Metabotropic Glutamate Receptors Are Involved in Long-Term Potentiation in Isolated Slices of Rat Medial Frontal Cortex

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Vickery, R. M., Shanida H. Morris, and Lynn J. Bindman. Metabotropic glutamate receptors are involved in long-term potentiation in isolated slices of rat medial frontal cortex. J. Neurophysiol. 78: 3039–3046, 1997. The prelimbic region of medial frontal cortex in the rat receives a direct input from the hippocampus and this functional connection is essential for aspects of spatial memory. Activity-dependent changes in the effectiveness of synaptic transmission in the medial frontal cortex, namely long-term potentiation (LTP) and long-term depression (LTD) can persist for tens of minutes or hours and may be the basis of learning and memory storage. Glutamatergic activation of ionotropic receptors is required to induce both LTP and LTD. We now present evidence of the involvement of metabotropic glutamate receptors in LTP in isolated slices of frontal cortex. Repetitive bursts of stimulation at theta frequencies (TBS) were applied to layer II, and monosynaptic EPSPs were monitored in layer V neurons of the prelimbic area. TBS was found to be more effective at inducing LTP than tetanic stimulation at 100 Hz and produced LTP that lasted >30 min in 8 out of 14 neurons. Tetanic stimulation at 100 Hz in the presence of the N-methyl-D-aspartate (NMDA) antagonist 2-amino-5-phosphonopentanoate (AP5) was reported to be a reliable method of inducing LTD in prelimbic cortex (Hirsch and Crépel 1991). However, we found that this protocol did not facilitate the induction of LTD. The role of metabotropic glutamate receptors (mGluRs) in LTP was assessed by using the selective, broad-spectrum antagonist (R, S)-α-methyl-4-carboxyphenylglycine (MCPG). This drug significantly reduced the incidence of LTP after TBS to only 1 of 14 neurons (P < 0.02, χ² test). The pooled responses to TBS in MCPG showed significantly reduced potentiation [(P < 0.02, analysis of variance (ANOVA)]. The broad-spectrum mGluR agonist (1S,3R)-1-aminoциclopentane-1,3-dicarboxylic acid (ACPD) and the selective group I agonist S-3 hydroxyphenylglycine (S-3HPG) both produced membrane depolarization, an increase in number of spikes evoked by depolarizing current pulses, and a reduction in the afterhyperpolarization. Similar effects were produced by these agonists even when synaptic transmission was blocked by use of the γ-aminobutyric acid-B (GABA_B) receptor agonist, 200 μM baclofen, which suggests that group I mGluRs are present on layer V neurons. We conclude that mGluRs participate in the production of LTP in prelimbic cortex, and that this excitatory effect could be mediated by the postsynaptic group I mGluRs.

INTRODUCTION

The hippocampus and medial frontal cortex are part of a neural pathway that is important for spatial memory formation. Behavioral experiments in the rat showed that lesions (Kesner et al. 1996; Kolb et al. 1994) or reversible inactivation (Floresco et al. 1997) of medial frontal cortex and its hippocampal inputs led to significant impairment in the performance of tasks that involved spatial memory. These effects were observed with up to a 30 min delay between training and test, implying that the disruption includes short-term memory formation (Floresco et al. 1997).

Long-term potentiation (LTP), a form of experimentally induced synaptic plasticity, can be elicited at the synapses between the hippocampal input and neurons in prelimbic cortex in vivo (Laroche et al. 1990). In awake rats, the LTP in the prelimbic cortex persists for 1 to 3 days (Doyere et al. 1993). The synapses are glutamatergic (Jay et al. 1992) and LTD induction requires N-methyl-D-aspartate (NMDA) receptor activation (Jay et al. 1995). The EPSPs elicited in layer V neurons by shocks applied to layer I in isolated slices of prelimbic cortex are also glutamatergic and require NMDA activation to elicit LTD (Hirsch and Crépel 1990, 1992). Tetanic stimulation at 50–200 Hz in layer I/II had mixed effects. Long-term depression (LTD) was elicited in about one-half of the cells, LTP in about one-third of the cells, and there was no change in the remainder (Hirsch and Crépel 1990, 1991; Nowicky and Bindman 1993).

LTP induction is known to be dependent on a rise in postsynaptic [Ca²⁺] in prefrontal neurons (Hirsch and Crépel 1992). In addition to Ca²⁺ influx via NMDA receptors, voltage-activated Ca²⁺ channels may also be important, as the probability of obtaining LTP is increased after block of K⁺ channels, which leads to greater membrane depolarization (Nowicky and Bindman 1993). Activation of group I metabotropic glutamate receptors (mGluRs), namely mGluR1 and mGluR5 (see Pin and Duvoisin 1995), is another possible contributor to raised intradendritic Ca²⁺. These mGluRs act via G-proteins, phospholipase C, and 1,4,5-inositol triphosphate (IP₃) to release Ca²⁺ from intracellular stores. The activation of mGluRs also leads to production of diacylglycerol (DAG), and an increase in protein kinase C (PKC) activity, which is linked to LTP production.

The effect of the mGluR antagonist (R,S)-α-methyl-4-carboxyphenylglycine (MCPG) on the induction of hippocampal LTD has been controversial, in that some workers found it blocked LTP and hence inferred an important role for mGluRs (Bortolotto et al. 1994; Riedel et al. 1994). Others however found no effect of MCPG (Selig et al. 1995).

Our aim was to investigate the role of mGluRs in synaptic plasticity in the prelimbic cortex, because both mGluR1 and mGluR5 were shown with immunohistochemistry to be present in frontal cortex (Roberts 1995; Romano et al. 1995). We first used tetanic stimulation in the presence of 2-amino-5-phosphonopentanoate (AP5) (Hirsch and Crépel 1991; Kato 1993) to increase the probability of LTD induction, but were unable to confirm published results.
We then investigated whether or not theta frequencies (TBS) would be more effective than tetanic stimulation in producing LTP, because theta rhythm stimulation (TBS) is effective in eliciting hippocampal LTP (see O’Keefe and Recce 1993) and hippocampal axons from CA1 and the subiculum may be among those activated by electrical stimulation in layer I or II (Jay and Witter 1991). The effects of mGluR antagonists on the induction of LTP with a TBS protocol were then studied. Abstracts of preliminary results were published (Morris et al. 1996; Vickery et al. 1996).

We confirmed that there was excitatory mGluR activity in the postsynaptic neurons by testing the action of group I mGluR agonists on intracellularly evoked firing in synaptically isolated layer V cells.

METHODS

Preparation

Coronal slices, 400 μm thick, containing the prelimbic area of medial frontal cortex were isolated from male Sprague-Dawley rats, killed by cervical dislocation. The majority of rats were between 80 and 100 g (26–33 days old) and no correlation was seen between age and LTP induction. After incubation at room temperature for >1 h, slices were submerged in artificial cerebrospinal fluid solution (ACSF) containing (in mM) 125 NaCl, 3.2 KCl, 26 NaHCO3, 1.2 NaH2PO4, 2 MgCl2, 2 CaCl2, and 10 d-glucose, bubbled with 95% O2-5% CO2, maintained at 31–33°C to within 0.5°C. The fluid was recirculated at a flow rate of 2 to 3 ml/min.

Drugs

Drugs were applied by bath perfusion in all experiments. Bicuculline methiodide (Sigma), used in all experiments, was diluted in ACSF to 1 μM. MCPG (Tocris-Cookson) was used at 500 μM in ACSF (Bortolotto et al. 1995) containing 0.5 μM NaOH once the stock solution was diluted. Control experiments showed the NaOH itself had no effect on the EPSP. (1S,3R)-1-aminoacyclopentane-1,3-dicarboxylic acid (ACPD; Tocris Cookson) was used at 50 μM and S-3-hydroxy phenylglycine (S-3HPG; Tocris-Cookson) at 200 μM. Baclofen (Sigma) was bath applied at 200 μM. d-2-amino-5-phosphonopentanoic acid (d-AP5; Sigma) was used at 40 μM.

Recording and stimulation

Cells were recorded within a restricted portion of the prelimbic (PL) area of medial frontal cortex as labeled by Conde et al. (1995) on the basis of the termination of afferents from medial dorsal thalamus. The PL area corresponds to the ventral portion of the prelimbic area labeled according to cytoarchitectonic maps of Zilles (1985). The dorsal boundary was at the level of the forceps minor of the corpus callosum and slices were between rostrocaudal levels bregma 3.2 and 2.2 (Paxinos and Watson 1982). Figure 1 shows all recording positions in experiments with TBS to elicit LTP. Two IL recordings and one layer III recording are included in the pooled data. Stimulating electrodes (not shown) were placed in layer II/III at border with layer I.

Intracellular recordings were made from layer V cells by using electrodes filled with 4 M K-acetate. Current was passed into the cell via a bridge circuit and used to monitor the input resistance with −0.1 nA pulses of 70 ms duration. Cell excitability and action potential amplitude were tested periodically by applying depolarizing current pulses. EPSPs were evoked by placing a bipolar stimulating electrode in layer II at the border of layer I and applying test shocks once every 15 or 20 s with a 0.05 or 0.1 ms, constant-voltage shock. In the control period subthreshold EPSPs [mean amplitude 4.7 ± 2.9 mV (SD)] were evoked for at least 20 min. Conditioning TBS consisted of a train of four shocks at 100 Hz, repeated 10 times at 5 Hz. Five TBS trains were applied at 1 min intervals. Conditioning shocks were increased to 0.1 or 0.2 ms duration and in some cells depolarizing current was applied to obtain firing in each theta burst within the train. The data were stored digitally with the PClamp analysis program (Axon Instruments). The resting potential (Vm) and EPSPs were measured and successive responses were averaged (n = 12 or 16) over 4 min for the entire experiment. The initial EPSP slope was taken over 1 ms from its onset (0 to 1 ms, presumed monosynaptic component). EPSP amplitudes or slopes measured later than 1 ms were presumed to be polysynaptic. We classified the change for each experiment as LTP if the mean slope at 24–36 min postTBS was ≥120% of the baseline slope measured over the 4 min period before the start of TBS, as LTD if the slope at 24–36 min was ≤80% of control, and as no change if the postTBS slope fell between the two criteria.

Statistical tests

Paired t-tests were carried out, comparing the initial normalized EPSP slope over the 4 min immediately before the start of TBS with that at 28–32 min after the end of the last train of TBS. A χ2 test was used with Yates’ correction. To analyze the effect of MCPG more thoroughly, we used a repeated measures, two-sample ANOVA, employing the SPSS software package, on raw (non-normalized) initial EPSP slopes.

RESULTS

The layer V medial frontal cortical neurons used in this study were regular spiking neurons (McCormick et al. 1985) with resting potentials more negative than −60 mV. In all the cells tested (~40% of sample) paired pulse facilitation was seen at a 50-ms interval.

Theta burst stimulation elicits LTP in medial frontal cortex

The effectiveness of TBS for inducing changes in synaptic strength in ACSF was tested in 14 cells from 14 slices obtained from 13 rats. TBS elicited LTP of the initial 1 ms of
the EPSP, a presumed monosynaptic component, in 8 out of 14 cells (57%), which persisted \( \approx 30 \) min after stimulation ended. An example of monosynaptic LTP elicited by TBS is shown in Fig. 2, A and B. LTD was produced in 1 of the 14 cells and no persistent effect was seen in the other 5 cells. There was LTP in the presumed polysynaptic EPSP component (the slope from 1 to 2 ms and amplitude at 4 ms) of two of the five neurons that showed no lasting monosynaptic plasticity.

The pooled data from the 13 cells, in which TBS induced LTP or in which there was no effect, are illustrated in Fig. 2C. Excluding the neuron that showed LTD, the mean change in EPSP slope in response to TBS was 150 \( \pm 19\% \) (SE) at 28–32 min. If the LTD is included, the mean EPSP slope at 28–32 min is 145 \( \pm 19\% \) (SE) and is significantly different from the control \( (P = 0.039, \text{two-tailed paired } t\text{-test, } n = 14) \).

Tetanic stimulation with NMDA-receptor antagonist did not produce plasticity

Having found a reliable way of inducing LTP, we then repeated the protocol of Hirsch and Crépel (1991) for LTD induction to obtain a control for investigation of the potential involvement of mGluRs. We found that, instead of increasing the probability of LTD induction, tetanic stimulation in the presence of the selective NMDA-receptor antagonist, d-AP5 did not elicit a significant long-term change in the pooled data. A total of seven cells from seven slices were tested by using four trains at 50 Hz for 1 s (4 cells) or 100 Hz for 0.5 s (3 cells) in slices bathed in 40 \( \mu \text{M} \) d-AP5. LTP was seen in two of the seven cells at 30 min posttetanus, with no persistent effects in the others. The pooled data shows neither significant LTP nor LTD at 30 min posttetanus, Fig. 3 \( (P = 0.23, \text{two-tailed paired } t\text{-test, } n = 5) \).

Antagonists of mGluR decrease the likelihood of LTP induction

The role of mGluRs in the induction of LTP was tested by using the TBS protocol, which had produced LTP in more than half the tested synapses in ACSF. In the presence of the mGluR antagonist MCPG, TBS produced LTP in only 1 of the 14 cells tested (14 slices from 14 rats). The effect of MCPG on reducing synaptic plasticity was significant \( (P < 0.02, \chi^2\text{-test}) \). A cell in which LTP could not be elicited in the presence of MCPG, but which did show LTP in response to identical TBS after the washout of the MCPG is shown in Fig. 4, A and B. The mean EPSP slope for the pooled data from all 14 cells (Fig. 4C, C) was not significantly different at 28–32 min after the end of TBS from the control level \( (120 \pm 18\%, P = 0.26, \text{two-tailed paired } t\text{-test}) \). In three cells bathed in MCPG, TBS elicited short-term potentiation (STP) that declined to baseline by 30 min. Polysynaptic LTP of latency \( >4 \) ms was seen in 2 of the 14 slices.

We compared the non-normalized initial EPSP slopes in the two groups of cells (in ACSF and MCPG) by using a repeated measures ANOVA test. The initial EPSP slopes taken from over a 16-min period before TBS were not significantly different \( (P = 0.42, n = 14 \text{ in both ACSF and MCPG}) \), which showed that the two groups of EPSPs arose from the same population. However for the period from 4 to 36 min after TBS ended, the ANOVA showed that the initial EPSP slopes in the MCPG were significantly different from those in ACSF \( (P = 0.011, n = 14 \text{ in both ACSF and MCPG, including the LTD in ACSF}) \), confirming that MCPG had a significant action in reducing the potentiation elicited by TBS.

MCPG has no effect on normal synaptic transmission or on cell membrane properties

MCPG had no effect on the initial slope of the EPSP during wash-in of the drug (Fig. 5A). The number of spikes

![Fig. 2. Monosynaptic long-term potentiation (LTP) results from TBS in artificial cerebrospinal fluid solution (ACSF). A: monosynaptic EPSP slope vs. time, each point representing average of 16 successive responses over 4 min. Error bars in this and subsequent graphs are \( \pm \) SE. Vertical dashed lines: start and finish of TBS. LTP in this cell has slow onset to maximum and lasted undiminished for 1 h. B: superimposed averaged EPSPs taken at times shown by a and b in A. C: graph of monosynaptic EPSP slope vs. time, normalized to mean of 6 averages in control period. Pooled data for 13 cells, excluding cell with long-term depression (LTD). When data for all 14 cells are included (not shown) all symbols overlap those illustrated in C.](http://jn.physiology.org/)

![Fig. 3. Failure to elicit LTD of EPSP slope in N-methyl-D-aspartate (NMDA)-receptor antagonist. Mean EPSP slope for 7 cells vs. time, normalized to mean of entire control period. Cells subjected to tetanic stimulation (100 Hz for 1 s, \( n = 3 \) or 50 Hz for 2 s, \( n = 4 \), in 4 trains at 10-s intervals) between vertical lines. Slices bathed in 40 \( \mu \text{M} \) d-2-amino-5-phosphonopentanoic acid (d-AP5) throughout experiment.](http://jn.physiology.org/)
depolarizing current pulses). Both agonists had a depolarizing effect that caused an increase in the number of spikes elicited by the current pulse. Therefore AHPs were measured while steady hyperpolarizing current was applied intracellularly to restore the membrane potential to control levels or to elicit the same number of spikes per depolarizing current pulse. In preliminary experiments, the broad-spectrum mGluR agonist ACPD was bath-applied at 50 μM, to four cells. It produced depolarization, an increase in the number of spikes per current pulse, and either a reduction in the AHP or reversal to an afterdepolarizing potential (ADP) (Fig. 6A), as found in sensorimotor cortex by Greene et al. (1994). These effects are excitatory and therefore likely to be mediated by group I mGluRs. We tested this hypothesis with the selective group I agonist S-3HPG at 200 μM in 3 cells. It produced reduction of the AHP in all the cells and depolarization of the membrane potential in two of the three cells (Fig. 6, B–D). The increase in mean input resistance (from 52.7 ± 9.4 MΩ to 53.4 ± 10.6 MΩ) was not significant.

To determine whether or not the effects of the group I agonists were mediated by postsynaptic receptors on the layer V cells from which our recordings were made, 200 μM baclofen was used to block the evoked release of transmitter and hence evoked EPSPs. In the presence of baclofen, nine cells were exposed to ACPD or S-3HPG. Membrane depolarization was seen in all nine cells. The AHP was then measured, while using steady hyperpolarizing current to ensure that the same number of spikes was evoked with and without the mGluR agonist. The bath application of ACPD in baclofen significantly reduced the AHP to 56.6 ± 11.3% (SE) of control (P = 0.018, two-tailed paired t-test, n = 5) and bath application of S-3HPG in baclofen significantly reduced the AHP to 63.0 ± 7.3% (SE) of control (P = 0.007, two-tailed paired t-test, n = 5). No consistent change in input resistance was observed. Washout of elicited by TBS was no different for neurons whether or not they were bathed in MCPG (Fig. 5B).

There were no effects on spike height, membrane potential, or input resistance because of wash-in of MCPG (Table 1).

**Site of action of mGluR agonists in medial frontal cortex**

The activity of mGluRs has not previously been examined in prelimbic cortex. Sixteen slices from 14 rats were used to examine the effect of the mGluR agonists ACPD and S-3HPG on the peak of the afterhyperpolarizing potential (AHP) after short trains of spikes (induced by 70–400 ms

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**FIG. 4.** TBS typically did not produce LTP in slices bathed in metabotropic glutamate receptor (mGluR) antagonist (R,S)-α-methyl-4-carboxyphenylglycine (MCPG). A: monosynaptic EPSP slope vs. time for one cell showing failure to induce LTP in MCPG. Identical stimulation did produce LTP after washout of MCPG (horizontal black bar: duration of exposure to MCPG). Inserts (above dotted lines): depolarization and spiking during 5th theta bursts in first train in MCPG and ACSF. Difference in number of spikes per train during TBS in MCPG vs. ACSF was not significant (P > 0.1, 2-tailed t-test). Calibration bar: 10 mV, 10 ms. B: superimposed averaged responses at times indicated in A of initial slope show lack of effect of TBS on initial slope in MCPG but potentiation in ACSF. Horizontal black bars (below traces): times over which values were averaged to obtain EPSP slope. C: graph of monosynaptic EPSP slope vs. time, normalized to 6 control points. Pooled data for 14 cells bathed in MCPG throughout recording period (()]. Increased slope after TBS is not significantly different from control. pooled data excluding cell displaying LTP (n = 13 cells) is also shown (○).

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**FIG. 5.** Lack of effect of MCPG on electrophysiology of test and conditioning responses. A: Graph showing monosynaptic EPSP slope vs. time, normalized to 6 points in control. Slices bathed in MCPG for time of horizontal black bar. B: Comparison of effect of TBS in MCPG and ACSF. Mean ± SE of total number of spikes during all 5 trains in TBS for 5 cells in MCPG and 5 cells in ACSF (CSF). Two of the cells were analyzed in both solutions.
the agonists produced partial recovery within 20 min (Fig. 7, A–F).

DISCUSSION

Synaptic plasticity in the prelimbic region of frontal medial cortex

We have established that TBS is more effective than 50–200 Hz tetanic stimulation in inducing LTP in the prelimbic area of medial frontal cortex. The physiological mechanism underlying the type of short-term memory described by Floresco et al. (1997) in prelimbic cortex would need to persist at least half an hour. The LTP in prelimbic cortex produced by stimulation of hippocampal afferents in awake rats persists for days, although there is some decline over this time. In the anesthetized rat, LTP in the hippocampal-prelimbic pathway endured for several hours. In our in vitro experiments, the presumed monosynaptic EPSPs in four of eight neurons showing LTP persisted undiminished at 60 min after TBS. The LTPs in the other four neurons started to decay at times ranging from 36 to 56 min after the end of TBS. Hirsch and Crépel (1990), also recording in vitro, monitored LTP of EPSP peak amplitude for at least 90 min at some synapses. Therefore LTP in prelimbic cortex could provide a substrate for behavioral changes spanning many hours.

In visual cortex Kato (1993) found that tetanic stimulation in the presence of ionotropic antagonists or activation by quisqualate in the presence of AP5, could induce homosynaptic LTD. In prelimbic cortex, we found that the addition of AP5 did not shift the induced synaptic plasticity away from LTP toward LTD as reported by Hirsch and Crépel (1991) but instead reduced the likelihood of inducing any persistent alteration of synaptic strength.

Location of mGluRs in prelimbic cortex

Immunostaining techniques show that both mGluR1 and mGluR5 mRNA and protein is abundant in cerebral cortex, including the frontal medial region of the adult female Sprague-Dawley rat. The mGluR5 is present in all cortical layers and most of the staining is on postsynaptic spines and dendritic shafts (Romano et al. 1995). mGluR1 immunostaining is denser in layers II/III than in layer V, and the mGluR1 mRNA is confined to nonpyramidal neurons. In contrast to the location of mGluR1, IP3 is concentrated within pyramidal cells (Fotuhi et al. 1993).

These observations prompted us to test the response of layer V neurons to mGluR agonists. We found that either ACPD or S-3HPG produced depolarization and a reduction in the AHP of layer V cells, even when layer V neurons were pharmacologically isolated by using baclofen. This suggests that at least some of the excitatory effect of the mGluR agonists resulted from activation of group I receptors on the layer V cells. On the immunohistochemical evidence, these mGluRs are most likely to be mGluR5. An unresolved problem is that MCPG did not have an significant antagonist action on mGluR5 receptors (Brabet et al. 1995), at least on those expressed in porcine kidney cells.

Effects of mGluR antagonism on synaptic transmission

MCPG has antagonist actions on both group I (mGluR1) and group II (mGluR2) mGluRs (Pin and Duvoisin 1995).
and might alter excitatory or inhibitory activity in prefrontal cortex. MCPG could increase glutamate release at synapses and/or reduce the NMDA receptor mediated component of EPSPs (Lu et al. 1997). However we saw no evidence of significant depressant or facilitatory actions of MCPG on test EPSPs. In hippocampus mGluRs are located beyond the perimeter of the synapse, whereas AMPA receptors lie along the synapse (Lujan et al. 1996). A possible functional implication of this arrangement is that mGluRs may be activated only when repetitive synaptic activity causes sufficient glutamate release so that it spills out of the synaptic region (Scanziani et al. 1997).

Repetitive high-frequency firing is an important feature of the TBS protocol used to induce LTP in this study. The number of spikes resulting from each stimulus burst is an indicator of the level of excitation achieved during TBS in our conditioning trains. There was no evidence of a significant change of firing rate during TBS in MCPG compared with that in ACSF. This suggests that the action of MCPG in reducing LTP may not be a direct consequence of altered synaptic transmission or membrane properties in the neurons.

It is interesting that in cerebral cortex, mGluR activation was shown to produce a Ca\(^{2+}\)-mediated decrease in a resting K\(^+\) current and also a Ca\(^{2+}\)-dependent increase in an inward cation current (Greene et al. 1994). Either of these changes might account for the membrane depolarization we observed on mGluR agonist application. The opposing changes in conductance reported in these two studies could explain our failure to see a consistent change in input resistance, at a comparable membrane potential, after the application of ACPD or S-3HPG.

**Effects of group I mGluR activation**

LTP induction is known to be dependent on both a rise in dendritic [Ca\(^{2+}\)] and the activation of PKC. It is therefore likely that MCPG is antagonising the excitatory group I mGluR actions of increasing [Ca\(^{2+}\)] via IP\(_3\), and increasing PKC activity via DAG. Indeed Frenguelli et al. (1993) showed the transient dendritic Ca\(^{2+}\) rise after tetanic stimulation of CA1 cells clamped at −35 mV was reduced by MCPG. This demonstrated that mGluR activation contributes to a postsynaptic increase in [Ca\(^{2+}\)] after trains of afferent action potentials.

In addition to activation of IP\(_3\) and DAG, postsynaptic group I mGluRs enhance cell excitability and hence Ca\(^{2+}\) entry, by way of membrane depolarization (Guérit et al. 1994), a decrease in adaptation of spike firing, and a reduction of a Ca\(^{2+}\)-dependent K\(^+\) current (AHP) (Charpak et al. 1990), even in the presence of baclofen (Davies et al. 1995).

It was recently reported that MCPG can also have an agonist role in eliciting a significant PLD response (Pellegrini-Giampietro et al. 1996). This action of MCPG, by enhancing DAG and therefore PKC activation, would facilitate the induction of LTP. Because we observed a reduced incidence of LTP in the presence of MCPG, this direct agonist role is not likely to have a significant effect in our experiments.

**mGluR involvement in synaptic plasticity**

In CA1, LTP (but not STP) was blocked by MCPG in the hands of one group (Bashir et al. 1993) but not of another (Thomas and O’Dell 1995). Selig et al. (1995) used TBS in animals of three different ages and found that MCPG had no effect in blocking LTP, although it did block the actions of ACPD. Furthermore LTP was induced in mGluR1-deficient mice at several different hippocampal regions, including the dentate (Conquet et al. 1994). However MCPG blocked LTP in dentate (Riedel et al. 1994). LTP was reduced in CA1 and dentate in mGluR5 deficient mice (Lu et al. 1997). Because mGluR activation is only one of several parallel pathways that can facilitate the production of LTP, it is perhaps not surprising that different experimental protocols can elicit variable results.

In conclusion, we have shown for the first time in the cerebral cortex that the probability of inducing LTP was significantly reduced when slices were preincubated in the...
mGluR antagonist MCPG. We have also demonstrated that group I mGluR mediated activity can be produced in prelimbic cortex, even in pharmacologically isolated layer V neurons. We propose that the action of MCPG in our experiments is likely to relate to postsynaptic group I mGluR mediated alterations in the level of either IP$_3$ and intradendritic [Ca$^{2+}$] or of DAG and changes in PKC activity. By influencing either or both of these pathways, mGluRs would facilitate the induction and expression of prelimbic LTP.

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