for example, synaptic plasticity might occur more easily during active waking. Sleep, however, has been suggested to play a significant role in declarative memory consolidation [47], as sleep deprivation has been shown to impair long-term synaptic plasticity significantly in the hippocampus in rats [48, 49]. These observations suggest that the temporal dissociation of NAergic activity from the neuronal circuit in the cortex and hippocampus during sleep could be essential for memory consolidation.

Like memory, LTP expression has different stages. There is an early-phase LTP (e-LTP), which usually lasts only 3–4 h after its induction and is independent

of protein synthesis. Following e-LTP is late-phase LTP (l-LTP), which can last several hours in slice preparations or even days in vivo and is dependent on protein synthesis [50, 51]. At the cellular level, e-LTP might resemble the acquisition of new memory, and the conversion of e-LTP to l-LTP might resemble memory consolidation. As discussed above, the NAergic system, acting on  $\beta$ -adrenergic receptors, may have a permissive effect on the induction of e-LTP, and it may have a similar effect on memory acquisition. In line with this argument, a behavioral study showed that coeruleocortical NAergic lesions produced by intracerebral injection of 6-OHDA impairs learning behavior in animals [52]. What about the effect of the NAergic system on l-LTP? Does it also enhance l-LTP expression? Given that sleep is important for memory consolidation, which resembles the conversion of e-LTP to l-LTP at the cellular level, and that neuronal activity of LC neurons is low during sleep, it might appear that lower endogenous levels of NE would be the ideal situation for e-LTP to convert to l-LTP. However, experimental results do not support this argument. At mossy fiber synapses, homosynaptic e-LTP and l-LTP are both enhanced by  $\beta$ -adrenergic receptor activation [17]. One important factor that should be borne in mind is that mossy fiber LTP is NMDA receptor-independent [53, 54]; furthermore, the effect of endogenous levels of NE must be taken into account. Thus, at CA1 synapses, where LTP is NMDA receptor-dependent, the role of the NAergic system on l-LTP requires further investigation.

It has been shown that slow-wave sleep and sleep spindles are possible candidate mechanisms for sleep to enhance memory directly [55]. In hippocampal slices, it is also been demonstrated that somatic spiking at theta frequency [56] or ripple complex activity can directly enhance the conversion of e-LTP to l-LTP [57]. Thus, at the cellular and molecular levels, changes in the synchronization of the neuronal spiking pattern might be a crucial factor in enhancing expression of l-LTP and memory. Thalamic neurons can change their spiking patterns and degree of synchronized firing depending on the extracellular levels of NE, and the modification of the functions of ionic channels by NE can account for the changed spiking activity [52]. If the NAergic system did have a significant effect on l-LTP, would it involve a similar mechanism and allow somatic activity-dependent modification of l-LTP? Again, this would be an interesting question to answer.

## Conclusions

A significant role of the NAergic system in modulating homosynaptic and associative forms of synaptic plasticity has been confirmed and the underlying molecular mechanism explored in detail. However, some questions remain to be answered, in particular the possible differential effects of the NAergic system on cortical plasticity during different states of brain functions, for example, during active awaking and/or sleep.

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