Reexamination of the Effects of MCPG on Hippocampal LTP, LTD, and Depotentiation

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SUMMARY AND CONCLUSIONS

1. We examined the effects of the metabotropic glutamate receptor (mGluR) antagonist α-methyl-4-carboxyphenylglycine (MCPG) on the induction of long-term potentiation (LTP), long-term depression (LTD), and depotentiation in CA1 hippocampal neurons using extracellular recording techniques.

2. MCPG (500 μM) strongly antagonized the presynaptic inhibitory action of the mGluR agonist 1-aminocyclopentane-(1S,3R)-dicarboxylic acid yet failed to block LTP induced with either tetanic stimulation (100 Hz, 1 s) or theta-burst stimulation.

3. To test the possibility that our failure to block LTP was due to prior activation of a “molecular switch” that in its “on” state obviates the need for mGluR activation to generate LTP, we gave repeated periods of prolonged low-frequency stimulation (LFS; 1 Hz, 10 min), a manipulation reported to turn the switch “off.” Although this stimulation saturated LTD, subsequent application of MCPG still failed to block LTD.

4. MCPG did not block LFS-induced depotentiation in older slices (4–6 wk) or LFS-induced LTD in older, young (11–18 days), or neonatal (3–7 days) slices.

5. These results demonstrate that MCPG-sensitive mGluRs are not necessary for the induction of LTD, LTD, or depotentiation in hippocampal CA1 pyramidal cells. The possibility remains, however, that their activation may modify the threshold for the induction of these long-term plastic changes.

INTRODUCTION

The mechanisms responsible for generating long-term potentiation (LTP) and long-term depression (LTD) in the CA1 region of the hippocampus have received considerable attention because of their potential involvement in several important nervous system functions. It is generally accepted that the induction of LTP requires synaptic activation of postsynaptic N-methyl-D-aspartate receptors (NMDARs) during postsynaptic depolarization resulting in a rise in postsynaptic calcium concentration (intracellular calcium concentration, [Ca⁺²]). Similarly, homosynaptic LTD appears to require a smaller NMDAR-mediated rise in [Ca⁺²] (Bear and Malenka 1994). Although there is compelling evidence indicating that a rise in [Ca⁺²] is a mandatory trigger for LTP, there is also evidence suggesting that activation of NMDARs and a large rise in [Ca⁺²] alone may not be sufficient for generating stable LTP (Kauer et al. 1988; Kullmann et al. 1992), implying that synaptic activity provides some additional essential component.

With the discovery of metabotropic glutamate receptors (mGluRs) and the subsequent development of specific agonists and antagonists, it became possible to examine whether mGluR activation was an additional factor required for generating NMDAR-dependent LTP and LTD. Application of the mGluR agonist 1-aminocyclopentane-(1S,3R)-dicarboxylic acid (ACPD) was reported to generate a slowly developing but long-lasting synaptic potentiation that did not require NMDAR activation but did exhibit mutual occlusion with tetanus-induced LTP (Bortolotto and Collingridge 1993). Although this result was suggestive, more direct and compelling evidence for a critical role of synaptic mGluRs in LTD was obtained when the specific mGluR antagonist (RS)-α-methyl-4-carboxyphenylglycine (MCPG) became available and was found to block tetanus-induced LTD as well as the ACPD-induced potentiation (Bashir et al. 1993a). Interestingly, MCPG blocked LTD in a qualitatively different manner than NMDAR antagonists, which block both LTD and short-term potentiation (STP) (Malenka 1991); instead, an LTD-inducing tetanus given in the presence of MCPG still elicited STP (lasting <1 h). These results suggested that mGluR activation was primarily necessary for the stabilization of LTD.

Because of the simplicity of the experiment demonstrating a block of LTD by MCPG, it appeared that a role for mGluRs in LTD had been firmly established in a manner reminiscent of the first demonstration of the block of LTD by an NMDAR antagonist (Collingridge et al. 1983). However, subsequent experiments by different groups either failed to find any effect of MCPG on tetanus-induced LTD (Chinesta et al. 1993; Manzoni et al. 1994), or showed an effect different from originally reported in that only the very late phases of LTD (2–4 h after induction) were affected (Brown et al. 1994; Richter-Levin et al. 1994; Riedel and Reymann 1993), or reported that MCPG application immediately after the tetanus blocked LTD in young (15 or 30 days) but not adult (60 days) animals (Izumi and Zorumski 1994). Examination of LTD in mice lacking mGluR1 did little to clarify the role of mGluRs in synaptic plasticity (Aiba et al. 1994; Conquet et al. 1994; Malenka 1994), and even the relationship between the slow-onset, ACPD-induced potentiation and LTD has been seriously questioned (Chinesta et al. 1994).

Taken together, these studies suggest that activation of mGluRs is not an absolute requirement for eliciting LTP but instead may play some sort of conditional or modulatory role. Consistent with this idea, data have been presented suggesting that mGluRs activate a “molecular switch” that then negates the need for further mGluR activation to induce LTP (Borto...
lotto et al. 1994). This hypothesis could explain all of the negative results using MCPG if it is assumed that, for unknown reasons, before LTP induction this switch was turned on. Because understanding the role of mGluRs in synaptic plasticity is of fundamental importance for elucidating the mechanisms of LTP, we have independently in our two laboratories reexamined the effects of MCPG on NMDAR-dependent LTP in area CA1 of the hippocampus. MGlur antagonists have also been reported to block homosynaptic LTD (Bashir et al. 1993b; Bolshakov and Siegelbaum 1994; Stanton et al. 1991), and we have also, therefore, independently examined the effects of MCPG on LTD and depotentiation. Following a recent example (Paulsen et al. 1993), and because of the similarity of our results, we have decided to publish our findings together. However, because of some differences in procedures, the methods and results from each laboratory are presented separately.

![Graph A](image)

**FIG. 2.** LTP and LTD in MCPG. A: average of LTP obtained in the presence of 500 μM MCPG. There is a 19-min gap in the recording due to LFS given to the other pathway. The magnitude of LTP was 165 ± 17% (mean ± SE) of the initial baseline slope, measured 45 min post-TBS (n = 4). B: comparison of LTD obtained in the presence and absence of 500 μM MCPG. In the case of LTD obtained in the presence of MCPG, the gap in the data represents LFS stimulation given to the other pathway during the course of experiment. The magnitude of LTD obtained in the absence of MCPG was 84 ± 6% (measured 55 min after the delivery of 1 Hz, n = 4), whereas LTD obtained in the same slice in the presence of MCPG was 84 ± 5% (n = 4).

**STUDY I: BROWN EXPERIMENTS**

**Methods**

Hippocampal slices were prepared from young adult Long-Evans rats (100–150 g) using standard techniques. Each animal was anesthetized using metofane vapor and was decapitated soon after the disappearance of any corneal reflexes. Slices were collected in ice-cold artificial cerebrospinal fluid (ACSF) bubbled with 95% O₂-5% CO₂ and gently transferred to an interface chamber (Medical Systems, Greenvile, NY) continually superfused with 35°C ACSF at a rate of 1 ml/min and supplied with an atmosphere of humidified 95% O₂-5% CO₂. The composition of ACSF was (in mM) 124 NaCl, 5 KCl, 1.25 NaH₂PO₄, 1.5 MgSO₄, 2.5 CaCl₂, 26 NaHCO₃, and 10 dextrose. The slices were left in the chamber for ≥1 h to equilibrate before the experiments were performed.

Synaptic responses were measured extracellularly in the stratum radiatum of CA1 using recording microelectrodes filled with ACSF (1–2 MΩ). Synaptic responses were evoked by stimulating Schaffer collaterals with 0.2 ms pulses 2–100 μA in amplitude delivered using bipolar stimulating electrodes (200 μm OD, FHC #16–60–3). In most cases, two stimulating electrodes were placed on either side of the recording electrode to stimulate two independent pathways. The absence of cross-pathway paired-pulse facilitation was the criterion used to determine that the pathways were independent...
of each other. Baseline responses were obtained by stimulating the two inputs alternately at 0.033–0.067 Hz using a stimulation intensity that yielded a half-maximal population excitatory postsynaptic potential (EPSP) slope. To induce LTP, four episodes of theta-burst stimulation (TBS) were delivered at 0.1 Hz, using the same stimulation intensity as for baseline. TBS consists of 10 stimulus trains delivered at 5 Hz; each train consists of four pulses at 100 Hz (Larson et al. 1986). Homosynaptic LTD was induced by delivering low-frequency stimulation (LFS; 900 pulses at 1 Hz) at the same stimulation intensity as baseline (Dudek and Bear 1992). Evoked extracellular field potentials were digitized at 20 kHz and stored on an AST 386 IBM-compatible computer using Experimentor’s Workbench (BrainWave Systems, Boulder, CO) until further analysis. Initial slopes of the recorded field potentials were measured as an indicator of synaptic strength.

In all two-pathway experiments (n = 4), the experimental design was kept approximately the same. After ~20 min of stable baseline, LFS was delivered to input 1 to test the magnitude of control LTD; then 500 μM of MC PG were bath applied to the slice. After 30 min of MC PG application, TBS was delivered to input 1 to test the magnitude of LTP in the presence of 500 μM MC PG. Then LFS was delivered after ~10 min to input 2, to assess the degree of LTD induced in a naive synaptic input in the presence of the drug. Finally, LFS was given to input 1 to assess depotentiation in MC PG.

A stock solution of MC PG [(RS)-α-methyl-4-carboxyphenylglycine; Tocris Cookson] was prepared at a concentration of 50 mM by dissolving MC PG in an equivalent concentration of NaOH solution. The stock solution was frozen in small aliquots and one of the aliquots was thawed on the day of experiment and diluted to 5-mM solution by adding normal ACSF. MC PG (5 mM) was then bath applied using a syringe pump (Harvard Apparatus, South-Natick, MA) at a rate (0.1 ml/min) that would result in an approximate concentration of 500 μM in the ACSF perfusing the slice. MC PG was applied ~30 min before attempting induction of synaptic plasticity. ACPD (Tocris Cookson) was dissolved in normal ACSF at a concentration of 10 μM.

Results

TWO-PATHWAY EXPERIMENTS. Figure 1 shows the records of a representative experiment in which responses to two pathways were monitored. Before application of MC PG, 1-Hz stimulation was delivered to one pathway to confirm that the slice could exhibit LTD. Then 500 μM of MC PG were bath applied for ~35 min. MC PG did not significantly alter the baseline responses, as can be seen in the traces of extracellular field potential recordings in Fig. 1B. To determine whether MC PG has any effect on LTP, TBS was given to input 1. TBS produced normal LTP. To test the effect of MC PG on LTD, LFS was given to input 2. LFS produced normal LTD. In addition, when the same 1-Hz stimulation
was given to the previously potentiated pathway (input 1), depotentiation resulted. These results suggest that MCPG at 500 μM does not significantly affect LTP or LTD formation.

The averaged data for LTP and LTD in the presence of 500 μM MCPG are shown in Fig. 2, A and B. The average magnitude of LTP obtained in the presence of MCPG was 165 ± 17% (mean ± SE) of baseline slope 45 min post-TBS (n = 4). Induction of LTD in a naïve pathway in the same slices reduced the response to 84 ± 5% of baseline (55 min post-LFS, n = 4) in the presence of MCPG, which is not significantly different from naïve LTD produced in the same slices in the absence of the drug (84 ± 6%, n = 4). These results show that, using our experimental conditions, MCPG at 500 μM does not affect LTP or LTD in CA1 cells.

EFFECT OF MCPG ON ACPD-INDUCED SYNAPTIC DEPRESSION.
To determine whether MCPG at 500 μM is acting as an antagonist at mGluRs under the conditions of our experiments, its effect on ACPD-induced synaptic depression was studied. ACPD is a selective agonist at some subtypes of mGluRs (Schoepf et al. 1990). Previous reports have shown that ACPD can produce a transient depression of the synaptic responses, probably mediated by a presynaptic mechanism (Baskys and Malenka 1991). After collecting baseline responses for ~20 min, 10 μM of ACPD were washed on to the slice. This produced a synaptic depression that lasted as long as ACPD was present. ACPD (10 μM) reduced the response to 77 ± 7% of baseline control measured 25 min after the start of the ACPD application (n = 3) (Fig. 3). Once the response in ACPD had stabilized, 500 μM of MCPG were bath applied for ~20 min. MCPG reversed ACPD-induced synaptic depression; the response returned to 93 ± 5% of control 15 min after the start of the MCPG application (n = 3). After washout of MCPG, synaptic transmission was again depressed by the 10 μM ACPD, back to 73 ± 1% of control, 10 min after the MCPG was turned off (n = 3). The synaptic response returned near to the original baseline after washout of 10 μM ACPD (95 ± 4% of initial baseline, 25 min after ACPD washout, n = 3). These results demonstrate that 500 μM MCPG can reversibly antagonize an effect mediated by ACPD.

STUDY 2: UCSF Experiments

Methods

Hippocampal slices were prepared from 4- to 6-wk-old Sprague-Dawley rats (except where noted), allowed to recover for 1–4 h,
and then transferred to a recording chamber where they were sub-
merged beneath a continuously superfusing ACSF (28–29°C) satu-
rated with 95% O2-5% CO2. The composition of our ACSF was
(in mM) 119 NaCl, 2.5 KCl, 2.5 CaCl2, 1.3 MgSO4, 1 NaH2PO4,
26.2 NaHCO3, and 11 glucose. Stimulating techniques, recording
techniques, data collection, and data analysis were the same as
those described previously (Huang et al. 1992; Mulkey and Ma-
lenka 1992). Each pathway was stimulated in alternation at either
0.1 or 0.033 Hz. For two-pathway experiments, stimulating elec-
trodes were placed on either side of the recording electrode. Data
in the text and in the summary graphs are presented as mean ±
SE. The mean percent change in EPSP slope was calculated by
averaging over a 10-min period taken 50–60 min after the induc-
tion of LTP and 20–30 min after the induction of LTD or depoten-
tiation, and this value was compared with the average of the 10-
min period preceding the induction protocol. LTP was elicited
using a 100-Hz, 1-1 s tetanus. LTD and depotentiation were elicited
by stimulating at 1 Hz for 10 min (LFS).

The active enantiomer of MCPG [(+)-a-methyl-4-carboxypheno-
nylglycine; Torcis Cookson] was prepared daily by first dissolving
it in an equimolar amount of NaOH and then diluting to a final
concentration of 500 µM in ACSF. It was bath applied to the slice
for ≥20 min before the induction of LTP, LTD, or depotentiation.
Solutions containing D-2-amino-5-phosphonovaleric acid (D-APV)
(Toris Cookson) or ACPD (Torcis Cookson) were prepared daily
from stocks (25 mM in water). Nifedipine (Sigma) was prepared
daily as a stock (20 mM) in dimethylsulfoxide which was protected
from light and diluted to its final concentration (20 µM in ACSF)
immediately before application.

Results

For all of our experiments examining LTP, we attempted to
match as closely as possible the conditions of previous
experiments that found a dramatic effect of MCPG on LTP
(Bashir et al. 1993a; Bortolotto et al. 1994). Thus we used
animals of the same age, the same LTP induction protocol,
and the same high concentration of MCPG (500 µM). Figure
4A shows that MCPG had no apparent effect on LTP induced
by a 100-Hz, 1-1 s tetanus. The average magnitude of LTP
was 147 ± 10% (n = 10) and the synaptic enhancement
was stable 1 h after the tetanus. To ensure that the MCPG
was effectively antagonizing mGluRs in these slices, we
examined its ability to inhibit the reversible depression of
synaptic transmission caused by the mGluR agonist ACPD
(Baskys and Malenka 1991). We first established that ACPD
(25 µM) depressed field EPSPs significantly (Fig. 4B, left
panel) in slices that had already exhibited LTP in MCPG
(Fig. 4A). ACPD was then reapplied to these same slices in
the presence of MCPG. This resulted in a large but reversible
reduction of the effects of ACPD on synaptic transmission (Fig.
4B, middle and right panels) (n = 8 pathways in 4 slices).
These results confirm that MCPG was effective under
our experimental conditions.

A possible explanation for the lack of effect of MCPG on
LTP is that during the preparation of our slices, the mGluR-
dependent molecular switch had been turned on and thus
mGluR activation was no longer necessary to generate LTP
(Bortolotto et al. 1994). Because LFS was reported to “de-
condition” or turn off the switch and thereby make LTP
induction sensitive to blockade by MCPG (Bortolotto et al.
1994), we reasoned that prior application of LFS to our
slices should reset the mGluR switch so that MCPG would
subsequently block LTP. To have an objective measure that

FIG. 6. MCPG does not affect LTD in young (11–18 days) slices or
depotentiation in older (4–6 wk) slices. A: summary (n = 8) of 2-pathway
experiments in which LFS was applied once to each pathway either in the
presence or absence of MCPG (500 µM). Although the LFS was given to
each pathway 40–60 min apart, the 2 pathways are shown superimposed
to facilitate comparison. Sample field EPSPs are shown above the graph.

B: summary (n = 16) of 2-pathway experiments in which LTP was elicited
in both pathways using repetitive tetani (100 Hz, 1 s, given 4 times 5 min
apart). LFS was then applied 20 min later either in the presence or absence
of MCPG (500 µM). LTP was induced in each path 60–90 min apart, but
as in A, to facilitate comparison, the 2 pathways are shown superimposed.
For both sets of experiments (A and B), the time of MCPG application
was randomized so that in half of the experiments the control pathway
received the LTD- or LTP-inducing stimuli 1st, and in half of the experi-
ments these stimuli were 1st given in the presence of MCPG that was then
washed out so that the control pathway could be examined.

LFS was effective, we initially performed experiments in
young slices (11–18 days), in which LFS elicits robust
LTD (Dudek and Bear 1992; Mulkey and Malenka 1992).
Furthermore, we always gave repetitive periods of LFS until
LTD was saturated to ensure that the switch was completely
“turned off.” Figure 5 shows an example (A) and a sum-
mary (B) of nine such experiments. Repetitive periods of
LFS caused a large depression (EPSP slope reduced to 48 ±
6% of baseline). After obtaining a new baseline for these
maximally depressed responses, MCPG was applied and was
still ineffective in blocking LTP, the magnitude of which
(147 ± 6%) was identical to that recorded in naive pathways
in the presence of MCPG (Fig. 4A). Because the role of
mGluRs in LTP may change during development (Izumi
and Zorumski 1994), we repeated these experiments using slices the same age (4–6 wk) as those in which the effectiveness of LFS in turning off the mGluR-dependent molecular switch had been demonstrated (Bortolotto et al. 1994). Figure 5C shows that after saturation of LTD with LFS (EPSP slope reduced to 82 ± 9% of baseline, n = 8), MCPG was again ineffective in blocking LTP (140 ± 9%). Thus we were unable to observe an effect of MCPG on LTP despite repeated attempts to turn off the postulated mGluR-dependent molecular switch.

We also examined the effects of MCPG on homosynaptic LTD in young (11–18 days) slices (Dudek and Bear 1992; Mulkey and Malenka 1992). In these two-pathway experiments, LFS was applied to one pathway in the absence of MCPG and to the other pathway in the presence of MCPG. Figure 6A shows that MCPG had no effect on LTD. LFS decreased EPSPs to 72 ± 5% of baseline in the absence of MCPG and to 76 ± 5% of baseline in its presence (n = 8). We further examined in older slices (4–6 wk) the effects of MCPG on depotentiation (Fujii et al. 1991) (Fig. 6B), which is routinely defined as the LTD that occurs on a pathway in which LTP was generated previously. Similar to our results on LTD, MCPG did not affect depotentiation. In the absence of MCPG, LFS caused a decrease in EPSP slope to 76 ± 3% of its potentiated value (n = 16); in the presence of MCPG the LFS-induced decrease reached 82 ± 3%.

Although we were unable to observe an effect of MCPG on LTD or depotentiation, it has been reported that in slices prepared from neonatal animals (3–7 days), a form of LTD exists that is blocked by MCPG or nitrendipine (Bolshakov and Siegelbaum 1994) and, unlike the homosynaptic LTD elicited in slightly older slices (Dudek and Bear 1992; Mulkey and Malenka 1992), is not dependent on NMDAR activation. Figure 7 summarizes our pharmacological examina-
tion of LTD in neonatal slices prepared from 3- to 7-day-old rats. Using our standard LFS, LTD was completely and reversibly blocked by d-APV (Fig. 7A). We then examined LTD elicited by 5-Hz stimulation applied for 3 min, the protocol used to elicit an MCGP and nifedipine-sensitive LTD (Bolshakov and Siegelbaum 1994). Surprisingly, we found that again LTD was reversibly blocked by d-APV (Fig. 7B, n = 4) but was unaffected by either MCGP (Fig. 7C, n = 5) or nifedipine (20 μM) (Fig. 7D, n = 4). The 5-Hz stimulation decreased EPSP to 84 ± 4% of baseline in the presence of MCGP, to 79 ± 5% of baseline in the presence of nifedipine, and to 81 ± 3% of baseline in control ACSF after washout of d-APV.

**DISCUSSION**

Because of the potential importance of mGluRs in generating LTP, LTD, and depotentiation in the hippocampus and the confusion in the literature concerning this issue, we have reexamined the effects of the mGluR antagonist MCGP on these phenomena. Experiments conducted independently in our two laboratories have failed to find any effect of MCGP on LTP, LTD, or depotentiation. We made significant efforts to replicate the experimental conditions in which MCGP was found to be effective. Most importantly, we have directly tested and failed to confirm what appeared to be the most likely explanation for the conflicting results concerning LTP: that mGluR activation is not absolutely required for LTD generation but instead functions as a molecular switch that when turned on negates the need for further mGluR stimulation during the induction of LTD (Bortolotto et al. 1994).

It is unlikely that MCGP was ineffective in blocking mGluRs in our experiments because it was found to inhibit effectively a well-documented action of ACPD and was applied at high concentrations (500 μM) for long periods of time (≥20 min) before the generation of LTP, LTD, or depotentiation. This confusion was chosen because it is the same as or higher than that used in previous studies that reported effects of MCGP on synaptic plasticity. However, it is difficult to rule out the possibility that during repetitive stimulation glutamate concentrations reach levels that are sufficient to compete with a high concentration of MCGP and thereby activate mGluRs.

We have also failed to confirm that the induction of LTD in neonatal hippocampus is blocked by MCGP or L-type calcium channel antagonists (Bolshakov and Siegelbaum 1994). Instead we found that, like LFS-induced homosynaptic LTD and depotentiation (Dudek and Bear 1992; Fuji et al. 1991; Mulkey and Malenka 1992), this form of LTD is blocked by d-APV and therefore requires activation of NMDARs. One difference between the two studies is that we used extracellular field recording to monitor synaptic strength, whereas the initial study used whole cell recording techniques. Because the cell was taken out of voltage clamp during the induction protocol (5 Hz for 3 min), this technical difference in recording techniques should have had no effect. However, changes in the intracellular milieu due to the whole cell recording may have modified the cells’ condition sufficiently to account for the discrepancy in results.

It is more difficult to explain the lack of effect of MCGP on LTP in the present study. Slices of different ages were examined, different recording chambers (interface and submerged) were used, and different LTP induction protocols were tested. Taken together with previous negative results (Brown et al. 1994; Chiniesta et al. 1993; Manzoni et al. 1994), we think that the experimental evidence favors the conclusion that MCGP-sensitive mGluRs are not necessary for the induction of LTD, even when synaptic strength has been maximally depressed and the hypothesized molecular switch is presumably turned off. It remains possible, however, that MCGP-sensitive mGluRs are capable of modulating the threshold for the induction of LTP and LTD, perhaps by influencing NMDAR function (Ben-Ari et al. 1992) or by affecting transmitter release (Baskys and Malenka 1991). Furthermore, it is also conceivable that MCGP-insensitive mGluRs may prove to be necessary for the generation of LTP and/or LTD.

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