Persistent ERK activation maintains learning-induced long-lasting modulation of synaptic connectivity

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Pyramidal neurons in the piriform cortex from olfactory-discrimination (OD) trained rats undergo synaptic modifications that last for days after learning. A particularly intriguing modification is reduced paired-pulse facilitation (PPF) in the synapses interconnecting these cells; a phenomenon thought to reflect enhanced synaptic release. The molecular machinery underlying this prolonged physiological modulation of synaptic connectivity is yet to be described. We have recently shown that extracellular regulated kinase (ERK) pathway and protein kinase C (PKC) are also required for learning-induced enhancement of intrinsic neuronal excitability. Here we examine whether these signal-transduction cascades are instrumental for the learning-induced, long-lasting PPF reduction. Days after learning completion, PD98059, a selective inhibitor of MEK, the upstream kinase of ERK, increased PPF in neurons from trained, but not in neurons from naïve and pseudo-trained rats. Consequently, the differences in PPF between neurons from trained rats and controls were abolished. The level of activated ERK in synaptoneurosomes was significantly higher in piriform cortex samples prepared from trained rats. Notably, ERK activation revealed that PPF reduction lags behind ERK activation by 2 d. Similarly, the PKC blocker, GF-109203X, enhanced PPF in neurons from trained rats only, thus abolishing the differences between groups. Interestingly, the PKC activator, OAG, had no effect, indicating that PKC activation is required, but not sufficient for long-lasting PPF reduction. Our data show that persistent ERK activation has a key role in maintaining learning-induced PPF reduction for days. This time frame of compartmental ERK-dependent synaptic modulation suggests a novel role for ERK in cortical function.

Results

Recordings in neurons from trained and pseudo-trained rats were performed 3 d after the last training session, when learning-related reduction in paired-pulse facilitation (PPF) first appears (Saar et al. 1999). In control saline Ringer solution (NSR), the averaged PPF in neurons from trained rats was significantly smaller compared with the averaged PPF values in neurons from pseudo-trained and naïve rats (Fig. 1), confirming our earlier report (Saar et al. 1999). Resting membrane potential ($-79.3 \pm 7.3 \, \text{mV}$, $n = 34$ in naïve, $-79.2 \pm 7.0 \, \text{mV}$, $n = 49$ in trained, and $-82.0 \pm 7.4 \, \text{mV}$, $n = 34$ in pseudo-trained) and input resistance ($33.4 \, \text{Mohms} \pm 12.7 \, \text{Mohms}$, $n = 24$ in naïve, $30.0 \pm 8.4 \, \text{Mohms}$, $n = 30$ in pseudo-trained) were not significantly different between the groups ($p > 0.05$).
Learning-induced long-lasting PPF reduction is not maintained after ERK inhibition

To examine whether the prolonged reduction in PPF is maintained by ERK activation, we applied the MEK-specific inhibitor PD98059 (38 µM). PD98059 significantly increased the PPF value in neurons from trained rats only. In neurons from naive and pseudo-trained rats the averaged PPF value was not affected by the inhibitor. Two typical examples of the different effect of PD98059 on neurons from a pseudo-trained and a trained rat are shown in Figure 1A. In neurons from trained rats the averaged PPF was significantly increased from 1.23 ± 0.15 (n = 19) in NSR to 1.42 ± 0.25 (n = 9) in PD98059 (P < 0.05). For naïves, the averaged values were 1.40 ± 0.31, (n = 18) in NSR and 1.31 ± 0.28 (n = 18) in PD98059. For pseudo-trained, the averaged values were 1.38 ± 0.15 (n = 18) in NSR and 1.50 ± 0.19 (n = 11) in PD98059.

Although the MEK inhibitor seemed to have a tendency to affect neurons from the pseudo-trained group too, the difference in PPF before and after PD98059 application stop short of being significant (P = 0.1). Following PD98059, no differences in PPF were observed between neurons of learning and control rats (Fig. 1B). These results further suggest that ERK activation is necessary for the maintenance of learning-relevant enhancement in synaptic transmission when it first appears.

Olfactory-discrimination learning induces long-term ERK activation in synaptoneurosomes

Since learning-induced enhancement of synaptic transmission is dependent on persistent ERK activation, we hypothesized that learning should be accompanied by an increased ERK phosphorylation in the synapses. Using Western blot analysis, we measured the total amount of ERK and its phosphorylation state as a measure of activation in the three experimental groups. The total amount of ERKII (normalized to naïve) was similar between the groups (1.00 ± 0.28 [n = 30] for naïves, 1.01 ± 0.31 [n = 25] for trained, and 1.03 ± 0.22 [n = 24] for pseudo-trained). However, as shown in Figure 2A, the level of phosphorylated ERK significantly increased after learning compared with naïve, but not with pseudo-trained (averaged values of pERK/ERK were 1.02 ± 0.18 [n = 27] for naïves, 1.27 ± 0.40 [n = 28] for trained, and 1.09 ± 0.34 [n = 25] for pseudo-trained) (Fig. 2B). The level of activated ERK in the pseudo-trained group had an intermediate averaged value between trained and the naïve groups, and was not significantly different from either (P = 0.33 for pseudo vs. naïves and P = 0.09 for pseudo vs. trained). Comparison of the

Figure 1. Learning-induced PPF reduction is dependent on ERK activation. (A) PPF was measured in response to two stimuli, with an interstimulus interval of 50 msec. Neuron was recorded at membrane potential of −80 mV. Each trace is a digital average of 10 responses to stimuli applied at 0.1 Hz. While PD98059 has no effect on PPF on a neuron from a pseudo-trained animal (upper trace), it increases PPF in a neuron from a trained rat (bottom trace). (B) As previously reported (Saar et al. 1999), the mean PPF in neurons from trained rats was significantly smaller compared with that in neurons from naïve and pseudo-trained. PD98059 application enhanced PPF in the trained group only, as result of which the difference between the trained and the two control groups was abolished. PPF in NSR was measured in 18 neurons from nine naïve rats, 19 neurons from 11 trained rats, and 18 neurons from 11 pseudo-trained rats. PPF in PD98059 was measured in 18 neurons from seven naïve rats, nine neurons from five trained rats, and 11 neurons from five pseudo-trained rats. Values represent mean ± SE.

Figure 2. Synaptosomal ERK is activated 3 d following learning. (A) Representative immunoblots for ERKII and phosphorylated ERKII prepared from piriform cortex synaptoneurosomes of each of the three groups (N, naïve; P, pseudo-trained; T, trained). (B) Protein expression level of ERKII is enhanced after olfactory learning. The protein level is normalized to the average value obtained from the naïve animals. Data was taken from 27 naïve, 29 trained, and 25 pseudo-trained rats. The trained group has a significantly higher level of protein expression compared with the naïve group (P < 0.05). Summarized data are presented as mean O.D ± SE. (C) Cumulative frequency distribution of normalized values from the three groups. Here, each data point represents a rat, and thus it is possible to see whether most data points in one group are modified by treatment. The curve of activated ERK level values in trained rats is smoothly shifted to the left, compared with the naïve group, indicating that such reduction occurred in most of the sampled neurons and not in a subgroup. Two-thirds of the data points of the pseudo-trained group overlap with the naïve group, and the remaining third fits more with the trained group.
Matsliah et al. 2007). Here we examined whether PKC is required for long-lasting learning-induced PPF reduction, and PKC (Seroussi et al. 2002). The effect of PKC on neuronal excitability is abolished by blocking MEK, indicating that PKC is upstream relative to the ERK pathway in the sequence of kinase cascade, underlying long-lasting neuronal excitability (Cohen-Matsliah et al. 2007). Here we examined whether PKC is required for long-term maintenance of PPF reduction.

The PKC blocker, GF-109203X, increased PPF significantly ($P < 0.05$) in neurons from trained rats (from 1.21 ± 0.16, $n = 17$ in control solution to 1.33 ± 0.13, $n = 9$ in GF-109203X). In sharp contrast, it had no effect on PPF in neurons from naive (from 1.39 ± 0.16, $n = 21$ in control solution to 1.36 ± 0.18, $n = 7$ in GF-109203X) and pseudo-trained rats (from 1.38 ± 0.16, $n = 21$ in control solution to 1.41 ± 0.10, $n = 6$ in GF-109203X). Consequently, the difference between groups was abolished in the presence of the PKC inhibitor (Fig. 3A,B).

The PKC activator OAG had no effect on PPF in any of the groups; in its presence, the averaged values of the naive (1.33 ± 0.13, $n = 9$), trained (1.21 ± 0.20, $n = 10$), and pseudo-trained rats (1.34 ± 0.20, $n = 9$) did not differ from their control values (Fig. 3C).

That OAG by itself does not reduce PPF in neurons from control rats raises the question as to whether PKC is acting upstream or in parallel with ERK. We thus examined whether OAG enhanced ERK activation. No differences were found in the pERKII/pERKII ratio between slices incubated in NSR and OAG (NSR: 1.03 ± 0.04; OAG: 0.96 ± 0.07, $n = 6$ rats in each group). As discussed below, these results support the notion that in synaptoneurosomes of the piriform cortex, PKC and ERK act in parallel.

Dynamics of learning-induced ERK phosphorylation
Temporal analysis of learning-induced modulation of synaptic transmission shows that PPF reduction does not appear at the time when rule learning is obtained.

Such PPF reduction occurs only on the third day after completion of training for the second pair of odors, e.g., 4 d after rule learning (Saar et al. 1999). This reduced value is then maintained for 5 d (Saar et al. 1999). Such a delay between rule learning and the occurrence of synaptic modification was found not only for PPF reduction, but also for enhanced PSP rise time (Saar et al. 2002) and increased number of spines (Knafo et al. 2005). Thus, the time after rule learning can be divided into two time periods; the period before synaptic modifications, including PPF reduction, is apparent (initial period), and the period after which these modifications are detected (second period).

Here we tested the dynamics of learning-induced synaptic ERK activation during these two time periods. We found that ERK activation levels are enhanced at both periods. Thus, the level of phosphorylated ERK in synaptoneurosomes is elevated prior to PPF reduction, and remains at this high level for the next several days (Fig. 4).

Discussion
Previous studies have shown that olfactory learning-induced long-lasting enhancement of neuronal excitability is dependent on long-term persistent activation of a second messenger cascade that includes ERK and PKC (Cohen-Matsliah et al. 2007). Here we show that these two key enzymes have also a pivotal role in maintaining learning-induced long-lasting enhancement of synaptic connectivity, as reflected by PPF reduction measured 3 d after learning. However, as discussed below, here they may act in parallel rather than within the same cascade.

ERK activation modifies synaptic transmission only after learning
Our data show that PPF in the axons interconnecting piriform cortex layer II pyramidal neurons is subjected to considerable modifications by ERK only after learning. PPF in the pseudo-trained rats is also affected to a minor extent, about one-third of that observed in trained neurons. Thus, while most of ERK activation can be attributed to the olfactory-discrimination learning
PKC activation is required for maintenance of PPF reduction

We have previously shown that the maintenance of the olfactory learning-induced reduction of the AHP is dependent on PKC (Seroussi et al. 2002), and that the effect of PKC on learning-induced neuronal excitability is mediated by ERK activation (Cohen-Matsliah et al. 2007). A similar sequence of events was suggested to describe the effect of PKC on the I_sp potassium current (Hu et al. 2003). We thus examined here whether PKC is also instrumental in maintaining learning-induced PPF reduction, at the same time when ERK appears to have such a role.

We found that blocking PKC activation enhances PPF in neurons from trained rats to the level observed in the two control groups. Thus, persistent PKC activation is necessary for maintaining such long-lasting PPF reduction. However, PKC activation by itself does not induce PPF reduction; application of its activator, OAG, did not affect PPF in any of the groups, indicating that an additional process is required. Thus, it may be possible that ERK and PKC are activated in parallel in an AND gate, which is necessary for maintaining long-lasting PPF reduction. That OAG application does not enhance ERK activation in brain slices, lends further support to this conclusion.

Time-specific effects of ERK on learning and memory

Direct evidence in support of a role for ERK in memory has been accumulating rapidly over the past decade. Although the evidence stems from findings involving different learning types and brain areas, they all show a pattern of temporal ERK activation, initiated minutes to several hours after training completion (Atkins et al. 1998; Berman et al. 1998; Blum et al. 1999; Schafe et al. 2000; Belelovsky et al. 2005; Herry et al. 2006). The picture emerging from these previous studies is that at relatively early stages of memory formation and consolidation, ERK modulates learning-relevant processes by affecting different substrates, which are yet to be identified.

Our study shows that for days after learning completion, ERK activation is still significantly enhanced at the synapses. Interestingly, such ERK activation occurs 2 d before PPF reduction occurs. This result suggests that enhanced and prolonged ERK activation is involved in the induction of the process leading to PPF reduction, rather than only in its maintenance.

How is ERK activation maintained for days? Previous work suggests that persistent activation of the kinases in the ERK cascade may form a positive feedback loop that could counteract the loss of ERK activity due to the protein turnover and signal withdrawal. Such a system has the potential to store information. However, such activation is restricted to small volumes (Bhalla and Lyengar 1999; Smolen et al. 2008). Since MEK and ERK are known to localize in synaptoneurosomes (Suzuki et al. 1995), and we have shown activation of ERK lasting days after learning in those cellular compartments, our results lend support to this hypothesis.

In conclusion, our study shows that ERK can be activated locally at synaptoneurosomes, many days following learning. Moreover, this induced ERK activation modulates synaptic function. This ERK activation is crucial for maintaining learning-induced PPF reduction in the first days after learning completion.

Materials and Methods

Animal training

Subjects and apparatus

Age-matched young adult Sprague-Dawley male rats were used. Prior to training they were maintained on a 23.5 h water-deprivation schedule, with food available ad libitum. Olfactory discrimination training protocol was performed daily on each trained and pseudo-trained rat in a 4-arm radial maze, as previously described (Saar et al. 1999, 2001), with commercial odors that are regularly used in the cosmetics and food industry.

Training

Olfactory training consisted of 20 trials per day for each rat as previously described (Saar et al. 2001). In short, in each trial the rat had to choose between two odors (positive and negative cue) presented simultaneously. Rats designated to the trained group were rewarded upon choosing the positive cue. Rats in the pseudo-trained group were rewarded in a random fashion, upon choosing any odor. The criterion for learning was at least eight positive-cue choices in the last 10 trials of a training day, as was previously used (Staubli et al. 1987; Saar et al. 1999, 2001). Rats in the naive group were water restricted, but not exposed to the maze. Typically, two to three trained rats and two to three pseudo-trained rats were trained at the same training period, and all of the
rats in the trained group had to meet the criteria for the first pair of odors before all trained and pseudo-trained rats were exposed to a second pair of odors. Training for a new pair began only after training for the second pair was completed for all rats. As previously described (Saar et al. 1999, 2001), rats indeed learned the second and third pairs of odors much faster than the first pair (7–8 d of training for the first pair and 1–2 d for the second and third pairs). Several rats were trained with a second and third pair of odors. Such training was always completed within 1 d. Thus, rule learning was considered to occur on the day when rats completed training for the first pair of odors.

**Slice preparation, stimulation, and recording**

A total of 400-µm coronal brain slices were cut as previously described (Saar et al. 1998) and kept in oxygenated (95% O₂ + 5% CO₂) normal saline Ringers’ (NSR) solution (in millimolar: NaCl 124, KCl 3, MgSO₄ 2, NaH₂PO₄ 1.25, NaHCO₃ 26, CaCl₂ 2, and glucose 10). Intracellular recordings were obtained from pyramidal cells in layer II of the piriform cortex, with 4 M K-acetate-filled sharp glass microelectrodes, at 35°C. Several piriform cortex slices were obtained from each rat.

PF responses were recorded within minutes after good recording conditions were established (resting potential of at least 65 mV and action potential amplitude of 80 mV or more). Tungsten electrodes were placed in layer lb of the piriform cortex to stimulate the intrinsic fibers. Electrical stimuli were applied at 0.1 Hz. The amplitudes of the responses were measured from digital averaging of 10 consecutive responses. To standardize the intracellular recording conditions, stimulus intensity was adjusted so that the averaged amplitude of 10 consecutive post-synaptic potentials (PSPs) in the recorded cell would be 10 mV at Vm = −80 mV. After drug application, the stimulus intensity was adjusted again to evoke a first PSP with amplitude of 10 mV.

The identity of the rat from which neurons were recorded (naïve, trained, or pseudo-trained) was not known to the person conducting the experiments and measurements.

**Drug application**

All drugs were applied into the perfusing Ringer solution at the following concentrations: MEK inhibitor PD98059 (Sigma), 38 µM; PKC activator 1-oleoyl-2-acetyl-sn-glycerol (OAG) (RBI), 10 µM; PKC inhibitor bisindolylmaleimide (GF-109203X, Sigma), 10 µM. Slices were exposed to drugs for at least 20 min before the recordings. In each recording condition, several cells were recorded before and after drug application, while others were recorded under one condition only (e.g., in control solution or in the presence of the drug).

**Sample preparation**

**Preparation of synaptoneurosomes**

Preparation of synaptoneurosomes of piriform cortex was obtained as described (Quinlan et al. 1999; Belelovsky et al. 2005). Briefly, tissues were homogenized in 4 mL of homogenization buffer (in millimolar: HEPES 10, EDTA 2, EGTA 2, DTT 0.5, 1% phosphatase inhibitor cocktail [Sigma] and 1% protease inhibitor cocktail [Sigma]). Eighty microliters of the homogenized tissue cocktail was resuspended in homogenizing buffer and subject to homogenization in a Tissumizer (Wheaton, Millville, NJ) for 1 min. The homogenate was filtered through a 5-µm filter (Millipore) and centrifuged at 1000g for 10 min at 4°C. The pellet containing the synaptoneurosomes was resuspended in homogenizing buffer and subject to SDS-PAGE following protein determination.

**Western blot analysis**

All gels were resolved by SDS-PAGE and transferred to nitrocellulose membrane (BioRad Laboratories, Inc.) for immunoblotting. Blots were visualized with enhanced chemiluminescence (ECL Plus, Amersham Biosciences) and quantified using a CCD camera (XRS, BioRad Laboratories, Inc.) and “Quantity-One” software. Here, we quantified ERKII (thus, in the Results section, ERK is intended to note ERKII). The ratio between phosphorylated ERK and the total amount of the protein for each rat was calculated and normalized to the naive group average run on the same gel.

To measure the effect of PKC activation on ERK phosphorylation in synaptoneurosomes, piriform cortices were isolated from 400-µm coronal brain slices. Slices were incubated in normal slice Ringer (NSR) for 60 min, followed by additional incubation of 40 min in NSR or OAG (10 µM). Subsequently, synaptoneurosomes were prepared from the slices, as described above.

**Reagents**

p44/42 MAP kinase antibody (1:10000), rabbit polyclonal; phospho-p44/42 MAP kinase (Thr202/Tyr204) antibody (1:500) were purchased from Cell Signaling. Goat anti-rabbit IgG was obtained from Jackson ImmunoResearch Laboratories, Inc. and used at a concentration of 1:20,000.

**Statistical analysis**

For all of the electrophysiological measurements, between-groups comparison was done using one-way ANOVA for the three groups (naïve, trained, and pseudo-trained), and post-hoc multiple t-tests were then applied to compare between each of the two groups. The effect of the drugs on each of the three groups was evaluated by comparing the recordings from the same group, with and without the treatment, using independent t-tests. Values throughout the text are presented as mean ± SD. Data in graphs are presented as mean ± SE.

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