J Neurophysiol 98: 2488–2492, 2007.
First published July 25, 2007; doi:10.1152/jn.00473.2007.

Long-Term Potentiation in the Hippocampal CA1 Region Does Not Require Insertion and Activation of GluR2-Lacking AMPA Receptors

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Submitted 26 April 2007; accepted in final form 16 July 2007

Gray EE, Fink AE, Sariñana J, Vissel B, O'Dell TJ. Long-term potentiation in the hippocampal CA1 region does not require insertion and activation of GluR2-lacking AMPA receptors. *J Neurophysiol* 98: 2488–2492, 2007. First published July 25, 2007; doi:10.1152/jn.00473.2007. Activity-dependent insertion of AMPA-type glutamate receptors is thought to underlie long-term potentiation (LTP) at Schaffer collateral fiber synapses on pyramidal cells in the hippocampal CA1 region. Although it is widely accepted that the AMPA receptors at these synapses contain glutamate receptor type 2 (GluR2) subunits, recent findings suggest that LTP in hippocampal slices obtained from 2- to 3-wk-old rodents is dependent on the transient postsynaptic insertion and activation of Ca^{2+}-permeable, GluR2-lacking AMPA receptors. Here we examined whether LTP in slices prepared from adult animals exhibits similar properties. In contrast to previously reported findings, pausing synaptic stimulation for as long as 30 min post LTP induction had no effect on LTP maintenance in slices from 2- to 3-mo-old mice. LTP was also not disrupted by postinduction application of a selective blocker of GluR2-lacking AMPA receptors or the broad-spectrum glutamate receptor antagonist kynurenate. Although these results suggest that the role of GluR2-lacking AMPA receptors in LTP might be regulated during postnatal development, LTP in slices obtained from 15- to 21-day-old mice also did not require postinduction synaptic stimulation or activation of GluR2-lacking AMPA receptors. Thus the insertion and activation of GluR2-lacking AMPA receptors do not appear to be fundamental processes involved in LTP at excitatory synapses in the hippocampal CA1 region.

INTRODUCTION

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)–type glutamate receptors are ligand-gated ion channels assembled from a combination of four subunits known as GluR1 through GluR4. Although functional AMPA receptors can be formed from various hetero- or homomeric combinations of these subunits, the subunit composition of the receptor dictates a number of functional properties of the receptors. For instance, the ion channel formed by hetero- or homomeric combinations of GluR1, GluR3, and GluR4 subunits is permeable to Ca^{2+} and exhibits pronounced inward rectification, whereas the channel of receptors containing GluR2 subunits is impermeable to Ca^{2+} and exhibits a linear current–voltage relationship (Jonas and Burnashev 1995). GluR2-containing AMPA receptors are also insensitive to toxins and dicationic adamantine derivatives that potently inhibit GluR2-lacking AMPA receptors, such as philanthotoxin (Brackley et al. 1993; Tóth and McBain 1998; Washburn and Dingledine 1996) and IEM-1460 (Buldakova et al. 2007; Magazanik et al. 1997; Samoilova et al. 1999). The subunit composition of AMPA receptors also has an important role in activity-dependent changes in synaptic strength such as long-term potentiation (LTP). For example, LTP at excitatory synapses onto hippocampal CA1 pyramidal cells is thought to be primarily due to the insertion of GluR1 subunit-containing AMPA receptors (Hayashi et al. 2000; Shi et al. 2001) that, over time, are replaced by a constitutively cycling pool of GluR2/3-containing receptors (for review see Malinow and Malenka 2002). Although it has been generally assumed that the GluR1-containing AMPA receptors inserted into the postsynaptic membrane following LTP induction also contain GluR2 subunits (Barry and Ziff 2002), recent findings suggest that GluR2-lacking AMPA receptors (presumably GluR1 homomers), rather than GluR1/2 subunit-containing receptors, are transiently inserted into the postsynaptic membrane immediately after LTP induction (Plant et al. 2006). Surprisingly, this study also found that the induction of stable LTP lasting >30 min requires activation of GluR2-lacking AMPA receptors for ≥ 10 min post LTP induction (Plant et al. 2006). This suggests that a prolonged increase in postsynaptic Ca^{2+} by GluR2-lacking AMPA receptor ion channels is required for the stabilization of LTP.

Importantly, the molecular mechanisms underlying LTP induction undergo pronounced changes during early stages of postnatal development (Wickström et al. 2003; Yasuda et al. 2003). Because relatively immature (2- to 3-wk-old) animals were used in the study of Plant et al. (2006) we examined whether activation of newly inserted GluR2-lacking AMPA receptors is also required for LTP at excitatory synapses onto hippocampal CA1 pyramidal cells in adult animals.

METHODS

Standard techniques were used to prepare 400-μm-thick slices from hippocampi obtained from halothane-anesthetized C57BL/6 mice (Charles River Laboratories, Wilmington, MA). All procedures were approved by the UCLA Institutional Animal Care and Use Committee. Slices were maintained in interface-type chambers (Fine Science Tools, Foster City, CA) at 30°C in oxygenated (95% O_2-5% CO_2) artificial cerebrospinal fluid (ACSF) containing (in mM): 124 NaCl, 4.4 KCl, 25 mM $NaHCO_3$, 1 NaH_2PO_4, 2 $CaCl_2$, 1.2 $MgSO_4$, and 10

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glucose (flow rate = 2–3 ml/min). A bipolar nichrome wire stimulating electrode was placed in stratum radiatum of the hippocampal CA1 region to activate Schaffer collateral fiber synapses onto CA1 pyramidal cells and the resulting excitatory postsynaptic potentials (EPSPs) were recorded using an extracellular glass microelectrode (filled with ACSF; resistance = 5–10 MΩ) placed in stratum radiatum or by using whole cell current-clamp recordings. The initial slope of EPSPs was used to measure the AMPA-receptor–mediated component of the postsynaptic potentials. Presynaptic fibers were stimulated once every 50 s during extracellular recordings and once every 20 s during whole cell recordings.

Inhibitory synaptic transmission was blocked during whole cell recordings by adding 100 μM picrotoxin to the ACSF. The CA3 region was removed and slices were bathed in a modified ACSF containing 4.0 mM $CaCl_2$, 2.4 mM $MgSO_4$, and 2.4 mM KCl to prevent spontaneous and evoked bursting that can occur in the absence of inhibition. In these experiments recording electrodes pulled from Schott 8250 glass tubing (A-M Systems, Carlsborg, WA) were filled with a solution containing (in mM): 122.5 cesium gluconate, 17.4 CsCl, 2.0 $MgCl_2$, 10.0 TEA-Cl, 0.2 mM EGTA, 2.0 ATP, 0.3 GTP, and 10 HEPES (pH = 7.2). Electrode and series resistances ranged from 3 to 7 and 10 to 30 MΩ, respectively. Hyperpolarizing current was injected through the recording electrode to maintain membrane potentials of −80 to −85 mV and a 50-ms-long −0.1-nA pulse of current was injected 170 ms after each evoked EPSP to monitor input and series resistance throughout the experiment. Data acquisition and analysis were performed using the Experimenter's Workbench and Common Processing software package (DataWave Technologies, Longmont, CO) or pClamp (Molecular Devices, Sunnyvale, CA). IEM-1460 was obtained from Tocris Bioscience (Ellisville, MO). All other compounds were obtained from Sigma–Aldrich (St. Louis, MO).

RESULTS

To examine whether LTP in the hippocampus of adult animals requires activation of GluR2-lacking AMPA receptors after high-frequency stimulation (HFS) we first examined the effects of pausing synaptic stimulation after HFS in slices obtained from 8- to 12-wk-old mice. In these experiments LTP was induced using two 1-s-long trains of HFS (100 Hz, intertrain interval = 10 s). A single pulse of presynaptic fiber stimulation was delivered 5 s after the second train of HFS and synaptic stimulation (delivered at 0.02 Hz) was then either delivered throughout the experiment or halted for the first 15 min post HFS. As shown in Fig. 1*A*, pausing synaptic stimulation for 15 min after HFS had no effect on the amount of LTP observed 30 min post HFS. In these experiments field EPSPs (fEPSPs) measured 30 min post HFS were potentiated to 199 ± 8% of baseline (n = 6) in slices where synaptic stimulation was omitted for 15 min post HFS compared with 195 ± 14% of baseline in interleaved control slices where synaptic stimulation was continued throughout the experiment (n = 5). Pausing synaptic stimulation for an even longer period of time post HFS (30 min) also had no effect on LTP (Fig. 1*B*).

To determine whether the stimulation protocol used to induce LTP might influence the dependence of LTP on postinduction synaptic stimulation we next examined whether pausing synaptic stimulation disrupted LTP in whole cell current-clamp recordings where LTP was induced by pairing 100 pulses of presynaptic fiber stimulation (at 2 Hz) with tonic depolarization of a postsynaptic cell to −10 mV, a protocol used by Plant et al. (2006). Presynaptic fibers were stimulated three times (at 0.05 Hz) immediately postpairing and then synaptic stimulation was either continued (at 0.05 Hz) for the remainder of the experiment or omitted for the next 15 min. As shown in Fig. 1*C*, EPSPs were potentiated to 258 ± 15% of baseline 30 min postpairing in cells where synaptic stimulation was paused for 15 min postpairing (n = 6) compared with

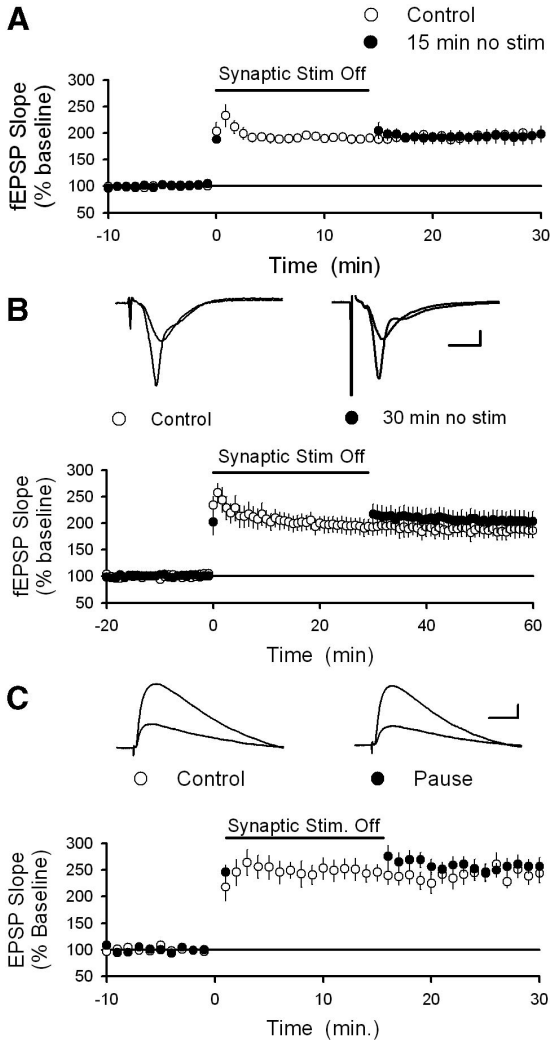

FIG. 1. Postinduction synaptic activity is not required for high-frequency stimulation (HFS)–induced long-term potentiation (LTP) in slices from adult animals. *A*: similar levels of LTP were induced in slices where synaptic stimulation was omitted for 15 min post HFS (filled symbols, n = 5) compared with interleaved control experiments (open symbols, n = 6). *B*: pausing synaptic stimulation for 30 min post HFS also fails to disrupt LTP maintenance. Sixty minutes post-HFS field excitatory postsynaptic potentials (fEPSPs) were potentiated 198 ± 18% of baseline in experiments where synaptic stimulation was halted for 30 min post HFS (filled symbols, n = 6) and were potentiated to 189 ± 11% of baseline in interleaved control experiments (open symbols, n = 7). *Inset*: superimposed traces recorded during baseline and 60 min post HFS in a control experiment (*left*) and in an experiment where synaptic stimulation was paused for 30 min post HFS (*right*). Calibration bars are 2 mV and 5 ms. Experiments in *A* and *B* were performed using interface-type recording chambers. *C*: maintenance of pairing-induced LTP does not require postinduction synaptic stimulation. Similar levels of LTP were induced in cells where synaptic stimulation was halted for 15 min postpairing (filled symbols, n = 6) and in interleaved control cells (open symbols, n = 8). Experiments were performed using a submerged-slice recording chamber. Traces show superimposed EPSPs recorded during baseline and 30 min post pairing in a control experiment (*left*) and in an experiment where synaptic stimulation was paused for 15 min postpairing (*right*). Calibration bars are 5 mV and 20 ms.

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241 ± 15% of baseline in interleaved control cells where synaptic stimulation was continued throughout the experiment ($n = 8$). Together, these results demonstrate that LTP can be induced in the CA1 region of hippocampal slices from adult animals even when synaptic stimulation is omitted for many minutes after HFS or pairing. Thus in contrast to findings obtained using slices from younger animals (Plant et al. 2006), our results suggest that activation of synaptic AMPA receptors after HFS or pairing is not required for the stabilization of LTP in the adult hippocampus.

To investigate whether the induction of LTP in the adult hippocampus is associated with the insertion of GluR2-lacking AMPA receptors into the postsynaptic membrane we next examined the sensitivity of potentiated synapses to effects of the selective GluR2-lacking AMPA receptor blocker IEM-1460 (Buldakova et al. 2007; Magazanik et al. 1997; Samoilova et al. 1999). As shown in Fig. 2*A*, bath application of IEM-1460 (100 or 200 μM) for 20 min beginning immediately post HFS had no effect on LTP. In these experiments synaptic transmission was potentiated to 194 ± 11% of baseline at the end of the IEM-1460 application ($n = 9$) compared with 198 ± 9% of baseline at the same time post HFS in control experiments ($n = 10$). At these concentrations a 20-min bath application of IEM-1460 strongly inhibited synaptic transmission in the CA1 region of GluR2-null mutant mice (Sans et al. 2003), indicating that the lack of effect of IEM-1460 in these experiments is not due to insufficient inhibition of GluR2-lacking AMPA receptors (Fig. 2*B*). These results suggest that the enhancement of synaptic transmission at this time point after LTP induction is not dependent on the insertion of GluR2-lacking AMPA receptors into synapses. Moreover, by 60 min post HFS fEPSPs were potentiated to 186 ± 11% of baseline in slices exposed to IEM-1460 ($n = 9$) compared with 180 ± 7% of baseline in interleaved control slices ($n = 10$). Thus activation of GluR2-lacking AMPA receptors also does not appear to be required for the maintenance of LTP in the adult hippocampus. Indeed, in a separate series of experiments we found that transiently blocking all ionotropic glutamate receptors with the broad-spectrum antagonist kynurenate (3.0 mM) for 20 min post HFS had no effect on LTP measured 60 min post HFS (Fig. 2*C*).

Because our results in slices from adult animals were so strikingly different from those of Plant et al. (2006) we wanted to confirm that synaptic activation of GluR2-lacking AMPA receptors is required for LTP in the hippocampus of immature mice under our experimental conditions. Surprisingly, omitting synaptic stimulation for 15 min postpairing had no effect on LTP in slices obtained from 15- to 17-day-old mice (Fig. 3*A*). Moreover, LTP was completely insensitive to a 20-min bath application of IEM-1460 (100 μM) delivered starting 5 min postpairing in cells recorded from slices obtained from 21- to 23-day-old mice (Fig. 3*B*). Thus as in the adult hippocampus, we find that activation of GluR2-lacking AMPA receptors is not required for the early expression and maintenance of LTP in the hippocampus of immature mice.

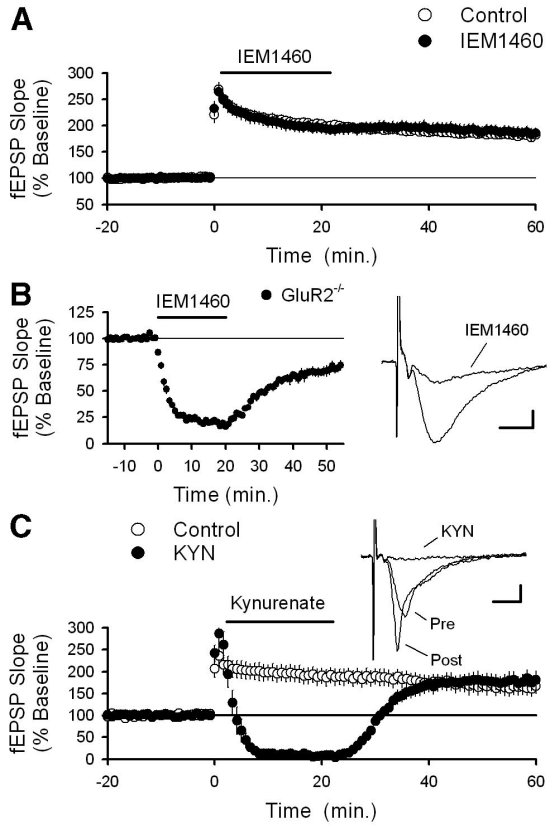

FIG. 2. Postinduction activation of glutamate receptor type 2 (GluR2)–lacking α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors is not required for HFS-induced LTP. *A*: IEM1-460 does not block potentiated synaptic transmission. IEM-1460 (100–200 μM, n values of 6 and 3, respectively) was bath applied for 20 min post HFS (indicated by the bar). Results with these concentrations of IEM-1460 were the same and were therefore combined. IEM-1460 had no effect on potentiated synaptic transmission (filled symbols, $n = 9$) compared with interleaved control experiments (open symbols, $n = 10$). *B*: a 20-min bath application of 100 μM IEM-1460 (indicated by the bar) strongly inhibits synaptic transmission in the CA1 region of GluR2-null mutant mice. Field EPSPs were reduced to 19 ± 0.9% of baseline in the presence of IEM-1460 ($n = 8$ slices from 2 mice, $P < 0.001$, paired t-test comparison to baseline). Responses shown on the *right* are superimposed fEPSPs recorded during baseline and 20 min after application of IEM-1460. Calibration bars are 0.25 mV and 5 ms. *C*: LTP is not disrupted by a 20-min bath application of 3.0 mM kynurenate (KYN, indicated by the bar) delivered immediately post HFS (filled symbols, $n = 4$). After washout of the antagonist, synaptic transmission recovered to a potentiated level nearly identical to that seen in interleaved control experiments (open symbols, $n = 4$). *Inset*: superimposed fEPSPs recorded during baseline (Pre), in the presence of kynurenate, and 60 min post HFS (Post) in a representative experiment. Calibration bars are 0.5 mV and 5 ms. Experiments in *A*, *B*, and *C* were performed using submerged-slice type recording chambers.

DISCUSSION

The idea that LTP induction involves a transient insertion of GluR2-lacking AMPA receptors into the synapse and that activation of these receptors is then required for the stabilization of LTP is an intriguing hypothesis. Our results, however, are inconsistent with both of these notions. In contrast to the findings of Plant et al. (2006) we find that blocking GluR2-lacking AMPA receptors with IEM-1460 has no effect on potentiated synapses, indicating that the expression of LTP is not due to the insertion of GluR2-lacking AMPA receptors. Moreover, omitting synaptic transmission or blocking all AMPA receptors with kynurenate for extended periods of time after LTP induction had no effect on LTP in our experiments. This indicates that postinduction increases in intracellular Ca^{2+} due to influx by GluR2-lacking AMPA receptor ion channels are not required for LTP stabilization. Although our findings are at odds with those reported by Plant et al. (2006), our

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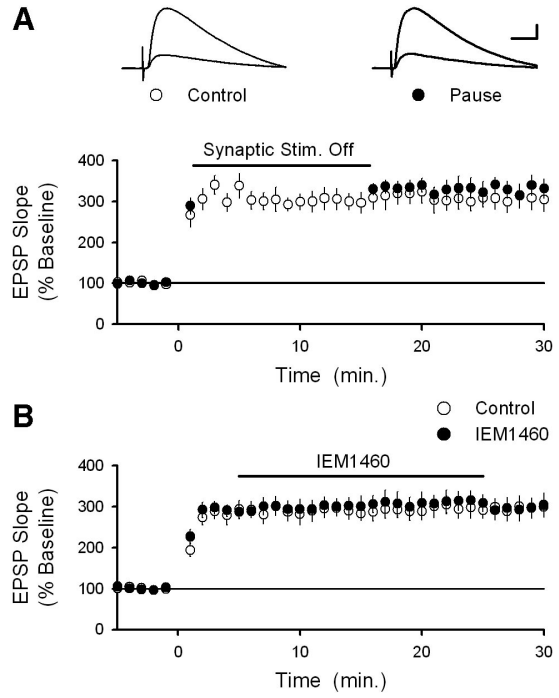

FIG. 3. Postinduction activation of GluR2-lacking AMPA receptors is not required for pairing-induced LTP in slices from immature mice. *A*: in CA1 pyramidal cells from 15- to 17-day-old mice EPSPs were potentiated to 329 ± 22% of baseline in experiments where synaptic stimulation was paused for 15 min postpairing (filled symbols, $n = 7$) and were potentiated to 306 ± 28% of baseline in interleaved control experiments (open symbols, $n = 6$). *Inset*: superimposed EPSPs recorded during baseline and 30 min postpairing in a control cell (*left*) and in a cell where synaptic stimulation was omitted for 15 min postpairing (*right*). Calibration bars are 5 mV and 20 ms. *B*: bath application of IEM-1460 (100 μM) for 20 min postpairing (indicated by the bar) has no effect on LTP in CA1 pyramidal cells from immature, 21- to 23-day-old, animals. Thirty minutes postpairing EPSPs were potentiated to 297 ± 27% of baseline in cells exposed to IEM-1460 (filled symbols, $n = 6$) and to 298 ± 23% of baseline in interleaved control cells (open symbols, $n = 7$). Experiments in *A* and *B* were performed using a submerged-slice recording chamber.

results are consistent with a number of previous findings. For instance, several studies have shown that transiently blocking all AMPA receptors at potentiated synapses with CNQX (6-cyano-7-nitroquinoxaline-2,3-dione) (Kauer et al. 1988; Muller et al. 1988) or kynurenate (Lüscher et al. 1998) has no effect on the maintenance of LTP. Similarly, the selective GluR2-lacking AMPA receptor blocker philanthotoxin has also been shown to have no effect on transmission at synapses that underwent LTP before delivery of the toxin (Matthies et al. 1992). In addition, our observation that LTP persists even when AMPA receptors are not activated for extended periods of time after induction is consistent with the finding that preventing increases in intracellular calcium with photoactivatable calcium chelators as soon as 2 s postinduction has no effect on LTP maintenance (Malenka et al. 1992). Finally, our findings are in complete agreement with those described in a recent report showing that GluR2-lacking AMPA receptors are not inserted into synapses following the induction of LTP in hippocampal slices from young animals (Adesnik and Nicoll 2007).

Although it is not clear why we were unable to replicate the findings of Plant et al. (2006), we suspect that one or more methodological differences may be involved. One possibility is that the techniques used to prepare and maintain slices in vitro, which can have a profound effect on both phosphorylation and expression of AMPA-receptor subunits in hippocampal slices (Ho et al. 2004; Taubenfeld et al. 2002), might be an important variable. Because our experiments were done at 30°C, whereas those of Plant et al. (2006) were done at room temperature, another possibility is that the involvement of GluR2-lacking AMPA receptors in LTP is temperature dependent (however, see Adesnik and Nicoll 2007). In any event, our findings indicate that the insertion of GluR2-lacking AMPA receptors into the postsynaptic membrane and the requirement for activation of these receptors for LTP maintenance are not fundamental properties of *N*-methyl-D-aspartate receptor-dependent LTP.

ACKNOWLEDGMENTS

We are grateful to members of the UCLA Learning and Memory Project for helpful comments.

GRANTS

This work was supported by National Science Foundation Grant 0543651 and National Institute of Mental Health Grant MH-609197 to T. J. O'Dell. Additional support was provided by a National Health and Medical Research Council of Australia Project Grant, a New South Wales (NSW) State Government BioFirst Award, and NSW State Government Spinal Cord Injury and Related Conditions Project Grant to B. Vissel.

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