A Novel Role for Protein Synthesis in Long-Term Neuronal Plasticity: Maintaining Reduced Postburst Afterhyperpolarization

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Memory consolidation, the process of transformation of short-term to long-term memory, has been shown to be protein synthesis dependent in a variety of different learning paradigms, brain structures, and species. At the cellular level, protein synthesis was shown to be crucial for induction of long-term synaptic plasticity; application of protein synthesis inhibitors prevents the transformation of early long-term potentiation (LTP) to late LTP. Thus, protein synthesis has been traditionally thought to affect long-term memory consolidation by stabilizing synaptic transmission. However, long-term memory is not supported only by modulation of synaptic strength; modifications in intrinsic neuronal properties also subserve learning-related behavioral changes. Learning-induced reduction in the postburst afterhyperpolarization (AHP), which results with enhanced neuronal excitability and decreased spike frequency adaptation, is apparent in hippocampal and cortical pyramidal neurons. Such postburst AHP reduction lasts for days after training completion and is implicated in maintaining learned skills. Short-term modulation of intrinsic neuronal excitability can be also induced *in vitro*. Intense synaptic activation induces AHP reduction and enhanced neuronal excitability in hippocampal pyramidal neurons. Here, we show that synaptic activation-induced short-term postburst AHP reduction can be transformed to long-term AHP reduction, such that persists for prolonged time periods. This long-lasting AHP reduction is protein synthesis dependent for up to 1 h after induction. We suggest that, much like synaptic plasticity, activity-induced long-lasting modulation of intrinsic neuronal excitability requires molecular consolidation. It would appear that both synaptic and intrinsic modifications and maintenance are activated jointly to enable long-lasting memories.

Introduction

Memory can be divided according to different temporal phases: acquisition, consolidation, and retrieval. The consolidation phase is divided into molecular consolidation (range of hours after acquisition) and system consolidation (range of weeks and months after acquisition) (Dudai, 2004). Molecular consolidation is thought to be a protein synthesis-dependent process (Alberini, 2008; Costa-Mattioli et al., 2009). The clear effect of protein synthesis inhibitors on long-term memory was studied extensively mainly in the context of late-phase long-term potentiation (LTP) (Abraham and Williams, 2008). Similar molecular mechanisms were proposed for maintenance of long-term synaptic modifications and learning processes (Davis and Squire, 1984; Costa-Mattioli et al., 2009). However, long-term memory is not supported only by modulation of synaptic strength; modifications in intrinsic neuronal properties also subserve learning-related behavioral changes (Saar and Barkai, 2003; Zhang and Linden, 2003; Disterhoft et al., 2004). Thus, the question arises

whether protein synthesis inhibitors affect memory consolidation via additional neuronal processes, such as modification and maintenance of neuronal excitability.

Learning-induced enhancement in neuronal excitability has been detected in hippocampal neurons following various training paradigms, such as classical conditioning of the trace eyeblink response (Moyer et al., 1996; Thompson et al., 1996), Morris water maze task (Oh et al., 2003), and olfactory-discrimination learning (Zelcer et al., 2006). Learning-induced enhanced excitability is manifested in reduced spike frequency adaptation in response to prolonged depolarizing current applications, which lasts for periods of days after learning (Moyer et al., 1996; Thompson et al., 1996; Saar and Barkai, 2003; Zelcer et al., 2006).

Neuronal adaptation is modulated by the postburst afterhyperpolarization (AHP), generated by potassium currents that develop after spike firing (Madison and Nicoll, 1984; Schwindt et al., 1988). This postburst AHP is reduced after learning (Moyer et al., 1996; Saar et al., 1998). Several studies indicate that the learning-induced reduction in neuronal adaptation and in AHP amplitude result from reduction in a Ca^{2+} -dependent potassium current (Power et al., 2002; Saar and Barkai, 2003). In particular, it has been suggested that changes in the sI_{AHP} current may account for learning-related intrinsic modifications in hippocampal and cortical neurons (Oh et al., 2003; Brosh et al., 2006).

Short-term reduction in the postburst AHP can be induced also *in vitro*, much like early LTP, by repetitive tetanic synaptic

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Figure 1. Experimental protocols and synaptic responses. **A**, Protocols of synaptic stimulation and protein synthesis inhibitor (anisomycin or cycloheximide) application. HFS or LFS was applied at time 0. The dotted line notes recording time in protein synthesis inhibitor-free solution, and the continuous line notes recording time with the protein synthesis inhibitor. Stimulation protocols for the three groups that were exposed to HFS [HFS-only, Ani-plus-HFS (or Cyclo-plus-HFS), and Ani-after-HFS] and the LFS group are presented. **B**, Typical synaptic responses to 20 stimuli delivered at 50 Hz. Stimulation electrode was placed in the Schaffer collaterals and the recording electrode in the CA1 cell body layer. Stimulus intensity was adjusted to evoke a fPSP with amplitude of 1–2 mV.

stimulation (Melyan et al., 2002). A similar effect is obtained by briefly exposing these neurons to kainate (Melyan et al., 2004).

The purpose of the present study was to explore whether long-term AHP reduction can be also induced by synaptic activation. Moreover, since late LTP is protein synthesis dependent (Krug et al., 1984; Otani et al., 1989; Manahan-Vaughan et al., 2000; Rosenblum et al., 2002; Sajikumar and Frey, 2003), we tested whether a similar obligatory role exists for protein synthesis in long-term induction of AHP reduction.

We show that synaptic activation-induced AHP reduction lasts for many hours, well into the range in which late LTP occurs and that the induction of such long-lasting reduction is protein synthesis dependent, at a specific well defined time window after synaptic activation.

Materials and Methods

Slice preparation, stimulation, and recording. Hippocampal slices were prepared from young adults (aged 2 months) Sprague Dawley male rats. Four hundred micrometer coronal brain slices were cut from the dorsal hippocampus and kept in oxygenated (95% O₂ plus 5% CO₂) Ringer's solution (in mM: 124 NaCl, 3 KCl, 2 MgSO₄, 1.25 NaH₂PO₄, 26 NaHCO₃, 2 CaCl₂, and 10 glucose).

Intracellular recordings were performed from CA1 pyramidal neurons at 36°C, with 4 M K-acetate-filled sharp glass microelectrodes. Cell input resistance (R_{in}) was determined by linear regression fit to a voltage/current curve at the range from resting potential to −15 mV from resting. Spike width was measured at the spike threshold.

Synaptic stimulation. Synaptic stimulation was delivered via a bipolar tungsten electrode, positioned at the Schaffer collaterals, to activate the glutamatergic synapses onto CA1 pyramidal neurons. Stimulus intensity was adjusted to evoke a field postsynaptic potential (fPSP) with amplitude of 1–2 mV.

Activity-induced AHP reduction was induced by applying high-frequency stimulation (HFS); 20 repetitive stimuli were applied at 50 Hz. Only slices in which the fPSP was stable for all stimuli in the train (see Fig. 1B) were used. After HFS, slices were kept without additional activation for 3 h before intracellular recordings were attempted. Such subsequent AHP recordings were performed in the vicinity of the fPSP recording site. Low-frequency stimulation (LFS) was applied with the same number of synaptic stimuli (20) at the frequency of 1 Hz.

Stimulating repetitively in these conditions did not induce LTP of the synaptic response; 1 h after repetitive stimulation, the averaged value of the fPSP was similar to that recorded before repetitive stimulation (ratio

of synaptic responses before and after stimuli application, 1.09 ± 0.19 ; $n = 9$; $p = 0.72$).

Postburst AHP measurements. To standardize AHP recordings, cell membrane potential was depolarized to −60 mV with DC current application via the recording electrode, and AHP amplitude was measured after an additional 100 ms depolarizing current step that generated six action potentials, after which the DC depolarization was maintained. AHP amplitude was determined from an average of 8–10 consecutive responses to stimuli applied once every 10 s. Under these conditions, a postburst AHP that lasted up to several seconds appeared in all CA1 pyramidal neurons. The stimulus intensity applied to evoke a burst of six action potentials on the 100-ms-long depolarizing pulse was adjusted to ensure that the last spike in the train would be evoked 10–15 ms before the end of the pulse. This procedure was undertaken to ensure that the firing frequency would be similar in neurons from all groups, so that the postburst AHP would not be affected by the firing frequency of the six action potential train.

Drug application. Protein synthesis inhibitors, anisomycin (10 μ M; Sigma-Aldrich) and cycloheximide (60 μ M; Fluka), were applied into the perfusing Ringer's solution. Slices were exposed to drugs either immediately after slice preparation or 1 h after repetitive synaptic stimulation. One neuron was recorded for each slice.

Statistical analysis. Between-group comparison was done using one-way ANOVA, and *post hoc* multiple nondirectional *t* tests were then applied to compare between each two groups. Values throughout the text are presented as mean $\pm$ SD. Data in graphs are presented as mean $\pm$ SE.

Results

Postburst AHP recordings were performed in 75 CA1 pyramidal neurons divided into seven groups (Fig. 1A): (1) control neurons that were not submitted to synaptic activation; (2) neurons that were recorded several hours after high-frequency synaptic stimulation (“HFS only”); (3) neurons that were recorded several hours after low-frequency synaptic stimulation (“LFS only”); (4, 5) neurons from slices that were treated with anisomycin or cycloheximide during HFS application (“Ani plus HFS” and “Cyclo plus HFS”); (6) neurons from slices that were exposed to anisomycin, without synaptic stimulation (“Ani only”); and (7) neurons from slices that were exposed to anisomycin 1 h after HFS application (“Ani after HFS”). The averaged amplitudes of the evoked field potentials was similar for the groups to which synaptic stimulation was applied [HFS, 1.4 ± 0.4 mV ($n = 12$); Ani plus HFS, 1.13 ± 0.3 mV ($n = 12$); Ani after HFS, 1.29 ± 0.5 mV ($n = 11$); $p = 0.88$]. Population spikes were not evident in any of the synaptic responses. The averaged value of the intensity of the current applied via the recording electrode to evoke six action potentials was also similar for all experimental groups [control, 0.61 ± 0.19 nA ($n = 16$); HFS, 0.65 ± 0.17 nA ($n = 12$); Ani plus HFS, 0.63 ± 0.16 nA ($n = 12$); Ani only, 0.74 ± 0.28 nA ($n = 24$); Ani after HFS, 0.79 ± 0.23 nA ($n = 11$); $p = 0.29$].

HFS-induced long-term AHP reduction

We first examined whether repetitive synaptic stimulation results with postburst AHP reduction, such that would be still evident in the time range in which late LTP is evident (>3 h). Since continuous intracellular recordings for such a long period of time is not technically feasible, intracellular recordings were performed 3–5 h after HFS application, at the sites at

which stable fPSPs were evoked in response to repetitive synaptic activation (Fig. 1B).

The averaged postburst AHP in HFS-only neurons (3.32 ± 1.2 mV; $n = 12$) was significantly smaller ($p < 0.05$) compared with the averaged AHP amplitudes in neurons from control neurons (5.53 ± 3.1 mV; $n = 16$) (Fig. 2A,B). Figure 2C shows that such HFS-induced AHP reduction was observed throughout the time that elapsed between synaptic stimulation and intracellular recordings. Twenty stimuli applied at 1 Hz (LFS group) did not have the same long-term effect on the postburst AHP, although a tendency toward AHP reduction was observed. The averaged value after stimulating at this frequency was 4.35 ± 1.11 mV ($n = 11$), which does not differ significantly for the averaged value of the control group ($p = 0.24$).

Postburst AHP reduction was not the result of a general change in passive and active membrane properties; resting membrane potential (-65 ± 3.5 mV in controls and -63 ± 2.7 after HFS; $p = 0.35$), input resistance (26.7 ± 8.7 M Ω in controls and 28.6 ± 6.5 after HFS; $p = 0.66$), spike amplitude (91.1 ± 18.4 mV in controls and 88 ± 10.8 after HFS; $p = 0.85$), and spike width (1.49 ± 0.3 ms in controls and 1.59 ± 0.26 after HFS; $p = 0.78$) did not differ between neurons from the two groups.

HFS-induced long-lasting AHP reduction is protein synthesis dependent

We next examined whether long-lasting AHP reduction is dependent on protein synthesis by testing how protein synthesis inhibitor anisomycin application modulates the effect of high-frequency stimulation. Application of anisomycin by itself did not have an effect of the postburst AHP amplitude; the averaged value of the Ani-only group was 4.89 ± 2.7 mV ($n = 24$). This value does not differ from that observed in the control group ($p = 0.61$).

When HFS was applied in the presence of anisomycin, it failed to induce AHP reduction. The averaged AHP value in the Ani-plus-HFS group was 5.0 ± 1.8 mV ($n = 12$). This value is similar to that obtained in the control and the Ani-only groups ($p = 0.65$) (Fig. 3A,B). Such lack of HFS effect was observed at all recording time points after repetitive stimulus application (Fig. 3C). Similar results were obtained with another protein synthesis inhibitor, cycloheximide. The averaged AHP value for neurons recorded 180–345 min after synaptic stimulation in presence of this inhibitor was 4.89 ± 0.76 mV ($n = 9$). This value does not differ from the average values of the control group ($p = 0.56$) and the Ani-plus-HFS group ($p = 0.73$).

Much like as shown for learning and late LTP (Frey et al., 1988; Meiri and Rosenblum, 1998), the effect of anisomycin on HFS-induced AHP reduction does not occur if the protein synthesis

Figure 2. HFS-induced long-lasting AHP reduction. **A**, Postburst AHP measurements in CA1 pyramidal 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. Typical examples of a neuron from the control group and a neuron from the HFS-only group are shown. **B**, Averaged AHP amplitude in neurons from the control and HFS-only groups. Averaged AHP amplitude in the HFS-only group is significantly smaller compared with the control group ($*p < 0.05$). AHP was measured in neurons from 16 control neurons, taken from 8 rats, and 12 neurons exposed to HFS, taken from 12 rats. Values represent mean $\pm$ SE. **C**, Values of AHP in neurons from the HFS-only group are similar at all time intervals after HFS (3–5 h). Reduced AHP, compared with the averaged value of controls (dotted line), was observed throughout this time window. Each dot notes the value of AHP in one cell.

Figure 3. Maintenance of AHP reduction is dependent on protein synthesis. **A**, Examples of AHPs taken from three neurons, representing the Ani-only, the Ani-plus-HFS, and the Ani-after-HFS groups. The AHP in neurons from the Ani-only and the Ani-plus-HFS groups resembles that observed in the control group, whereas the AHP of the neuron taken from the Ani-after-HFS group is similar to those recorded in the HFS group. **B**, Averaged AHP amplitude in neurons from the three anisomycin-treated groups. Averaged AHP amplitude in the Ani-plus-HFS group is significantly smaller compared with the Ani-only and the Ani-after-HFS groups ($*p < 0.05$), which do not differ between them. AHP was measured in 24 Ani-only neurons taken from 12 rats, 12 Ani-plus-HFS neurons taken from 12 rats, and 11 Ani-after-HFS neurons taken from 11 rats. Values represent mean $\pm$ SE. **C**, HFS-induced AHP reduction is maintained in the Ani-after-HFS group. Values of AHPs in neurons from the Ani-plus-HFS and the Ani-after-HFS groups are shown 3–5 h after applications of tetanic stimulation. Reduced AHP in neurons from the Ani-after-HFS group was observed throughout this time window. Each dot notes the value of AHP in one cell. For clarity of presentation, 9 of 11 neurons from the Ani-after-HFS group are presented. Values represent mean $\pm$ SE.

blocker is applied an hour after synaptic stimulation. The averaged AHP value in the Ani-after-HFS group was 3.2 ± 1.3 mV ($n = 11$). This value is significantly ($p < 0.05$) smaller than those obtained for the Ani-only and the Ani-plus-HFS groups (Fig. 3A,B) and is similar to that obtained for the HFS group. This lack of effect was observed throughout the time points tested, from 215 and up to 440 min after repetitive stimulus application (Fig. 3C).

HFS-induced AHP reduction is observed in most sampled neurons

Since synaptic activation is induced by applying a strong electrical stimulation to the afferent excitatory inputs into the CA1 pyramidal neurons, it is expected that AHP reduction will occur in a significant portion of the pyramidal cell population in the activated area. Indeed, most of the neurons sampled from the two

Figure 4. AHP amplitude is reduced in most neurons exposed to HFS without anisomycin. Cumulative frequency distribution of AHP amplitudes in neurons that were not exposed to HFS (control and Ani-only groups) and in neurons that were exposed to HFS without anisomycin presence (HFS and Ani-after-HFS groups). The curve of the AHP amplitudes in neurons exposed to HFS without anisomycin is shifted to the left of the graph that shows AHP values for neurons recorded without previous application of tetanic stimulation.

groups in which HFS was applied without the presence of protein synthesis blocker (the HFS-only and the Ani-after-HFS groups) had smaller AHPs (averaged value of 3.41 ± 1.17 ; $n = 22$) than the average AHP that was sampled in the groups that did not receive any synaptic activation, the control and the Ani-only groups (averaged value of 5.24 ± 2.84 ; $n = 39$). Twenty-one of 22 neurons in the group that was treated with HFS without a protein synthesis blocker had an AHP with amplitude lower than the average recorded in neurons that did not receive synaptic stimulation. A cumulative frequency distribution of AHP amplitudes is shown in Figure 4. With each point representing one cell, it is noticeable that the reduction of the averaged AHP amplitude after HFS is a result of reduction in AHP in most of the sampled neurons. Hence, AHP reduction is widely distributed throughout the neuronal population after application of a strong tetanic stimulation, rather than being restricted to a small portion of the cells.

Discussion

The notion that memory has different temporal phases rises from behavioral, pharmacological, and molecular correlates and electrophysiological measurements. Memory consolidation is defined as the time after acquisition that memory is still susceptible to distractions, such that would impair obligatory protein synthesis-dependent processes (Abraham and Williams, 2008; Alberini, 2008; Costa-Mattioli et al., 2009). Protein synthesis inhibitors can potentially affect different cellular processes in different cells within the brain, including neurons, glia, and the vascular system. To date, the behavior-relevant role of protein synthesis inhibitors was studied extensively in relation to synaptic function (Abraham and Williams, 2008; Alberini, 2008; Costa-Mattioli et al., 2009). Our data show that protein synthesis is also crucial for the maintenance of experience-dependent modification of neuronal excitability.

Long-lasting learning-induced enhancement of neuronal excitability has been shown in CA1 hippocampal neurons after classical conditioning of the trace eyeblink response (Moyer et al., 1996), the Morris water maze task (Oh et al., 2003), and olfactory-discrimination learning (Zelcer et al., 2006). This enhanced excitability is manifested in reduced spike frequency adaptation in response to prolonged depolarizing current applications, which results from postburst AHP reduction (Madison and Nicoll, 1984; Moyer et al., 1996; Zelcer et al., 2006).

Long-term reduction in the slow AHP can be also induced in CA1 pyramidal neurons by synaptically released glutamate, evoked by tetanic stimulation of the Schaffer collateral and commissural fibers (Melyan et al., 2002). Here, we show that such synaptic activation-induced postburst AHP reduction requires protein synthesis for its long-term maintenance. Moreover, such protein synthesis is crucial in a time window similar to the time frame in which late-phase LTP and long-term memory are disrupted by protein synthesis inhibitors.

Long-lasting maintenance of HFS-induced AHP reduction

Biophysical properties underlying neuronal excitability are best studied with two techniques: whole-cell patch-clamp and intracellular recordings with sharp electrodes. Unfortunately, both techniques do not allow continuous recordings for periods of many hours. Because of this technical constraint, the mechanism underlying postburst AHP reduction have been studied to date at two time windows. The first, during and up to 45 min after HFS application (Melyan et al., 2002, 2004), and the second, after 1 to several days after behavioral manipulations (Moyer et al., 1996; Zelcer et al., 2006). The combination of these two approaches leaves the time window of several hours after synaptic activation, when protein synthesis-dependent processes are expected to occur (Krug et al., 1984; Otani et al., 1989; Frey et al., 1993, 1988; Nguyen et al., 1994), unexplored. To cover this crucial phase, we recorded from pyramidal neurons 3–7 h after application of high-frequency synaptic stimulation to their afferent glutamatergic synapses.

Indeed, such a treatment results in an across-the-board reduction of the postburst AHP in virtually all cells to which HFS was applied without protein synthesis blockers. Thus, HFS-induced postburst AHP reduction in brain slices is not temporally restricted for tens of minutes but may proceed for longer, much like how early LTP develops into late LTP.

Role of protein synthesis in maintaining enhanced neuronal excitability

It is widely accepted that induction and maintenance of long-term activity-dependent synaptic plasticity involves modulation of the excitatory synaptic connection “hardware” and that this process requires a critical phase of protein synthesis (for review, see Sorra and Harris, 2000; Yuste and Bonhoeffer, 2001). Here, we show a protein synthesis-dependent process that results with a physiological rather than a morphological change. Such protein synthesis seems to be completed within an hour after HFS application; anisomycin does not prevent AHP reduction if applied after this time interval. Notably, it has been shown that protein synthesis is also required for a different form of intrinsic plasticity, termed intrinsic excitability-LTP (Xu et al., 2005). This enhanced long-lasting excitability affects the action potential threshold and is attributed to a shift in the activation curve of the voltage-gated sodium channel. It does not persist for many hours if protein synthesis blocker is present during stimulus application (Xu et al., 2005).

Do the newly synthesized protein(s) affect the AHP-generating channels directly? Previous studies show that the maintenance of AHP reduction and enhanced neuronal excitability are dependent on the cAMP and PKA (protein kinase A) pathways (Lopez de Armentia et al., 2007; Oh et al., 2009), as well as on persistent PKC and extracellular signal-regulated kinase (ERK) activation (Seroussi et al., 2002; Cohen-Matsliah et al., 2007). PKC and ERK are also essential for the induction of such AHP reduction (Melyan et al., 2002; Grabauskas et al., 2007). Thus, it is

likely that synaptic activity-induced protein synthesis is required for maintaining the ERK and PKC system activity rather than affecting the potassium channel itself.

In conclusion, our data show that activity-induced long-lasting modulation of intrinsic neuronal properties, such that result with enhanced neuronal excitability, requires protein synthesis that occurs during a specific time window after synaptic activation. In that respect, persistent changes in the membrane properties of pyramidal neurons resemble long-term changes in synaptic transmission.

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