(+)-MCPG Blocks Induction of LTP in CA1 of Rat Hippocampus via Agonist Action at an mGluR Group II Receptor

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Breakwell, N. A., M. J. Rowan, and R. Anwyl. (+)-MCPG blocks induction of LTP in CA1 of rat hippocampus via agonist action at an mGluR group II receptor. J. Neurophysiol. 79: 1270–1276, 1998. We investigated the effect of metabotropic glutamate receptor (mGluR) ligands on the induction of long-term potentiation (LTP) of field excitatory postsynaptic potentials (EPSPs) in CA1 of rat hippocampus, in particular the manner by which the nonsubtype selective mGluR ligand α-methyl-4-carboxyphenylglycine ([(+)-MCPG] blocks LTP induction. Normalized control LTP was blocked by (+)-MCPG (250 μM), but not by the mGluRI selective antagonist (S)-4-carboxyphenylglycine (4-CPG), the mGluRII selective antagonist 1/(2S,3S,4S)-2-methyl-2-(carboxycyclopropyl) glycine (MCCG), or the mGluRIII antagonist (S)-2-amino-2-methyl-4-phosphonobutanoic acid/α-methyl (MAP4). In contrast the mGluRII agonist (1S,3S)-1-amino-cyclopentane-1,3dicarboxylic acid ([1S,3S]-ACPD); 10 or 25 μM completely and consistently blocked LTP. The block of LTP by both (1S,3S)-ACPD and (+)-MCPG could be prevented by preincubation with the mGluRII antagonist MCCG. These studies demonstrate that (+)-MCPG blocks LTP induction through an agonist action at an mGluRII receptor and not through a nonselective antagonist action.

INTRODUCTION

The activity-dependent increase in synaptic efficacy known as long-term potentiation (LTP) is believed to be a candidate mechanism for inducing the plastic changes in synapses required for information storage. Typically induced by a high-frequency train of afferent stimulation (HFS; e.g., 100 Hz, 1 s.), LTP in area CA1 of the rat hippocampus is reliably blocked by the ionotropic glutamate receptor antagonist 2-amino-5-phosphonopentanoic acid (APV) (Collingridge 1985).

Recently, activation of metabotropic glutamate receptors (mGlRs) has also been implicated in LTP induction. Eight mGluR subtypes have been classified into three major groups: 1) mGluRI comprised of the phosphoinositide hydrolysis linked mGlRs 1 and 5, 2) mGluRII (mGluR 2 and 3), and 3) mGluRIII (mGluR 4, 6, 7, and 8). Both mGluRII and mGluRIII are believed to be linked to inhibition of adenylate cyclase and reduced forskolin stimulated 3',5'-cyclic-monophosphate (cAMP) formation (Pin and Duvoisin 1995). However, considerable controversy exists over the involvement of mGlRs in HFS-induced LTP, especially regarding whether mGluR antagonists block LTP. Although several studies have shown a block of LTP induction in hippocampus by the nonsubtype selective mGluR antagonist α-methyl-4-carboxyphenylglycine (MCPG) both in vitro (Bashir et al. 1993; Bortolotto et al. 1994; Breakwell et al. 1996; Wang et al. 1995) and in vivo (Riedel and Reymann 1993), a number of other studies found no evidence for such a block (Chinestra et al. 1993; Manzoni et al. 1994; Selig et al. 1995). In this study we examined the mGluR subtypes responsible for the block of LTP by (+)-MCPG. Recently a number of subtype-selective mGluR antagonists, the phenylglycine derivatives, have been developed (Hayashi et al. 1994). In this study we report the effects on LTP of the induction of mGluR antagonists selective for mGluRII ([S]-4-carboxyphenylglycine (4-CPG)); mGluRIII, [(S)-4-carboxycyclopropyl] glycine (CCG) 1/(2S,3S,4S)-2-methyl-2-(carboxycyclopropyl) glycine; (MCCG)); and mGluRIII, [(S)-2-amino-2-methyl-4-phosphonobutanoic acid/α-methyl (MAP4)] (see Sekiyama et al. 1996).

In addition we examined the effect of the mGluRII agonist (1S,3S)-1-amino-cyclopentane-1,3-dicarboxylic acid ([1S,3S]-ACPD) (Jane et al. 1994, 1995) on HFS-induced LTP. This agent was previously found to depress the fast component of dorsal root-evoked potentials in isolated spinal cord of the newborn rat (Jane et al. 1994; Pook et al. 1992) and depressed field excitatory postsynaptic potentials (EPSPs) in CA1 in hippocampal slices from young rats by a presynaptic action at mGluRII (Vignes et al. 1995). This drug is of interest to LTP induction because reports suggest that HFS in the presence of (1S,3S)-ACPD can block LTP in CA1 in vivo (Holscher et al. 1997).

METHODS

All experiments were carried out on hippocampal slices obtained from male Wistar rats (4–5 wk). Slices were prepared as described previously (Breakwell and Publicover 1994). Briefly, the brain was removed rapidly and cooled to ≤5°C in 95% O2-5% CO2 saturated saline containing (in mmol/l) 120 NaCl, 2.5 KCl, 1.25 NaH2PO4, 26 NaHCO3, 2 MgSO4, 2 CaCl2, and 10 D-glucose, pH 7.4. Hippocampal slices (400 μm) were prepared with a Campden vibroslicer (Campden Instruments, London, UK). Slices were maintained at 30°C in a holding chamber before transfer to a submersion-type recording chamber maintained at 30–31°C. All drugs were added directly to the perfusate and were purchased from Tocris Cookson (Bristol, UK).

Potentials were recorded extracellularly with standard saline-filled glass microelectrodes placed in the stratum radiatum of area CA1, stimuli being applied to the Schaffer collateral-commisural pathway through a bipolar, insulated tungsten wire electrode. Test stimuli (0.033 Hz, width 150 μs) with intensity adjusted to give 30–40% of maximal population EPSP slope, were applied throughout all experiments. Potentials were fed through an ITC-16 interface (Instrutech, New York) to a Macintosh microcomputer. Maximum EPSP slope was measured by using Axodata/Axograph (Axon Instruments).
MCPG block LTP via agonist action

was bath applied 30 min before HFS. LTP induction was blocked in all of the slices tested, although a short-term potentiation, which decayed to baseline within 40 min, was observed. Mean normalized EPSP slope at HFS + 40 min was 1.13 ± 0.09 (Fig. 2), not significantly different from baseline ($P = 0.71, n = 6$) and significantly lower than slices not treated with (+)-MCPG ($P = 0.04$). We also examined the traces of EPSPs recorded during the high-frequency bursts but were unable to observe any significant differences between control traces and those recorded in the presence of (+)-MCPG, either within each stimulus train or across the eight trains per tetanus (Fig. 3, A and B).

**HFS-induced LTP is not inhibited by mGluR subtype selective antagonists**

Three mGluR subtype selective antagonists were used to investigate which mGluR group was responsible for the

**RESULTS**

**HFS-induced LTP is blocked by (+)-MCPG**

We began our investigations by ensuring that consistent LTP could be induced in control medium. HFS ($8 \times 8/200 \text{ Hz}, 200$-ms interpulse interval; stimulation intensity increased to circa 70% of maximum) was applied to a set of slices maintained in control saline. This protocol consistently induced an LTP that was maintained for $\approx 60$ min. At HFS + 40 min, mean normalized EPSP slope was $1.77 \pm 0.32$ (SE), significantly higher than baseline ($P = 0.047, n = 7$; Fig. 1). In a second set of slices we investigated whether (+)-MCPG, the nonsubtype selective mGluR antagonist, could block LTP of the dendritic EPSP. (+)-MCPG (250 $\mu$M) was bath applied 30 min before HFS. LTP induction was blocked in all of the slices tested, although a short-term potentiation, which decayed to baseline within 40 min, was observed. Mean normalized EPSP slope at HFS + 40 min was 1.13 ± 0.09 (Fig. 2), not significantly different from baseline ($P = 0.71, n = 6$) and significantly lower than slices not treated with (+)-MCPG ($P = 0.04$). We also examined the traces of EPSPs recorded during the high-frequency bursts but were unable to observe any significant differences between control traces and those recorded in the presence of (+)-MCPG, either within each stimulus train or across the eight trains per tetanus (Fig. 3, A and B).

**FIG. 1.** High-frequency stimulation (HFS) induces a long-term potentiation (LTP) of excitatory postsynaptic potential (EPSP) slope. A: example EPSPs (average of 3 consecutive traces) recorded during the experiment in Fig. 1B at times indicated to the left of each trace. B: normalized dendritic EPSP slopes (mean of 4 consecutive points) in response to Schaffer collateral stimulation (0.033 Hz) recorded in standard saline. HFS was delivered at time 0 (†). C: pooled data for 7 similar experiments, mean ± SE.

Values given in the text are normalized mean ± SE; $P$ values refer to paired $t$-tests in which potentials before HFS were compared with potentials at HFS + 40 min and, where stated, to standard $t$-tests or analysis of variance (ANOVA) comparisons in which different treatment groups were compared.

**FIG. 2.** α-Methyl-4-carboxyphenylglycine [(+)-MCPG; 250 $\mu$M] blocks HFS–induced potentiation. A: example EPSPs (average of 3 consecutive traces) recorded during the experiment in Fig. 2B at times indicated to the left of each trace. B: normalized dendritic EPSP slopes (mean of 4 consecutive points) in response to Schaffer collateral stimulation (0.033 Hz). (+)-MCPG (bar) was bath applied 30 min before HFS and did not have any effect on baseline transmission. However, following HFS, LTP was not induced; a short-term potentiation (STP) decayed to baseline within 30 min. C: pooled data for 6 similar experiments, mean ± SE.
that seen in control conditions \((P = 0.015)\). We also examined the traces recorded during the high-frequency bursts but were unable to observe any significant differences between control traces and those recorded in the presence of \((1S,3S)\)-ACPD \((10 \mu M)\), either within each stimulus train or across the eight trains per tetanus (Fig. 3, A and C).

**MCCG prevents the block of LTP by \((1S,3S)\)-ACPD \((10 \mu M)\) and by MCPG \((500 \mu M)\)**

We next demonstrated that the block of LTP observed in the presence of \((1S,3S)\)-ACPD \((10 \mu M)\) could be prevented by preincubation with the mGluRII selective antagonist MCCG \((500 \mu M)\). Slices were exposed to MCCG for not less than 30 min before application of \((1S,3S)\)-ACPD \((10 \mu M)\) as well as a nonsubtype selective ligand \((-)\)-MCPG. All drugs were preincubated for not \(\leq 30\) min before tetanic stimulation. The mGluRI selective antagonist 4-CPG \((500 \mu M)\) did not prevent induction of LTP. Mean normalized EPSP slope at HFS \(+ 40\) min was \(1.62 \pm 0.18\) \((n = 7; \text{Fig. 4A})\). The mGluRII selective antagonist MCCG \((500 \mu M)\) had no effect on baseline recordings and similarly did not affect the induction of LTP. Mean normalized EPSP slope at HFS \(+ 40\) min was \(1.38 \pm 0.07\) \((n = 5; \text{Fig. 4B})\).

Exposure of slices to the mGluRIII antagonist MAP4 \((500 \mu M)\) again failed to inhibit LTP induction because a long-lasting potentiation of EPSP slope was observed \((1.76 \pm 0.49, n = 4; \text{Fig. 4C})\). One-way ANOVA was performed for control LTP and the three drug conditions and was not found to be significant \((P = 0.79)\).

**LTP induction was blocked by \((1S,3S)\)-ACPD**

The effect of the mGluRII agonist \((1S,3S)\)-ACPD on tetanically induced LTP was examined. \((1S,3S)\)-ACPD was bath applied for not \(< 20\) min before HFS. There was no evidence of depression of the field EPSP by \((1S,3S)\)-ACPD at the concentrations tested \((10 \text{ and } 25 \mu M; \text{Fig. 5})\) and this finding was not reversed even when concentrations as high as \(100 \mu M\) were bath applied (data not shown). At low concentrations \((10 \text{ or } 25 \mu M)\), \((1S,3S)\)-ACPD consistently and reliably blocked LTP induction in all slices tested \((0.97 \pm 0.08, n = 9, \text{Fig. 5, B and C}; 0.99 \pm 0.08, n = 6, \text{Fig. 5D})\).

Mean EPSP slope following HFS in the presence of \((1S,3S)\)-ACPD \((10 \mu M)\) was significantly lower than

<FIG. 3> Traces of responses recorded during high-frequency stimulation. Each trace represents the average of the 7th and 8th bursts from 8 \times 8 bursts at 200 Hz. Typically the total depolarization increased over the 1st 2–3 bursts so that by the 4th burst the amplitude of the second EPSP was maintained in the subsequent 6 EPSPs. We observed no significant differences between control traces (A) and those recorded in the presence of \((+)-\text{MCPG (B})\) or \((1S,3S)-1\text{-aminocyclopentane-1,3-dicarboxylic acid ([1S,3S]-ACPD) (C}), either within stimulus trains or through the 8 trains per tetanus.

<FIG. 4> mGluR subtype selective antagonists fail to block LTP. Normalized dendritic EPSP slopes (mean of 4 consecutive points) in response to Schaffer collateral stimulation \((0.033 \text{ Hz})\). Drugs were preincubated for 30 min before HFS \((\text{arrow})\). A: mGluRI antagonist 4-CPG \((500 \mu M; \text{bar})\) had no consistent effect on baseline transmission and did not affect the induction of LTP \((\text{mean of 4 \pm SE})\). B: similar set of experiments in the presence of the mGluRII antagonist \((1/2S,3S,4S)-2\text{-methyl-2-(carboxycyclopropyl)glycine (MCCG) (500 \mu M)})\). MCCG \((\text{bar})\) did not affect baseline transmission or the induction of LTP \((\text{mean of 4 \pm SE})\). C: mGluRIII antagonist \((S)-2\text{-amino-2-methyl-4-phosphonobutanoic acid/alpha-methyl-AF4 (MAP4; 500 \mu M; bar})\) did not have any consistent effect on baseline or inhibit the induction of LTP \((\text{mean of 4 \pm SE})\).
DISCUSSION

We have shown that LTP induction in CA1 in vitro is prevented by \((+)-\text{MCPG}\) and by \((1S,3S)\)-ACPD (10 or 25 \(\mu\)M). We present evidence that both of these agents inhibit LTP induction by acting as agonists at the mGluRII receptor, because the mGluRII selective antagonist MCCG prevented the block of LTP by both \((+)-\text{MCPG}\) and \((1S,3S)\)-ACPD (10 or 25 \(\mu\)M). We have substantiated earlier findings in which we demonstrated a consistent block of LTP of the somatic EPSP, the population spike, and EPSP-spike potentiation by \((+)-\text{MCPG}\) (Breakwell et al. 1996) by showing a complete block of LTP of the dendritic EPSP. A large short-term potentiation (STP) persisted that decayed to baseline after 30 min, suggesting an STP not mediated by mGluRs.

\[
\frac{\text{A}}{-10} \quad 60 \quad \text{mV} \quad \text{5ms}
\]

\[
\frac{\text{B}}{-50} \quad -25 \quad 0 \quad 25 \quad 50 \quad \text{slope prep.}
\]

\[
\frac{\text{C}}{-50} \quad -25 \quad 0 \quad 25 \quad 50 \quad \text{normalized dendritic EPSP slopes}
\]

\[
\frac{\text{D}}{-50} \quad -25 \quad 0 \quad 25 \quad 50 \quad \text{mean normalized dendritic EPSP slopes}
\]

FIG. 5. Low concentrations of \((1S,3S)\)-ACPD block LTP. \(A\): example EPSPs (average of 3 consecutive traces) recorded during the experiment in Fig. 4B at times indicated to the left of each trace. \(B\): normalized dendritic EPSP slopes (mean of 4 consecutive points) in response to Schaffer collateral stimulation (0.033 Hz). \((1S,3S)\)-ACPD (10 \(\mu\)M) was bath applied (bar) for 30 min before HFS (arrow). \((1S,3S)\)-ACPD did not cause a presynaptically mediated depression of field EPSPs as noted elsewhere (see text) but did block LTP. An STP similar to that seen in control saline (Fig. 1) was not affected by \((1S,3S)\)-ACPD. \(C\): mean of 9 similar experiments in which \((1S,3S)\)-ACPD (10 \(\mu\)M; bar) blocked LTP in every experiment. \(D\): mean of 6 similar experiments in \((1S,3S)\)-ACPD (25 \(\mu\)M; bar). LTP was also blocked in every experiment and there was no significant difference between the two concentrations used.

\[
\text{muc} \mu\text{M}
\]

In all slices tested, HFS was found to induce LTP in the presence of both MCCG and \((1S,3S)\)-ACPD (10 \(\mu\)M) in contrast to \((1S,3S)\)-ACPD (10 \(\mu\)M) alone, which prevented LTP induction on every occasion. The mean normalized EPSP slope at 40-min posttetanus was 1.39 ± 0.06, significantly higher than that seen in slices exposed to \((1S,3S)\)-ACPD (10 \(\mu\)M) alone \((P = 0.009, n = 4; \text{Fig. 6})\). Preincubation with MCCG was also able to prevent the block of LTP by \((+)-\text{MCPG}\) (250 \(\mu\)M). MCCG was preincubated for 30 min before a 30-min bath application of \((+)-\text{MCPG}\).

HFS delivered in the presence of both drugs resulted in an LTP measuring 1.53 ± 0.16 \((n = 8; \text{Fig. 7})\), which was significantly higher than that seen in \((+)-\text{MCPG}\) alone \((P = 0.019)\) but not significantly different from HFS in control saline \((P = 0.47)\).

\[
\text{muc} \mu\text{M}
\]

FIG. 6. MCCG prevents the block of LTP by \((1S,3S)\)-ACPD (10 \(\mu\)M). \(A\): example EPSPs (average of 3 consecutive traces) recorded during the experiment in Fig. 5B at times indicated to the left of each trace. \(B\): normalized dendritic EPSP slopes (mean of 4 consecutive points) in response to Schaffer collateral stimulation (0.033 Hz). The mGluRII antagonist MCCG (500 \(\mu\)M; thick bar) was bath applied 20 min before \((1S,3S)\)-ACPD (10 \(\mu\)M; thin bar). HFS at time 0 (arrow) resulted in normal LTP in contrast to the block of LTP seen in \((1S,3S)\)-ACPD (10 \(\mu\)M) alone (Fig. 5). \(C\): mean of 4 similar experiments in which HFS–induced LTP on each occasion (mean ± SE).
Such a block of LTP by (+)-MCPG supports previous studies in vitro (Bashir et al. 1993; Bortolotto et al. 1994) and in vivo (Riedel and Reymann 1993).

MCPG is a nonsubtype selective mGluR ligand with reported antagonism of the mGluRI agonist (1S,3R)-ACPD-induced effects (Jane et al. 1993; Pin and Duvoisin 1995; Selig et al. 1995), of mGluRII agonist (1S,3S)-ACPD-induced effects (Bushell et al. 1996; Pin and Duvoisin 1995; Vignes et al. 1995), and weak antagonism of mGluRII agonist L-AP4–mediated effects (Bushell et al. 1996; Vignes et al. 1995). We therefore attempted to establish which mGluR group was responsible for the block of LTP by (+)-MCPG. We have shown (Fig. 4) that none of the mGluR subtype selective antagonists used in this study were able to attenuate LTP induction, suggesting that none of the antagonistic actions of (+)-MCPG can account for its block of LTP. Furthermore, it is unlikely that a combined antagonist action can account for the block of LTP by (+)-MCPG because in two slices (data not shown) we observed LTP in the presence of a cocktail of all three mGluR subtype selective antagonists. These results are in agreement with other in vivo, studies that failed to block LTP with mGluR subtype selective antagonists. The mGluRI antagonists 4-CPG (Bordi and Ugolini 1995) and (RS)-1-aminoindan-1,5-dicarboxylic acid/UPF 523 (AIDA) (Holscher et al. 1997) failed to block LTP as did the group II antagonists MCCG (Holscher et al. 1997) and (RS)-α-methylserine-O-phosphate monophenyl ester (MSOPPE) (Manahan-Vaughan 1997). The failure to block LTP in vivo by selective antagonists of mGluR subtypes is further evidence that (+)-MCPG does not block LTP induction by an antagonist action at mGluRs.

(1S,3S)-ACPD is a well known and widely used agonist at mGluRII (e.g., Holscher et al. 1997; Jane et al. 1994–1996; Pin and Duvoisin 1995; Pook et al. 1992). In the present studies we demonstrated that at low concentrations (1S,3S)-ACPD reliably and completely blocked LTP induction, strongly suggesting that it is activation of an mGluRII receptor that is responsible for the block of LTP. This is in agreement with other work that has shown previously that LTP in CA1 in vivo can be blocked by injection of (1S,3S)-ACPD (Holscher et al. 1997) and that LTP in dentate gyrus in vitro can be blocked by bath application of the mGluRII agonist (2S,2R,3S)-2-(2,3-dicarboxycyclopentyloxy)glycine (DCG-IV) (Huang et al. 1997a). (1S,3S)-ACPD did not block potentiation via a presynaptic reduction of synaptic responses, because neither a baseline depression by (1S,3S)-ACPD during low-frequency stimulation nor a reduction in the depolarization during high-frequency stimulation was observed. This is in contrast to studies in spinal cord (Jane et al. 1994; Pook et al. 1992) and CA1 (Vignes et al. 1995) from young rats in which (1S,3S)-ACPD potently depressed synaptic potentials by a presynaptic action. However, a developmental loss of mGluRII has been well documented (Ishida et al. 1993) and in the present experiments adult rats were used. Indeed, in older animals it has also been shown previously that high concentrations of (1S,3S)-ACPD fail to affect baseline recordings (Desai et al. 1992; Gereau and Conn 1995). We therefore propose that (1S,3S)-ACPD blocks LTP via a postsynaptic site of action. There is previous evidence for a postsynaptic action of (1S,3S)-ACPD because it caused an increase in holding current in rat spinal ventral horn neurons (Cao et al. 1995), reduced spike frequency adaptation, and caused postsynaptic depolarization in rat CA1 cells (Davies et al. 1995; Desai et al. 1992).

To further establish that the block of LTP by (1S,3S)-ACPD is mGluRII mediated, we added the mGluRII antagonist MCCG (Jane et al. 1995). MCCG is a highly selective antagonist at expressed mGluRII in Chinese hamster ovary cells, having no effect at mGluRI or mGluRIII (Sekiyama et al. 1996). MCCG similarly antagonized coexpressed mGluRII–mediated stimulation of inositol phosphate formation (Gomez et al. 1996). The block of LTP by (1S,3S)-ACPD in the present studies was prevented by the addition of MCCG, thus strongly supporting the hypothesis that activation of mGluRII, or a receptor with a similar pharmacological profile to mGluRII, mediates a block of LTP induction. A second important experiment was, therefore, to establish
if blocking the proposed agonist action of (+)-MCPG with MCCG could also reverse the block of LTP seen with (+)-MCPG alone. The experiments described in Fig. 7 demonstrated that LTP could readily be induced in the presence of MCCG and (+)-MCPG, indicating that (+)-MCPG does block LTP through an agonist action at an MCCG sensitive receptor. There is previous evidence for an agonist action of MCPG in the basolateral amygdala (Bradley Keele et al. 1995) because MCPG reduced EPSPs in a manner similar to (1S,3S)-ACPD but did not reduce α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)– or N-methyl-d-aspartate (NMDA)–mediated postsynaptic responses. Further evidence for an agonist action of MCPG arises from the fact that MCPG is able to stimulate phospholipase D (PLD) activity in rat hippocampus (Pelligrini-Giampietro et al. 1996). The block of LTP by (1S,3S)-ACPD and by (+)-MCPG was similar in that a large STP was followed by decay to baseline within 40 min of HFS, suggesting that the mechanisms leading to a block of LTP were also similar (i.e., an agonist action at mGluRII– or mGluRII–like receptor).

The proposed (+)-MCPG block of LTP by an agonist action may also help to explain the inconsistent effects reported in previous studies that have investigated the effect of MCPG on LTP induction in CA1 in vitro. Thus whereas a block of LTP induction was observed in several studies (Bashir et al. 1993; Bortolotto et al. 1994; Breakwell et al. 1996), a number of other studies have found no evidence for such a block (Chineastra et al. 1993; Manzoni et al. 1994; Selig et al. 1995). The experiments described by Brown et al. (1994) demonstrated that MCPG blocked LTP induction only by weak tetanic stimulation but not by stronger theta-burst stimulation, suggesting that the failure of MCPG to block LTP in the studies of Chinestra and others may have been due to the use of a stronger net stimulation. A block of LTP induction by the weak agonist action of MCPG may be relatively easily overcome by strong stimulation protocols.

The question of which mGluR is responsible for preventing the induction of LTP is complicated by the fact that (1S,3S)-ACPD is an agonist at mGluRII which includes mGluR 2 and mGluR 3 (Jane et al. 1994). The (1S,3S)-ACPD–induced depression of dorsal root–evoked potentials in the isolated cord of neonatal rats (Pook et al. 1992) and the depression of field EPSPs in young rats in dentate gyrus (Bushell et al. 1996) and in CA1 (Vignes et al. 1995) are believed to be caused by activation of a presynaptic autoreceptor, mGluR 2. We did not, however, observe any presynaptic mGluR 2–like effects, i.e., depression of evoked potentials by (1S,3S)-ACPD or (+)-MCPG, either during low- or high-frequency stimulation in the present study. In fact MCPG is a potent antagonist (Sekiyama et al. 1996) at mGluR 2 and has been shown to block all of the above effects; e.g., (+)-MCPG (1 mM) blocked the depression of evoked potentials by (1S,3S)-ACPD in postnatal day (P)14 rats (Vignes et al. 1995) and the depression of potentials in CA3 by DCG-IV in 20- to 30-day-old rats (Kamiya et al. 1996). Moreover, the phenylglycine derivative 4-CPG is reported to be an agonist at mGluR 2 (Sekiyama et al. 1996), yet we have shown that 4-CPG does not block LTP, making it unlikely that agonist activity at mGluR 2 is responsible for the block of LTP. Furthermore, mGluRII has been localized to CA1, but the absolute optical density of the hybridization signal was significantly greater for mGluR 3 than for mGluR 2 (Fuothi et al. 1994).

Taken together, these findings make it unlikely that the block of LTP induction by (+)-MCPG and (1S,3S)-ACPD is mediated by mGluR 2 and instead lead us to suggest that the block of LTP is mediated either by an agonist action at mGluR 3 (the MCPG profile for which has yet to be determined in detail although one study showed that MCPG was not an antagonist at mGluR 3 but was at mGluR 2 (Emile et al. 1996)) or at an as yet unidentified mGluR, probably of the mGluRII type. An mGluRII–mediated block of LTP in dentate gyrus has previously been described; here also, the best candidate mGluR subtype appeared to be mGluR 3 because MTPG, a mGluRII antagonist inactive at mGluR 2 (Thomsen et al. 1996), prevented this block of LTP (Huang et al. 1997a).

Activation of this mGluR probably results in activation of an intracellular messenger because mGluRs are well known to activate various second messengers, including stimulation of phosphoinositide hydrolysis (see Pin and Duvoisin 1995) and activation of phospholipase D (PLD) (Boss and Conn 1992), leading to increases in protein kinase C. Activation of PLD is particularly interesting as a candidate intracellular messenger as both (1S,3S)-ACPD (Boss and Conn 1992) and MCPG (Pelligrini-Giampietro et al. 1996) have been shown to stimulate PLD. Prolonged activation of intracellular messengers may lead to desensitization of a second messenger pathway necessary for LTP induction. In this report we have provided further evidence that activation of mGluRs play an important role in governing synaptic plasticity. Our data strongly suggest that induction of LTP can be completely blocked by activating mGluRII, probably mGluR 3. In addition, we have demonstrated that the non subtype selective mGluR ligand (+)-MCPG is a partial agonist and it is this action that is likely to explain the block of LTP by (+)-MCPG.

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