Mol Neurobiol (2009) 39:171–177
DOI 10.1007/s12035-009-8060-5

Long-Lasting Maintenance of Learning-Induced Enhanced Neuronal Excitability: Mechanisms and Functional Significance

Drorit Saar · Edi Barkai

Received: 1 December 2008 / Accepted: 18 February 2009 / Published online: 10 March 2009

Abstract Pyramidal neurons in the piriform cortex of olfactory discrimination trained rats show enhanced intrinsic neuronal excitability that lasts for several days after learning. Such enhanced intrinsic excitability is mediated by long-term reduction in the postburst after hyperpolarization which is generated by repetitive spike firing. The molecular machinery underlying such long-lasting modulation of intrinsic excitability, as well as its exceptional durability, is yet to be fully described. In this review, we present recent advancements that reveal the identity of the current that is modulated after learning and the second messenger system by which enhanced excitability is maintained. We also discuss the significance of such long-lasting modulation to the local network's sensitivity to noradrenaline, a major learning-relevant neuromodulator.

Keywords Olfactory learning · Pirifom cortex · Pyramidal neurons · Postburst AHP · Second messenger systems · Noradrenaline

Introduction

Learning-related cellular changes can be divided into two general groups: modifications that occur at synapses and modifications in the intrinsic properties of the neurons. While it is commonly agreed that changes in strength of connections between neurons in the relevant networks underlie memory storage, it has been pointed out that modifications in intrinsic neuronal properties may also account for learning-related behavioral changes.

D. Saar · E. Barkai (✉)
Department of Neurobiology, Faculty of Sciences,
Haifa University,
Haifa 31905, Israel
e-mail: ebarkai@research.haifa.ac.il

Learning-Induced Enhancement of Neuronal Excitability

Learning-induced enhancement in neuronal excitability has been shown in hippocampal neurons following classical conditioning of the trace eyeblink response [1, 2] and the Morris watermaze task [3] and in piriform cortex neurons following operant conditioning [4–6]. Learning specific modifications in neuronal excitability were shown also in cerebellar neurons [7] and in *Hermissenda* [8] after classical conditioning. In hippocampal and piriform cortex neurons, this enhanced excitability is manifested in reduced spike frequency adaptation in response to prolonged depolarizing current applications [1, 2, 5]. Olfactory discrimination learning also results in enhanced neuronal excitability in CA1 hippocampal neurons [9].

Neuronal adaptation in neocortical, hippocampal, and piriform cortex pyramidal neurons is modulated by medium and slow after hyperpolarizations (AHPs), generated by potassium currents, which develop following a burst of action potentials [5, 10–13]. Indeed, it was shown in hippocampal and piriform cortex pyramidal neurons that the postburst AHP amplitude is reduced after learning [1, 4].

Functional Significance of Postburst AHP Reduction

Several findings suggested that AHP reduction and its consequent enhancement in neuronal excitability are not the mechanism by which memories for specific sensory inputs or sequences of events are stored. Rather, it may be the mechanism that enables neuronal ensembles to enter into a

state which may be best termed "learning mode". This state lasts for up to several days and its behavioral manifestation is enhanced learning capability in tasks that depend on these particular neuronal ensembles. Specifically, enhanced neuronal excitability sets a time window in which most neurons in the relevant neuronal network are more excitable, and thus, activity-dependent synaptic modifications are more likely to occur [1, 4]. The main evidences supporting this notion are:

(a) The averaged AHP amplitude in neurons from hippocampus and piriform cortex tends to return back to its initial value within days when training is suspended. This recovery is not accompanied by memory loss. However, rule learning (manifested as the enhanced ability to acquire new memories rapidly and efficiently) is strongly correlated with reduced postburst AHP; return of AHP to its initial value is accompanied by reduced learning capability.
(b) Before olfactory training, application of a cholinergic agent reduces the postburst AHP and blocking cholinergic activity delays rule learning. However, once rule learning is established, acetylcholine's ability to affect the AHP is abolished and it also does not affect further acquisition of memories [5].
(c) Learning impairment in aged animals is accompanied by enhanced postburst AHP [14].
(d) LTP is more readily induced when the AHP is reduced [15, 16]. Moreover, learning-induced postburst AHP reduction in the piriform cortex occurs 2 days before enhanced synaptic connectivity appears [17–19].
(e) Application of apamin, a venom that reduces the AHP by blocking the I_{AHP} current, enhances hippocampal-dependent memory encoding, but not retention [20].
(f) Finally, in a recent study, it was shown that in the process of olfactory discrimination learning the postburst is reduced and neuronal excitability is transiently enhanced in CA1 pyramidal neurons, while synaptic transmission remains at its control value. Such olfactory learning-induced increased excitability in hippocampal neurons enhances the rats' learning capability in another hippocampus-dependent task, the Morris water maze [9]. These evidence suggest that enhanced excitability of CA1 neurons may serve as a mechanism for generalized enhancement of hippocampus-dependent learning capability.

Which potassium current(s) is modified after learning? How are such modifications maintained for periods of days after training completion? How do such modifications affect the responses to learning-relevant neuromodulators? This review aims to describe the partial answers we currently have to these intriguing questions.

Learning-Induced Reduction in Postburst AHP Is Caused by Reduction in the sI_{AHP}

The potassium currents underlying the postburst AHP have been studied most extensively in hippocampal neurons. They have been characterized based on their latency from the action potentials, their duration, and their pharmacological properties. Five such currents are now identified: the voltage-dependent muscarin-sensitive I_M, the calcium and voltage-dependent I_C, the apamin-sensitive calcium-dependent I_{AHP}, and the apamin-insensitive calcium-dependent sI_{AHP} [21–24].

Several studies indicate that the learning-induced reduction in neuronal adaptation and in AHP amplitude results from reduction in one or more Ca^{2+}-dependent potassium currents [5, 25, 26]. Three such currents could have been potentially affected: the I_C which contributes to the fast AHP, the apamin-sensitive I_{AHP} which is thought to underlie the part of the medium AHP, and the apamin-insensitive sI_{AHP} which is thought to underlie the slow AHP [21, 22–24]. The I_C is not modified after learning [1, 5, 25]. Thus, the I_{AHP} and the sI_{AHP} remain as the two potassium currents most likely to be affected by learning.

The I_{AHP} is mediated by small conductance Ca^{2+}-activated K^+ channels (SK; for review, see [27]). Three SK channels genes (SK1, SK2, and SK3) are expressed in the brain [28]. The apamin-sensitive portion of the postburst AHP is thought to be mediated by the SK2 and the SK3 channels [24, 27, 28], while SK1 channels have a significantly lower sensitivity to apamin. The identity of the channel that mediates the sI_{AHP} is yet unknown [27].

To examine whether the reduction in postburst AHP amplitude is mediated by reduction in the I_{AHP}, we applied its specific blocker apamin [29]. In piriform cortex neurons, the postburst AHP has a considerably shorter duration than in hippocampal neurons, and the two types of AHP may overlap [5].

Whenever the medium and slow AHP were clearly distinguishable, apamin affected only the first postburst negative peak (Fig. 1a). More frequently, the medium and the slow AHPs did not have separate peaks. In these occasions, apamin reduced the amplitude of the single peak (Fig. 1b). Apamin significantly reduced the AHP in neurons from all groups; in neuron from trained rats, the averaged AHP value decreased from 4.98 mV±1.70 (n=32) in normal slice Ringer's solution (NSR) to 2.76 mV±1.81 (n=20) in apamin (p<0.01). In neuron from naive rats, the averaged AHP value decreased from 6.76 mV±1.82 (n=24) in NSR to 4.73 mV±0.92 (n=9) in apamin (p<0.01), and in neurons from pseudotrained rats, the averaged AHP value decreased from 6.78±1.80 mV (n=23) in NSR to 4.76 mV± 2.34 (n=16) in apamin (p<0.01). Thus, in the presence of

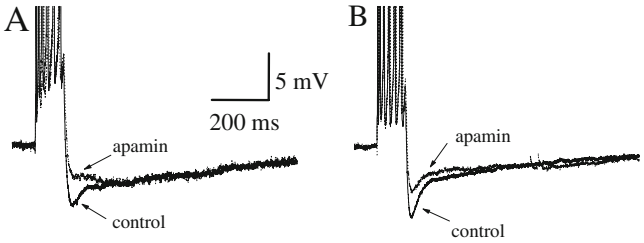

Fig. 1 Apamin reduces the medium AHP in piriform cortex neurons. Neurons were held at membrane potential of −60 mV and the postburst AHP was generated by a 100-ms depolarizing current step injection via the recording electrode, with intensity sufficient to generate a train of six action potentials. **a** When the medium and the slow AHPs' peaks were clearly distinguishable, apamin affected only the amplitude of the first peak. **b** In the more common type of response, when the medium and slow AHPs overlapped, the amplitude of the single apparent peak was reduced by apamin

apamin, the difference in AHP amplitude between neurons from trained rats and controls was maintained (Fig. 2a), and the proportion of the AHP amplitude reduced by apamin was greater in neurons from trained rats (Fig. 2b). The contribution of the apamin-sensitive portion of the AHP to the AHP amplitude was calculated by subtracting for each cell the amplitude of the AHP in the presence of apamin from the averaged amplitude of AHP in its group, in NSR. The averaged value of the apamin-sensitive part of the AHP was similar in all groups (2.03 mV+1.81 in naïve, 2.22 mV+1.69 in trained, and 2.12 mV+1.80 in pseudotrained), indicating that this part remains intact after olfactory learning. These data suggest that learning induced enhancement in neuronal excitability is mediated by long-term reduction of the slow AHP.

Role of Second Messenger Systems in Maintaining Prolonged AHP Reduction

How are such modifications maintained for periods of days after training completion? The sI_{AHP} is reduced by protein kinase C (PKC)-dependent activation of glutamate-mediated kainate receptors [30, 31]. Accordingly, olfactory learning-induced postburst AHP reduction is mediated by persistent PKC activation [32]. The mechanism by which such long-lasting PKC-dependent AHP reduction persists was unknown until recently.

A wide range of studies testify to the importance for extracellular-signal regulated kinase (ERK) in memory formation across many species and brain areas (reviewed in [33]). In a time frame of minutes and up to a few hours, ERK activation increases transiently after acquisition of fear conditioning [34, 35], taste learning [36], and water maze training [37]. ERK is crucially involved in both short- and long-term modulation of synaptic transmission [34, 38–42]. Such short-term ERK-dependent modifications may be due to enhancement of intrinsic neuronal excitability by modulating the I_A potassium current [43, 44].

In a recent study [45], we examined whether the long-lasting reduction in postburst AHP amplitude requires also persistent ERK activation, by testing the effect of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK; the obligatory ERK activator) blockers on the postburst AHP and neuronal excitability before and after olfactory learning. The MEK inhibitors, PD98059 (38 μM) and UO126 (30 μM), significantly increased the AHP amplitude in neurons from trained rats only. In neurons from naïve and pseudotrained rats, the averaged AHP value was not affected by these agents. In neurons from trained rats, the averaged AHP value was significantly increased from 5.57 mV±1.80 (n=48) in NSR to 6.89 mV±2.51 (n=12) in PD98059 (p<0.05). For naives, the averaged values were 7.04 mV±1.89 (n=21) in NSR and 6.34 mV± 1.20 (n=11) in PD98059. For pseudotrained, the averaged values were 7.94 mV±1.72 (n=26) in NSR and 7.18±1.89 (n=13) in PD98059. Two typical examples for the different effect of PD98059 on neurons from a pseudotrained and a trained rat are shown in Fig. 3a, b. Following PD98059 application, the difference in AHP amplitude between neurons from trained rats and controls was abolished (Fig. 3c). Similar results were obtained with the second specific MEK inhibitor, UO126. In neurons from trained rats, the averaged AHP value was significantly increased to 7.56 mV±1.38 (n=7; p<0.05). In neurons from naives, the averaged value in UO126 was 7.81 mV±1.11 (n=5), and in neurons pseudotrained, the averaged value in UO126 was

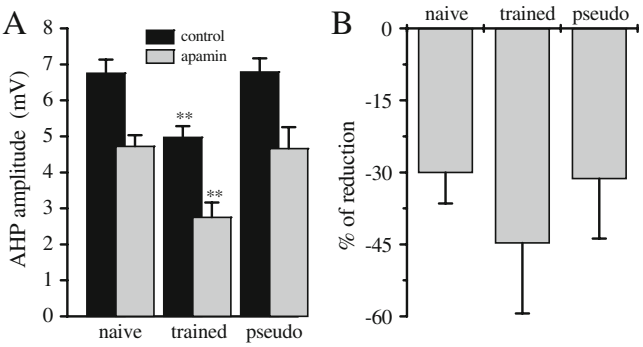

Fig. 2 Apamin affects the AHPs in neurons from the three groups to the same extent. **a** Averaged AHP amplitude in neurons from the three groups recorded in NSR and after apamin application. Averaged AHP amplitude in trained rats is significantly smaller compared to naive and pseudotrained rats (**p<0.01). This difference is maintained after apamin application. AHP in NSR was measured in neurons from seven naive rats, eight trained rats, and seven pseudotrained rats. AHP in apamin was measured in neurons from five naive rats, eight trained rats, and eight pseudotrained rats. Values represent mean ± standard error. **b** The percentage of the AHP amplitude reduced by apamin application is greater in neurons from trained rats

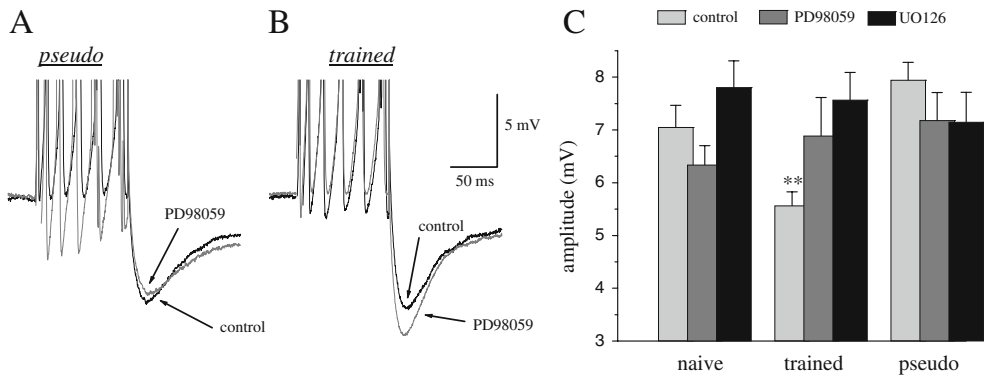

Fig. 3 MEK inhibitors increase the AHP in neurons from trained rats only. AHP measurements in piriform cortex neurons. Neurons were held at membrane potential of −60 mV and the postburst AHP was generated by a 100-ms depolarizing current step injection via the recording electrode, with intensity sufficient to generate a train of six action potentials. While PD98059 application had no effect on a neuron from a pseudotrained rat (**a**), it enhanced the AHP in a neuron from a trained rat (**b**). **c** Averaged AHP amplitude in neurons from the three groups recorded in NSR, under PD98059 and under UO126. Averaged AHP amplitude in trained rats is significantly smaller compared to naive and pseudotrained rats (**$p<0.01$). This difference is abolished after PD98059 or UO126 application. AHP in NSR was measured in neurons from nine naive rats, 15 trained rats, and ten pseudotrained rats. AHP in PD98059 was measured in neurons from five naive rats, eight trained rats, and six pseudotrained rats. AHP in PD98059 was measured in neurons from four naive rats, five trained rats, and five pseudotrained rats. Values represent mean ± standard error

7.15 mV±1.48 (n=7). These values were not different from the averaged values recorded in NSR (Fig. 3c).

MEK Inhibitors Reduce Neuronal Excitability in Neurons from Trained Rats Only

A direct consequence of the learning-induced AHP reduction is enhanced neuronal excitability. Such enhancement is manifested by increased frequency of repetitive firing in response to a prolonged depolarizing pulse applied via the recording electrode [5, 6]. To examine whether ERK activation also underlies the maintenance of such learning-induced neuronal excitability (as would be expect form its effect on the AHP), we compared the effect of its inhibitor on the number of spikes generated by a 1-s depolarizing pulse, with stimulus intensity of $I_{th}\times 2$.

As previously described [5], the averaged number of action potentials evoked in neurons from trained rats in NSR (21.9±9.1, n=30) was significantly ($p<0.05$) higher compared with neurons from pseudotrained rats (16.9±7.7, n=17). As shown in Fig. 4, application of PD98059 reduced significantly ($p<0.01$) the averaged number of spikes in neurons from trained rats (13.1±7.0, n=18), but had no effect on the averaged value in neurons from pseudotrained rats (14.2±7.7, n=13). Similar results were obtained with UO126. In neurons from trained rats, the

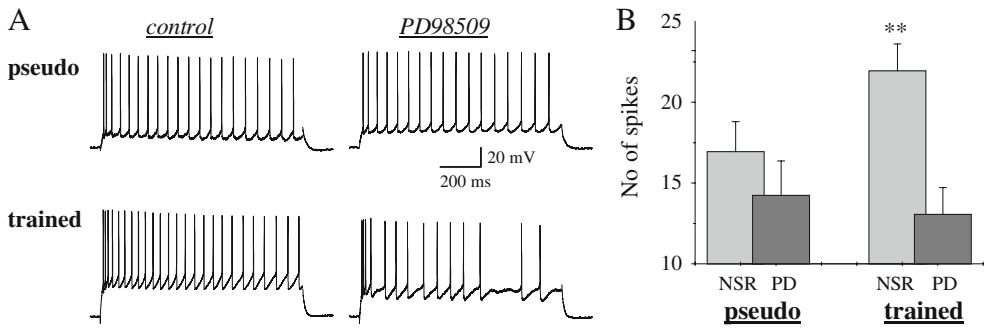

Fig. 4 PD98059 reduced neuronal excitability in neurons from trained rats. **a** Examples for the effect of PD98059 on repetitive spike firing in a neuron from a pseudotrained and a neuron from a trained rat. With stimulus intensity of $I_{th}\times 2$, a 1-s depolarizing pulse generates repetitive firing throughout the stimulation period. While PD98059 has no effect on the pseudotrained neuron, repetitive firing of the trained neuron is significantly suppressed by the same agent. **b** While PD98059 application has no effect on the number of spikes evoked in neurons from pseudotrained rats, it reduces significantly the averaged number of spikes in neurons from trained rats (**$p<0.001$). Consequently, the difference in spike numbers between neurons from the pseudotrained and trained groups disappears in the presence of the ERK inhibitor. Number of spikes in NSR was measured in neurons from eight pseudotrained and 11 trained rats. Number of spikes in PD98059 was measured in neurons from five pseudotrained and seven trained rats. Stimulus intensity was kept constant in each cell throughout the recording period. Values represent mean ± standard error

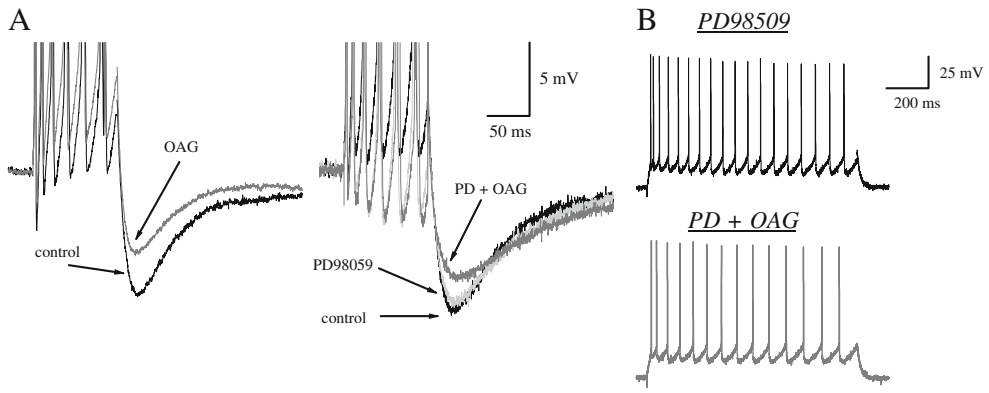

Fig. 5 PKC activation does not reduce the AHP amplitude in the presence of the ERK inhibitor. **a** An example of the effect of the PKC activator, OAG, on a neuron taken from a naive rat in control conditions (*left trace*) and the lack of such effect on another neuron from a naïve rat in the presence of PD98059 (*right trace*). **b** According to its lack of effect on the AHP, OAG does not enhance the firing rate of a naïve neuron in the presence of PD98059

averaged number of spikes was reduced to 17.0 (n=6). In neurons from naives, the averaged value in UO126 was 17.4 (n=5) and in neurons pseudotrained 18.2 (n=8). Thus, the difference in repetitive spike firing was also abolished by UO126.

PKC-Induced AHP Reduction Is ERK Dependent

Recordings performed in pirifom cortex neurons after olfactory learning show that the PKC blocker, GF-109203X, increases the AHP in neurons from trained rats only and that the PKC activator, OAG, reduced the AHP in neurons from control groups more than in neurons from trained rats [32]. In particular, the PKC activator reduced the AHP in neurons from naïve rats by 40% [32]. We hypothesized that if PKC-induced reduction of the AHP is mediated via ERK activation, application of PD98059 should block its effect [45]. As previously shown [32], the PKC activator OAG (10 μM) reduces significantly the postburst AHP in neurons from naïve rats (from 7.2 mV± 2.4 in control conditions to 5.1 mV±0.54 after OAG application (n=6)). An example of OAG effect on such a naïve neuron is shown in Fig. 5a. In sharp contrast, in the presence of the MEK inhibitor, the PKC activator did not have a significant effect of the averaged AHP amplitude in neurons from naïve rats (6.20 mV±2.35, n=8 in PD98059, compared with 5.46 mV±1.36 in the same eight neurons after OAG application) and accordingly, it also did not affect the repetitive spike firing (Fig. 5a, b).

Learning-Induced Modulation of Noradrenaline's Effect on Neuronal Excitability

Noradrenaline (NE) has several actions in target structures that would suggest a role in learning and memory processes, particularly in odor discrimination tasks [46–51]. NE was

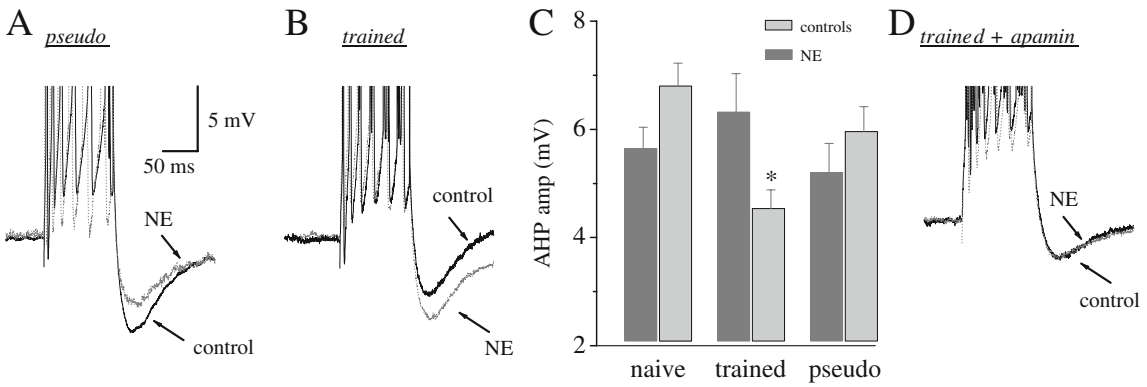

Fig. 6 NE enhances the AHP amplitude in neurons from trained rats only. **a** Averaged postburst AHP in control conditions and in NE are shown in two neurons from pseudotrained rats. In these neurons, NE reduces the AHP, as previously reported. **b** In neurons from trained rats, the effect of NE on the AHP is reversed; NE significantly increases the averaged postburst AHP amplitude. **c** The difference in AHP between the different groups is abolished by application of NE. AHP was measured in neurons taken from 15 naive rats, seven trained rats, and five pseudotrained rats. Values represent mean ± standard error. **d** In the presence of apamin, NE loses its ability to enhance the AHP in a neuron from a trained rat

shown to enhance neuronal excitability [11, 24, 52]. This action is mediated by reducing the sI_{AHP} conductance, while the I_{AHP} is enhanced [24].

That I_{AHP}/sI_{AHP} conductances ratio is increased after learning may modulate the effect of NE on neuronal excitability, to the point where it would enhance the postburst AHP instead of reducing it. Consequently, NE may play different roles in neuronal excitability prior to and after learning.

Indeed, we have shown that NE application has different effects on neurons from trained rats and controls [29]. NE (10 μM) application to neurons from control rats reduced significantly the amplitude of the postburst AHP ($p<0.05$). The average AHP amplitude with NE was 5.64 mV±1.96 ($n=24$) in neurons from naïve rats and 5.20 mV±1.89 ($n=12$) in neurons from pseudotrained rats. The same treatment increased significantly ($p<0.01$) the averaged AHP in neurons from trained rats to 6.32 mV±2.65 ($n=14$). As a result of these opposing effects, NE abolished the difference in the AHP amplitudes between neurons from trained and control rats (Fig. 6a–c).

To examine whether the enhancing effect of NE on the postburst AHP after learning results from increasing the I_{AHP} conductance, we tested its effect on neurons from trained rats, in the presence of apamin. In these conditions, NE did not enhance the AHP in any of the four tested neurons (Fig. 6d). The averaged value of the AHP in apamin was 2.7±1.6 mV and in apamin + NE was 3.3±1.7 mV.

What functional significance may such a modification in NE effect on neuronal excitability have? While it is commonly accepted that synaptic strengthening is involved in learning and memory processes, it was pointed out by several studies that a compensation mechanism that would prevent over-strengthening of synaptic connections which are not relevant to memory storage should also be activated [53, 54]. Such a mechanism would prevent runaway synaptic enhancement, thus preventing a situation in which the neuronal network becomes hyperexcitable, loses its ability to store memories, and responds with an epileptic-like activity to relatively mild stimulations [53, 55]. Thus, after olfactory learning, NE may act to counterbalance these modifications and preserve the piriform cortex ability to subserve olfactory learning by increasing the threshold for inducing neuronal activation to the point where synaptic changes are induced.

Conclusions

Our data show that learning-induced enhancement of neuronal excitability is not the result of reduction in the I_{AHP} current. Thus, it is probably mediated by reduction in conductance of the other calcium-dependent potassium current, the sI_{AHP}.

Long-term maintenance of enhanced intrinsic excitability is dependent on persistent PKC and ERK activation. After learning, the effect of NE on neuronal excitability is reversed. The change in NE's effect after learning may act to counterbalance learning-induced hyperexcitability and preserve the piriform cortex ability to subserve olfactory learning.

References

1. Moyer JR, Thompson LT, Disterhoft JF (1996) Trace eyeblink conditioning increases CA1 excitability in a transient and learning specific manner. J Neurosci 16:5536–5546
2. Thompson LT, Moyer JR, Disterhoft JF (1996) Transient changes in excitability of Rabbit CA3 neurons with a time course appropriate to support memory consolidation. J Neurophysiol 76:1836–1849
3. Oh MM, Kuo AG, Wu WW, Sametsky EA, Disterhoft JF (2003) Watermaze learning enhances excitability of CA1 pyramidal neurons. J Neurophysiol 90(4):2171–2179
4. Saar D, Grossman Y, Barkai E (1998) Reduced after-hyperpolarization in rat piriform cortex pyramidal neurons is associated with increased learning capability during operant conditioning. Eur J Neurosci 10:1518–1523
5. Saar D, Grossman Y, Barkai E (2001) Long lasting cholinergic modulation underlies rule learning in rats. J Neuorsci 21(4):1385–1392
6. Saar D, Barkai E (2003) Long-term modifications in intrinsic neuronal properties and rule learning in rats. Eur J Neurosci 17:2727–2734
7. Schreurs BG, Gusev PA, Tomsic D, Alkon DL, Shi T (1998) ntracellular correlates of acquisition and long-term memory of classical conditioning in Purkinje cell dendrites in slices of rabbit cerebellar lobule HVI. J Neurosci 18(14):5498–5507
8. Alkon DL, Nelson TJ, Zhao W, Cavallaro S (1998) Time domains of neuronal Ca^{2+} signaling and associative memory: steps through a calexcitin, ryanodine receptor, K^+ channel cascade. TINS 21 (12):529–537
9. Zelcer I, Cohen H, Richter-Levin G, Lebiosn T, Grossberger T, Barkai E (2006) A cellular correlate of learning-induced meta-plasticity in the hippocampus. Cerebral Cortex 16(4):460–468
10. Schwindt PC, Spain WJ, Foehring RC, Chubb MC, Crill WE (1988) Slow conductances in neurons from cat sensorimotor cortex in-vitro and their role in slow excitability changes. J Neurophysiol 59(2):450–467
11. Madison DV, Nicoll RA (1984) Voltage clamp analysis of cholinergic action in the hippocampus. J Physiol 354:319–331
12. Constanti A, Sim JA (1987) Calcium-dependent potassium conductance in guinea-pig olfactory cortex neurons in vitro. J Physiol 387:173–194
13. Barkai E, Hasselmo ME (1994) Modulation of the input/output function of rat piriform cortex pyramidal cells. J Neurophysiol 72(2):644–658
14. Moyer JR, Power JM, Thompson LT, Disterhoft JF (2000) Increased excitability of aged rabbit CA1 neurons after trace eyeblink conditioning. J Neurosci 20(14):5476–5482
15. Sah P, Bekkers JM (1996) Apical dendritic location of slow afterhyperpolarization current in hippocampal pyramidal neurons: implications for the integration of long-term potentiation. J Neurosci 16(15):4537–4542
16. Norris CM, Halpain S, Foster TC (1998) Reversal of age-related alterations in synaptic plasticity by blockade of L-type channels. J Neurosci 18(9):3171–3179
17. Barkai E, Saar D (2001) Cellular correlates of olfactory learning in the rat piriform cortex. Rev Neurosci 12(2):111–120

18. Saar D, Grossman Y, Barkai E (1999) Reduced synaptic facilitation between pyramidal neurons in the piriform cortex after odor learning. J Neurosci 19(19):8616–8622
19. Knafo S, Grossman Y, Barkai E, Benshalom G (2001) Increased spine density on piriform cortex pyramidal neurons after odor learning. Eur J Neurosci 13:633–638
20. Stackman RW, Hammond RS, Linardatos E, Gerlach A, Maylie J, Adelman JP, Tzounopoulos T (2002) Small conductance Ca^{2+}-activated K^+ channels modulate synaptic plasticity and memory encoding. J Neurosci 22(23):10163–10171
21. Storm JF (1989) An after-hyperpolarization of medium duration in rat hippocampal pyramidal cells. J Physiol 409:171–190
22. Sah P (1996) Ca^{2+}-activated K^+ currents in neurons: types, physiological roles and modulation. Trends Neurosci 19(4):150–154
23. Gasparini S, DiFrancesco D (1999) Action of serotonin on the hyperpolarization-activated cation current (I_h) in rat CA1 hippocampal neurons. Eur J Neurosci 11:3093–3100
24. Stocker M, Krause M, Pedarzani P (1999) An apamin-sensitive Ca^+-activated k^+ current in hippocampal pyramidal neurons. Proc Natl Acad Sci U S A 96:4662–4667
25. Sanchez-Andres JV, Alkon DL (1991) Voltage-clamp analysis of the effects of classical conditioning on the hippocampus. J Neurophysiol 65:796–807
26. Power JM, Wu WW, Sametsky E, Oh MM, Disterhoft JF (2002) Age-related enhancement of the slow outward calcium-activated potassium current in hippocampal CA1 pyramidal neurons in vitro. J Neurosci 22(16):7234–7243
27. Sah P, Faber ES (2002) Channels underlying neuronal calcium-activated potassium currents. Prog Neurobiol 66(5):345–353
28. Sailer CA, Hu H, Kaufmann WA, Trieb M, Schwarzer C, Storm JF, Knaus HG (2002) Regional differences in distribution and functional expression of small-conductance Ca^{2+}-activated K^+ channels in rat brain. J Neurosci 22(22):9698–9707
29. Brosh I, Rosenblum K, Barkai E (2006) Learning-induced reversal of the effect of noradrenalin on the postburst AHP. J Neurophysiol 96:1728–1733
30. Melyan Z, Wheal HV, Lancaster B (2002) Metabotropic-mediated kainate receptor regulation of IsAHP and excitability in pyramidal cells. Neuron 34(1):107–114
31. Melyan Z, Lancaster B, Wheal HV (2004) Metabotropic regulation of intrinsic excitability by synaptic activation of kainate receptors. J Neurosci 24(19):4530–4534
32. Seroussi Y, Brosh I, Barkai E (2002) Learning-induced reduction in post-burst after-hyperpolarization (AHP) is mediated by activation of PKC. Eur J Neurosci 16(5):965–969
33. Adams JP, Sweatt JD (2002) Molecular psychology: roles for the ERK MAP kinase cascade in memory. Annu Rev Pharmacol Toxicol 42:135–163
34. Atkins CM, Selcher JC, Petraitis JJ, Trzaskos JM, Sweatt JD (1998) The MAPK cascade is required for mammalian associative learning. Nat Neurosci 1:602–609
35. Schafe GE, Atkins CM, Swank MW, Bauer EP, Sweatt JD, LeDoux JE (2000) Activation of ERK/MAP kinase in the amygdala is required for memory consolidation of pavlovian fear conditioning. J Neurosci 20:8177–8187
36. Berman DE, Hazvi S, Rosenblum K, Seger R, Dudai Y (1998) Specific and differential activation of mitogen-activated protein kinase cascades by unfamiliar taste in the insular cortex of the behaving rat. J Neurosci 18:10037–10044
37. Blum S, Moore AN, Adams F, Dash PK (1999) A mitogen-activated protein kinase cascade in the CA1/CA2 subfield of the dorsal hippocampus is essential for long-term spatial memory. J Neurosci 19:3535–3544
38. English JD, Sweatt JD (1996) Activation of p42 mitogen-activated protein kinase in hippocampal long term potentiation. J Biol Chem 271(40):24329–24332
39. English JD, Sweatt JD (1997) A requirement for the mitogen-activated protein kinase cascade in hippocampal long term potentiation. J Biol Chem 272(31):19103–19106
40. Rosenblum K, Futter M, Jones M, Hulme EC, Bliss TV (2000) ERKI/II regulation by the muscarinic acetylcholine receptors in neurons. J Neurosci 20:977–985
41. Rosenblum K, Futter M, Voss K, Erent M, Skehel PA, French P, Obosi L, Jones MW, Bliss TV (2002) The role of extracellular regulated kinases I/II in late-phase long-term potentiation. J Neurosci 22:5432–5441
42. Thomas GM, Huganir RL (2004) MAPK cascade signalling and synaptic plasticity. Nat Rev Neurosci 5:173–183
43. Sheng M, Tsaur ML, Jan YN, Jan LY (1992) Subcellular segregation of two A-type K^+ channel proteins in rat central neurons. Neuron 9:271–284
44. Yuan LL, Adams JP, Swank M, Sweatt JD, Johnston D (2002) Protein kinase modulation of dendritic K^+ channels in hippocampus involves a mitogen-activated protein kinase pathway. J Neurosci 22:4860–4868
45. Cohen-Matsliah S, Brosh I, Rosenblum K, Barkai E (2007) A novel role for ERK in maintaining long-term memory-relevant excitability changes. J Neurosci 27:12584–12589
46. Gervais R, Pager J (1983) Olfactory bulb excitability selectively modified in behaving rats after local 6-hydroxydopamine treatment. Behav Brain Res 9(2):165–179
47. Przybyslawski J, Roullet P, Sara SJ (1999) Attenuation of emotional and nonemotional memories after their reactivation: role of beta adrenergic receptors. J Neurosci 19(15):6623–6628
48. Hasselmo ME, Linster C, Patil M, Ma D, Cekic M (1997) Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. J Neurophysiol 77(6):3326–3339
49. Sullivan RM, Wilson DA (1991) Neural correlates of conditioned odor avoidance in infant rats. Behav Neurosci 105:307–312
50. Sullivan RM, Wilson DA (1993) Role of the amygdala complex in early olfactory associative learning. Behav Neurosci 107:254–263
51. Sullivan RM, Wilson DA (1994) The locus-coeruleus, norepinephrine and memory in newborns. Brain Res Bull 35:467–472
52. Foehring RC, Schwindt PC, Crill WE (1989) Norepinephrine selectively reduces slow Ca- and Na-mediated K currents in cat neocortical neurons. J Neurophysiol 61(2):245–256
53. Barkai E, Bergman RE, Horwitz G, Hasselmo ME (1994) Modulation of associative memory function in a biophysical simulation of rat piriform cortex. J Neurophysiol 72(2):659–677
54. Quinlan E, Lebel D, Brosh I, Barkai E (2004) A molecular mechanism for stabilization of learning-induced synaptic modifications. Neuron 41:185–192
55. Hasselmo ME, Barkai E (1995) Cholinergic modulation of activity-dependent synaptic plasticity in the piriform cortex. J Neurosci 15(10):6592–6604