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Activation of group-II metabotropic glutamate receptors blocks induction of long-term potentiation and depotentiation in area CA1 of the rat in vivo

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Abstract

The metabotropic glutamate receptor group-II agonist (1*S*,3*S*)-1-aminocyclopentane-1,3-dicarboxylic acid (1*S*,3*S*-ACPD; 5 μl/10 mM, i.c.v.) prevented the induction of long-term potentiation and depotentiation in the CA1 area of the hippocampus in urethane-anaesthetised rats. These effects were prevented by the group-II metabotropic glutamate receptor antagonists α-methyl-(2*S*,3*S*,4*S*)-α-(carboxycyclopropyl)glycine (MCCG; 5 μl/100 mM) and (*RS*)-α-methyl-4-tetrazolylphenylglycine (MTPG; 5 μl/500 mM). The group-I antagonist (*RS*)-1-aminoindan-1,5-dicarboxylic acid (AIDA; 5 μl/200 mM) or the group-III antagonist α-methyl-L-2-amino-4-phosphonobutyrate (MAP4; 5 μl/100 mM) did not affect the block of the induction of long-term potentiation by 1*S*,3*S*-ACPD. It is concluded that activation of group-II metabotropic glutamate receptors can block both high-frequency stimulation-induced long-term potentiation and low-frequency stimulation-induced depotentiation in the CA1 area in vivo.

Keywords: Metabotropic glutamate receptor; 1*S*,3*S*-ACPD ((1*S*,3*S*)-1-aminocyclopentane-1,3-dicarboxylic acid); Excitatory postsynaptic potential; Depotentiation; CA1 area; Hippocampus; MCCG (α-methyl-(2*S*,3*S*,4*S*)-α-(carboxycyclopropyl)glycine); MTPG ((*RS*)-α-methyl-4-tetrazolylphenylglycine); AIDA ((*RS*)-1-aminoindan-1,5-dicarboxylic acid); MAP4 (α-methyl-L-2-amino-4-phosphonobutyrate)

1. Introduction

The metabotropic glutamate receptor family comprises several subtypes. So far, 8 different subtypes have been cloned and described. Their mRNA has been expressed in oocytes where the pharmacological properties were identified (Tanabe et al., 1993; Genazzani et al., 1993; Nakanishi, 1994; Duvoisin et al., 1995). Three different groups of metabotropic glutamate receptors were established according to the pharmacological sensitivity and second messenger systems linked to the receptors via G-proteins. Cloned metabotropic glutamate receptors 1α, β and 5 (group-I) are linked to a phospholipase C, while metabotropic glutamate receptors 2, 3, 4, 6, 7 and 8 are negatively linked to an adenylate cyclase. Metabotropic glutamate receptors 2, 3 (Watkins and Collingridge, 1994; Pin and Duvoisin, 1995) constitute group-II and are activated by (1*S*,3*S*)-1-aminocyclopentane-1,3-dicarboxylic acid (1*S*,3*S*-ACPD). Furthermore, the metabotropic glutamate receptors 4, 6, 7 (Genazzani et al., 1993; Tanabe et al., 1993; Nakanishi, 1994) and 8 (Duvoisin et al., 1995), constituting group III, can be differentiated from group-II receptors by their sensitivity to L-(+)-2-amino-4-phosphonobutanoic acid (L-AP4).

Little is known regarding the role of the different subtypes of metabotropic glutamate receptors in plasticity in the hippocampus. With the development of subtype-selective metabotropic glutamate receptor agonists/antagonists it is hoped that it may be possible to resolve some of the controversy which has arisen using non-selective agents (Bortolotto et al., 1994; Selig et al., 1995; Thomas and O'Dell, 1995; Wang et al., 1995).

We have previously shown that injection of the group-II metabotropic glutamate receptor agonist 1*S*,3*S*-ACPD (Jane et al., 1994, 1995) blocked the induction of long-term potentiation and depotentiation in the CA1 area of the rat hippocampus in vivo but did not prevent learning of spatial

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Table 1
The apparent K_d of MCCG, MAP4 and MTPG for the 1*S*,3*S*-ACPD-induced depression of synaptic transmission in neonatal rat spinal cord (Jane et al., 1994, 1995)

Antagonist	K_d
MCCG	103±28 ($n=5$)
MTPG	77±7 ($n=7$)
MAP4	n.e. [a] ($n=4$)

Values are expressed as mean (in μM)±S.E.M. [a] No effect at 300 μM MAP4.

and nonspatial tasks in a water maze or radial arm maze (Hölscher et al., 1997). In contrast to the more commonly used non-selective 1*S*,3***R***-ACPD (Glaum et al., 1992), 1*S*,3***S***-ACPD seems to act predominantly at presynaptic sites. The drug potently depressed the fast component of dorsal root evoked potentials in an isolated spinal cord preparation of the newborn rat (Pook et al., 1992; Jane et al., 1994). It also depressed field excitatory postsynaptic potentials (e.p.s.p.s) in the CA1 area in the hippocampal slice taken from young rats (Vignes et al., 1995). However, 1*S*,3*S*-ACPD apparently has some postsynaptic activity as well (Davies et al., 1995).

In the present study, in order to determine whether or not the effect of 1*S*,3*S*-ACPD on long-term potentiation and depotentiation induction was due to activation of metabotropic glutamate receptors and to identify which metabotropic glutamate receptor subtype might be involved, selective antagonists for group I, II and III (Table 1) were injected in combination with 1*S*,3*S*-ACPD. The novel group-I antagonist (*RS*)-1-aminoindan-1,5-dicarboxylic acid (AIDA) (Pellicciari et al., 1995) was tested to investigate if metabotropic glutamate receptor 1 or 5 mediated the effects of 1*S*,3*S*-ACPD. Furthermore, the group-II antagonists α-methyl-(2*S*,3*S*,4*S*)-α-(carboxycyclopropyl)glycine (MCCG) and (*RS*)-α-methyl-4-tetrazolylphenylglycine (MTPG) were investigated (Jane et al., 1995). Unfortunately, MCCG also has some agonist-like activity and can depress e.p.s.p.s at relatively high concentrations (Bushell et al., 1996). Furthermore, the effect of α-methyl-L-2-amino-4-phosphonobutyrate (MAP4; Jane et al., 1995; Bushell et al., 1996), an antagonist that acts predominantly at group-III mGlu receptors was also tested.

2. Materials and methods

2.1. Surgery and electrode implantation

Male Wistar rats weighing 200–250 g (12–14 weeks of age) were used. The procedure adopted was similar to that

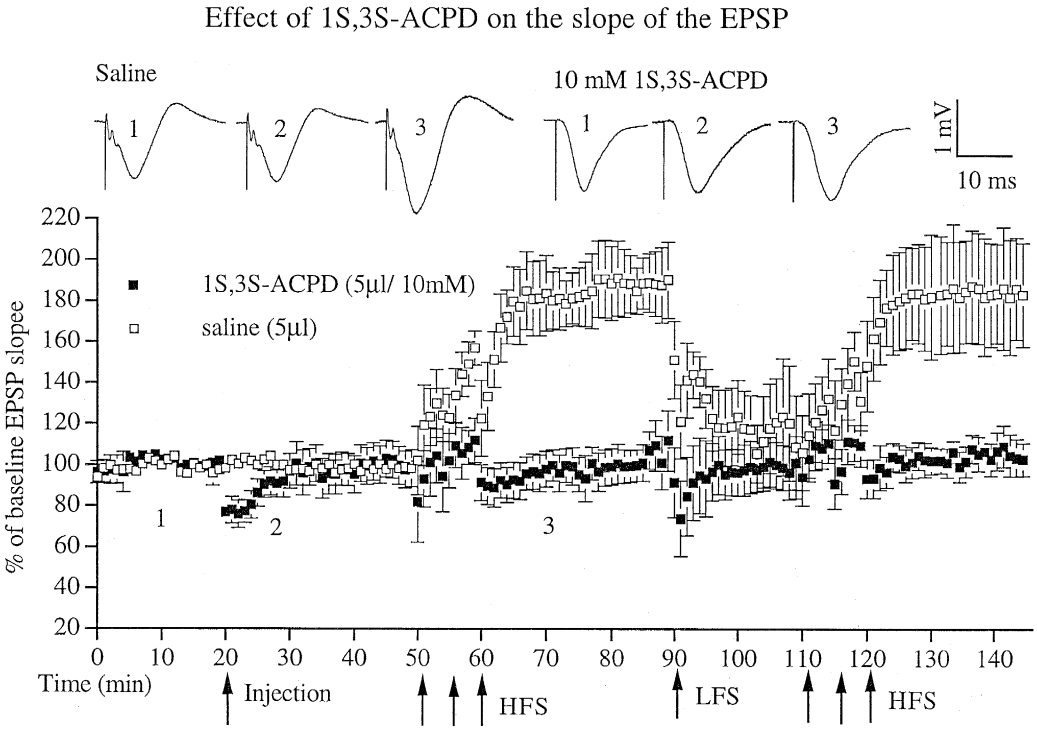

Fig. 1. 1*S*,3*S*-ACPD inhibited the induction of long-term potentiation of field e.p.s.p.s in area CA1 of the rat hippocampus in vivo ($n=8$ per group). In the control group, high-frequency stimulation (HFS) induced long-term potentiation of the e.p.s.p. slope ($P<0.001$). Low-frequency stimulation (LFS) induced depotentiation of the potentiated e.p.s.p. slope ($P<0.001$). A second high-frequency stimulation again induced long-term potentiation ($P<0.001$). Injection of 5 μl of a 10 mM 1*S*,3*S*-ACPD solution did not affect baseline e.p.s.p.s at the time of the high-frequency stimulation, 30 min after the injection. Neither high-frequency stimulation, low-frequency stimulation, nor a second high-frequency stimulation induced changes in the e.p.s.p. slope in 1*S*,3*S*-ACPD-injected animals. Comparison between drug and control group after high-frequency stimulation showed a significant difference ($P<0.001$).

described previously (Doyle et al., 1996). The rats were anaesthetised with urethane (ethyl carbamate, 1.5 g/kg, i.p.) for the duration of all experiments. Some animals were maintained on a halothane/oxygen (1% halothane in pure oxygen; flow rate, 1 l/s) gas mixture during the implantation procedure. Recovery from halothane was assessed by measuring electro-encephalogramme (EEG) activity, and usually took less than 30 min.

The animal was put into a stereotaxic frame and a cannula was inserted into the right lateral ventricle (coordinates 3.5 mm downward into the ventricle, 1.5 mm posterior to bregma, and 0.5 mm lateral to the midline). The cannula was made out of a 0.7 mm diameter syringe needle, length 12 mm. The final position was fixed with acrylic dental cement. Recordings of field e.p.s.p.s were made from the CA1 stratum radiatum of the right hippocampal hemisphere in response to stimulation of the Schaffer collateral/commissural pathway. Burr holes (1.5 mm in diameter) were drilled over the unilateral electrode implantation sites which were identified using stereotaxic co-ordinates relative to bregma and lambda, with the recording site located 3 mm posterior and 2 mm right of the midline, and the stimulating electrode 4 mm posterior to bregma and 3 mm right of the midline. Bipolar stimulating and monopolar recording electrodes consisted of two pieces of Teflon-coated twisted tungsten wire attached to a connecting socket. The electrodes were slowly lowered through the cortex and the upper layers of the hippocampus into the CA1 region until the appearance of a negative deflecting field e.p.s.p. The electrodes were then fixed in place with cyanoacrylate glue and acrylic dental cement for the stimulation and recording of evoked field e.p.s.p.s. Stainless steel screws fixed to the skull served as ground (anterior 7 mm, lateral 5 mm) and reference (posterior 8 mm, lateral 1 mm) electrodes.

2.2. Stimulation and recording

In all experiments control e.p.s.p.s were evoked at a frequency of 0.033 Hz, and an input-output curve (i/o, stimulus intensity versus e.p.s.p. amplitude) plotted at this test frequency. For baseline e.p.s.p.s, the stimulation voltage intensity was adjusted to give an e.p.s.p. amplitude of 75% of maximum. Long-term potentiation was induced using three sets of trains of stimuli, each set consisting of 10 trains of 20 stimuli, inter-stimulus interval 5 ms (200 Hz), inter-train interval 2 s and inter-set interval of 5 min. The low-frequency stimulation used to induce depotentiation consisted of 900 stimuli at 10 Hz which in previous studies in this laboratory was found to evoke maximal depotentiation (Doyle et al., 1996).

2.3. Drugs

All drugs used in this study were obtained form Tocris Cookson (UK) and dissolved in saline (NaCl solution

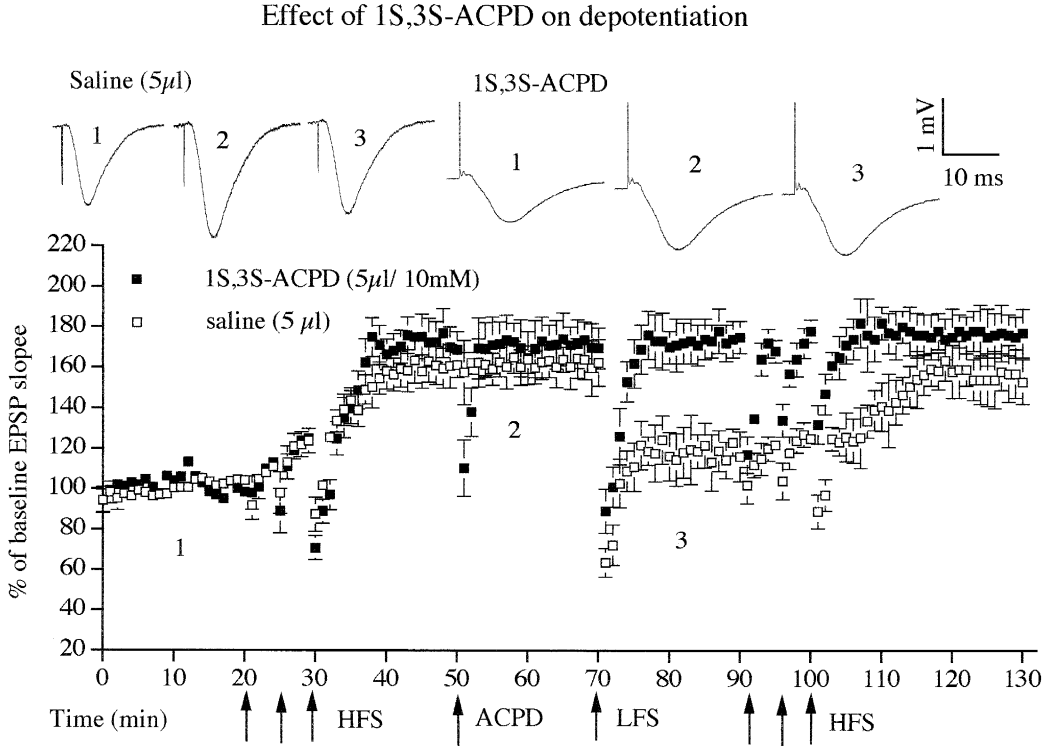

Fig. 2. 1S,3S-ACPD inhibited the induction of depotentiation ($n = 7$ per group). In the control group high-frequency stimulation (HFS) induced long-term potentiation and subsequent low-frequency stimulation (LFS) induced depotentiation ($P < 0.001$) of e.p.s.p.s. Injection of 5 μl of a 10 mM 1S,3S-ACPD solution 20 min after high-frequency stimulation prevented the induction of depotentiation by low-frequency stimulation 30 min later. Comparison between drug and control group after low-frequency stimulation showed a significant difference ($P < 0.001$).

0.9%). AIDA was a gift from Prof. Pellicciari. The pH was measured and adapted to 7.4 with NaOH when necessary.

2.4. Data analysis

All recording and stimulating was performed using an on-line computerised oscilloscope/stimulator and data analysis interface system (MacLab/2e). Unless otherwise stated all data are expressed as mean ± S.E.M. % baseline e.p.s.p. amplitude. Results were analyzed by Student *t*-test or Welch *t*-test, which does not assume equal standard deviations between data sets.

3. Results

3.1. Effect of 1S,3S-ACPD on the induction of long-term potentiation

High-frequency stimulation induced stable long-term potentiation of the slope of the e.p.s.p. in the saline-injected control group (to 178 ± 16% 30 min after high-frequency stimulation; $n = 8$; $P < 0.001$ compared to pre-high-frequency stimulation baseline; Fig. 1). Subsequent low-frequency stimulation (10 Hz) produced a significant depotentiation to 120 ± 24% of baseline (measured 30 min after low-frequency stimulation, $P < 0.001$ compared to potentiated level). A second high-frequency stimulation induced long-term potentiation again (175 ± 32% of baseline measured 30 min after the second high-frequency stimulation; $P < 0.001$ compared to depotentiated level).

Injection of 5 μl of a 10 mM solution i.c.v. transiently depressed baseline transmission for 10–15 min with full recovery within 30 min of the injection. Neither high-frequency stimulation applied at 30 min after the 1*S*,3*S*-ACPD injection, nor a second high-frequency stimulation at 90 min induced long-lasting changes in the e.p.s.p. slope. Thus a significant block of long-term potentiation induced by both the first ($n = 8$, $P < 0.001$) and second high-frequency stimulation ($P < 0.001$ compared to the control group; Fig. 1) was apparent.

3.2. Effect of 1S,3S-ACPD on the induction of depotentiation

In a separate group of animals this dose of 1*S*,3*S*-ACPD, administered immediately after the first high-frequency stimulation, also prevented low-frequency stimulation-induced depotentiation. Whereas low-frequency stimulation reduced the slope of e.p.s.p.s from 173 ± 8 to 113 ± 5 in

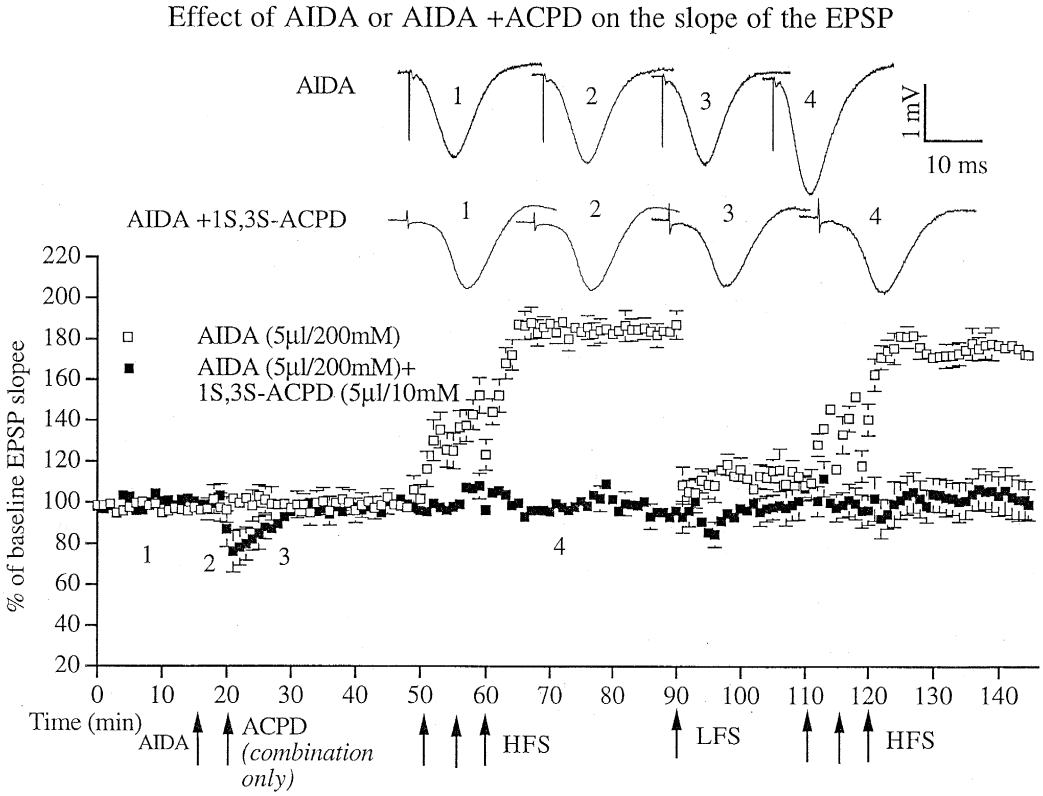

Fig. 3. The metabotropic glutamate receptor group-I antagonist AIDA did not affect the induction of long-term potentiation or the block of long-term potentiation induction by 1*S*,3*S*-ACPD ($n = 6$ per group). AIDA (5 μl/200 mM) on its own had no effect on baseline or high-frequency stimulation (HFS) and low-frequency stimulation (LFS)-induced changes in the e.p.s.p. slope compared to saline-injected controls (Fig. 1). Also, AIDA had no effect on the block of depotentiation by 1*S*,3*S*-ACPD.

controls it did not induce any significant change in animals which had been injected with 5 μl of a 10 mM solution of 1*S*,3*S*-ACPD i.c.v. ($n = 7$; 172 ± 11 to 170 ± 13; $P < 0.001$ compared to the control group; Fig. 2).

3.3. Effect of metabotropic glutamate receptor antagonists on baseline synaptic transmission

In order to study the effects of the metabotropic glutamate receptor antagonists on the response to 1*S*,3*S*-ACPD, it was necessary to carry out preliminary dose ranging experiments. Possible effects on baseline transmission were investigated by injecting different doses i.c.v. and measuring the peak change in e.p.s.p. amplitude over the subsequent 10 min period. Whereas AIDA and MTPG had no effect at a dose of up to 5 μl/500 mM, both MCCG and MAP4 depressed the baseline in a dose-dependent manner (Table 2). MCCG significantly reduced the amplitude of the e.p.s.p. at a dose of both 5 μl/200 mM and 5 μl/500 mM ($n = 6$ per group; $P < 0.01$ compared to pre-injection levels). Similarly, MAP4 at a dose of both 5 μl/200 mM and 5 μl/500 mM also reduced baseline transmission ($n = 6$ per group; $P < 0.05$ and $P < 0.01$, respectively, compared to pre-injection levels). Only doses which did not affect the baseline were used in subsequent experiments.

Table 2
Effect of metabotropic glutamate receptor antagonists on the baseline field e.p.s.p. slope in the CA1 area of the rat hippocampus in vivo

Antagonist	Concentration			
	50 mM	100 mM	200 mM	500 mM
AIDA	0.2 ± 0.1	0.1 ± 0.05	1.4 ± 0.4	1.6 ± 0.8
MCCG	0.1 ± 0.2	0.2 ± 0.1	23 ± 4 [b]	34 ± 8.3 [b]
MTPG	0.1 ± 0.1	0.5 ± 0.5	2.4 ± 0.5	3.1 ± 1.1
MAP4	0.1 ± 0	1.5 ± 0.5	9 ± 4.5 [a]	18 ± 5.2 [b]

An i.c.v. injection of 5 μl of the stated drug concentration was given 5 min before measurement of the slope of the e.p.s.p. Values express the magnitude of the depression of e.p.s.p. slope as the decrease in % from pre-injection values ± S.E.M., $n = 4$ per group. [a] $P < 0.05$, [b] $P < 0.01$.

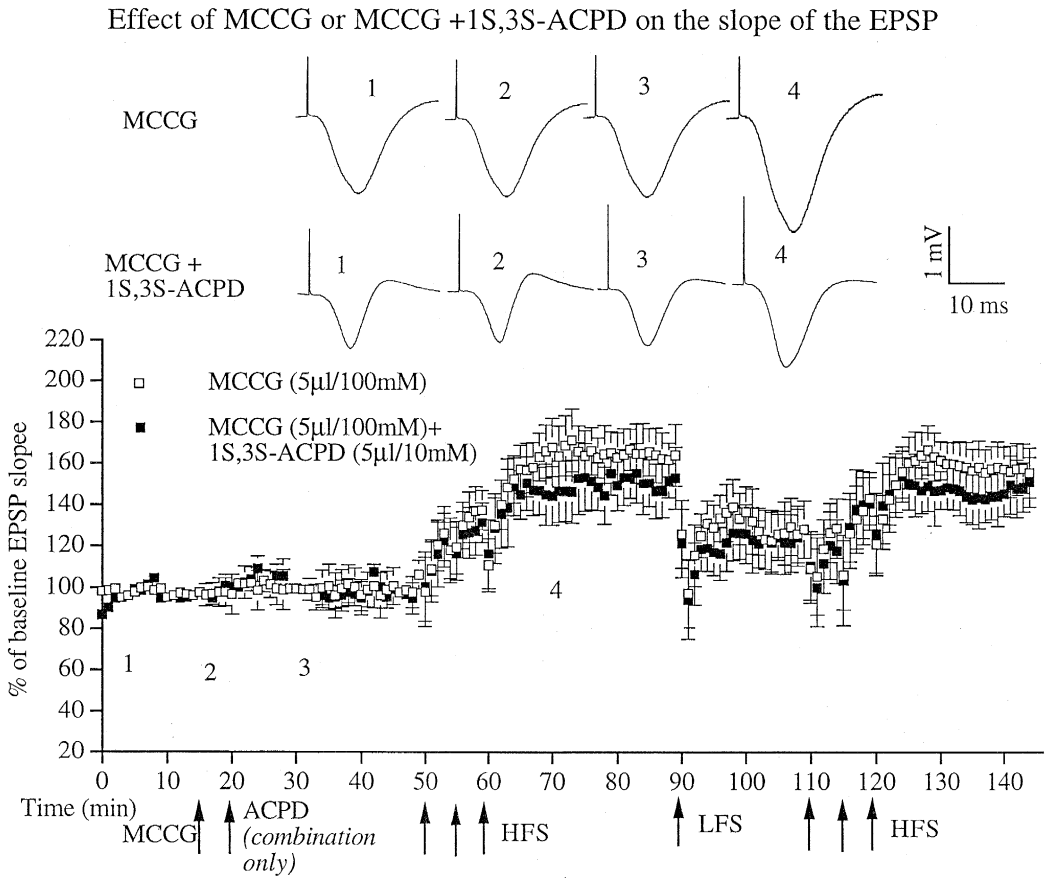

Fig. 4. The metabotropic glutamate receptor group-II antagonist MCCG did not affect the induction of long-term potentiation but did prevent the 1*S*,3*S*-ACPD block of long-term potentiation ($n = 6$ per group). MCCG (5 μl/100 mM) alone did not affect high-frequency stimulation (HFS)-induced long-term potentiation, nor did it affect depotentiation after low-frequency stimulation (LFS) compared to saline-injected controls (Fig. 1). There was a significant difference between the effect of 1*S*,3*S*-ACPD on its own (Fig. 1) and of MCCG plus 1*S*,3*S*-ACPD when measured 20 min after the first or second high-frequency stimulation ($P < 0.001$). MCCG also prevented the block of depotentiation by 1*S*,3*S*-ACPD. There was a significant difference between the effect of 1*S*,3*S*-ACPD on its own (Fig. 2) and of MCCG plus 1*S*,3*S*-ACPD when measured 20 min after the low-frequency stimulation ($P < 0.001$).

3.4. Effect of the group-I metabotropic glutamate receptor antagonist AIDA on the response to 1S,3S-ACPD

The metabotropic glutamate receptor group-I antagonist AIDA (5 μl of a 200 mM solution i.c.v.) did not affect long-term potentiation induction, nor did it affect depotentiation after low-frequency stimulation ($n = 6$; Fig. 3). At this dose, AIDA had no effect on the block of long-term potentiation by 1*S*,3*S*-ACPD. A *t*-test did not reveal any difference between the effect of 1*S*,3*S*-ACPD on its own and of AIDA plus 1*S*,3*S*-ACPD ($n = 6$, Fig. 3).

3.5. Effect of the group-II metabotropic glutamate receptor antagonists MCCG and MTPG on the response to 1S,3S-ACPD

Injection of the metabotropic glutamate receptor group-II antagonist MCCG (5 μl of a 100 mM solution i.c.v.) did not affect the induction of long-term potentiation or depotentiation ($n = 6$; Fig. 4). At this dose, MCCG prevented the block of long-term potentiation by 1*S*,3*S*-ACPD. There was a significant difference between the effect of 1*S*,3*S*-ACPD on its own and of MCCG plus 1*S*,3*S*-ACPD when measured 20 min after the first high-frequency stimulation and second high-frequency stimulation ($n = 6$, $P < 0.001$). MCCG also prevented the block of depotentiation by 1*S*,3*S*-ACPD. Low-frequency stimulation induced depotentiation in animals which had been injected with MCCG plus 1*S*,3*S*-ACPD, significantly different from in the presence of 1*S*,3*S*-ACPD alone ($n = 6$, $P < 0.001$; Fig. 4).

The metabotropic glutamate receptor group-II antagonist MTPG (5 μl of a 500 mM solution i.c.v.) was also without effect on the induction of depotentiation and long-term potentiation. It did however prevent the block of long-term potentiation by 1*S*,3*S*-ACPD. There was a significant difference between the effect of 1*S*,3*S*-ACPD on its own and of MTPG plus 1*S*,3*S*-ACPD when measured 20 min after the first ($t = 32.7$, df = 10, $P < 0.001$) and second high frequency stimulation ($n = 6$, $P < 0.001$). MTPG also opposed the block of depotentiation by 1*S*,3*S*-ACPD. Low-frequency stimulation produced depotentiation of the slope of e.p.s.p.s after injection of MTPG plus 1*S*,3*S*-ACPD ($n = 6$, $P < 0.001$) compared to 1*S*,3*S*-ACPD alone (Fig. 5).

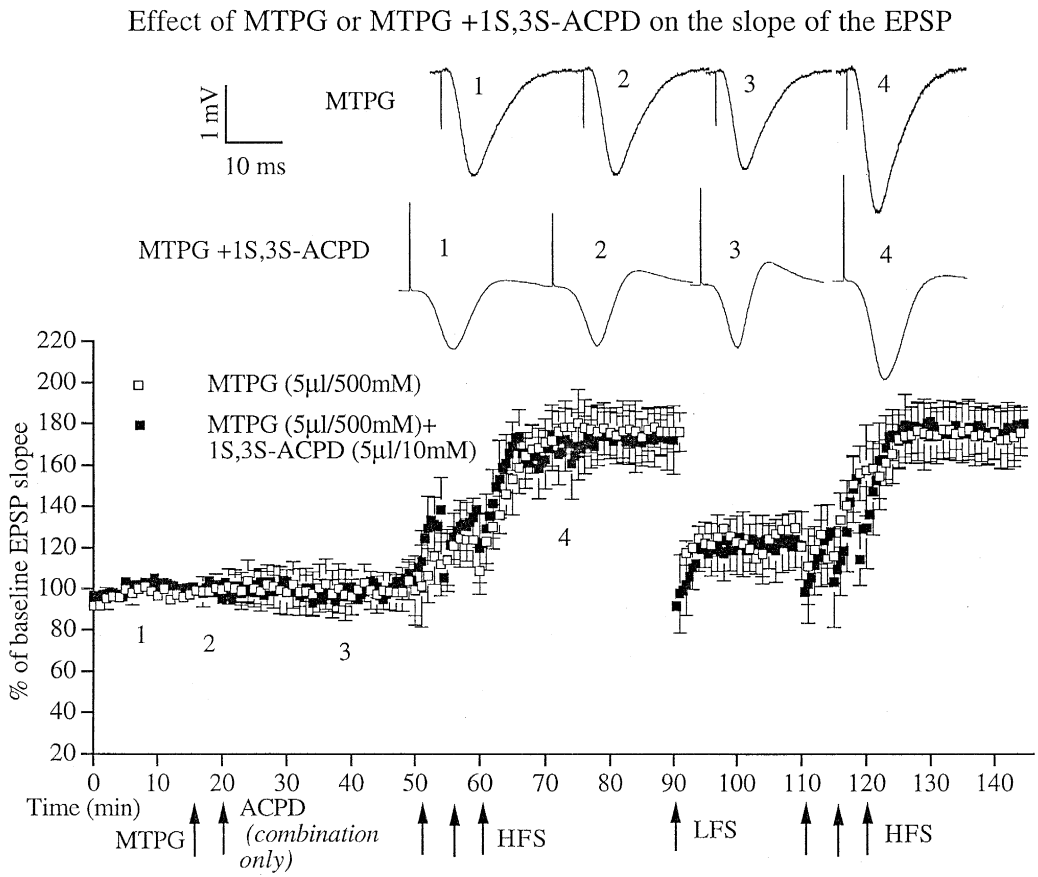

Fig. 5. The metabotropic glutamate receptor group-II antagonist MTPG did not affect long-term potentiation induction but did prevent the 1*S*,3*S*-ACPD block of long-term potentiation induction ($n = 6$ per group). MTPG (5 μl/500 mM) alone did not affect high-frequency stimulation (HFS)-induced long-term potentiation, nor did it affect depotentiation after low-frequency stimulation (LFS) compared to saline-injected controls (Fig. 1). MTPG did however prevent the transient baseline reduction and the block of long-term potentiation produced by 1*S*,3*S*-ACPD ($P < 0.001$). MTPG also prevented the block of depotentiation by 1*S*,3*S*-ACPD ($P < 0.001$).

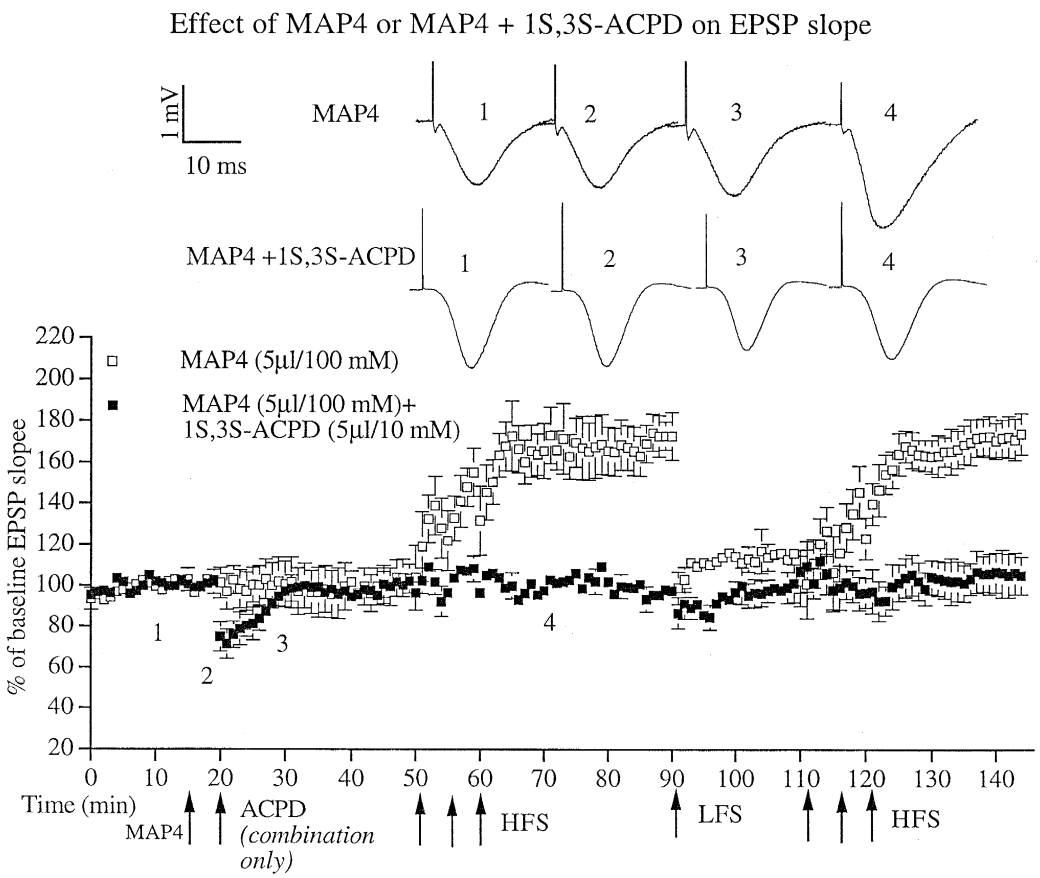

Fig. 6. The metabotropic glutamate receptor group-III antagonist MAP4 did not affect long-term potentiation induction or the 1*S*,3*S*-ACPD block of long-term potentiation induction ($n = 6$ per group). MAP4 (5 µl/100 mM) on its own had no effect on baseline or high-frequency stimulation (HFS), and low-frequency stimulation (LFS)-induced changes in e.p.s.p. slope compared to saline-injected controls (Fig. 1). Also, MAP4 had no effect on the block of long-term potentiation or depotentiation by 1*S*,3*S*-ACPD.

3.6. Effect of the group-III metabotropic glutamate receptor antagonist MAP4 on the response to 1S,3S-ACPD

Injecting the metabotropic glutamate receptor group-III antagonist MAP4 i.c.v. (5 µl of a 100 mM solution) did not affect long-term potentiation induction, nor did it affect depotentiation after low-frequency stimulation. Long-term potentiation was induced again after the second high-frequency stimulation. There was no difference between the control and the MAP4 group. At this dose, MAP4 had no effect on the block of long-term potentiation by 1*S*,3*S*-ACPD. A *t*-test did not find a difference between the effect of 1*S*,3*S*-ACPD on its own and of MAP4 plus 1*S*,3*S*-ACPD ($n = 6$, Fig. 6).

4. Discussion

The results presented here show that antagonists of group-I or -III metabotropic glutamate receptors did not have any effect on the block of long-term potentiation evoked by the agonist 1*S*,3*S*-ACPD. Both metabotropic glutamate receptor group-II antagonists prevented the block by 1*S*,3*S*-ACPD, with MTPG completely preventing the block and MCCG preventing it by approximately 90%. Since the block of long-term potentiation induction by the metabotropic glutamate receptor group-II agonist 1*S*,3*S*-ACPD was prevented by group-II but not by group-I and -III antagonists we can assume that this effect of 1*S*,3*S*-ACPD was mediated via activation of group-II metabotropic glutamate receptors. The dose of MAP4 used in this study was higher than the dose used in a previous experiment (5 µl of an 80 mM solution i.c.v.) which prevented the effect of L-AP4 (Hölscher et al., 1996). We therefore believe that the MAP4 dose used in this study was high enough to block group-III receptors. Since AIDA has a pA_2 of 4.2 for mGluR 1α (F. Moroni, personal communication), the dose we chose in our studies is well within the concentration that blocks this group-I metabotropic glutamate receptor.

Antagonists of metabotropic glutamate receptors did not affect baseline transmission on their own. This does not necessarily imply that these receptors are not activated physiologically or pathologically. For example, exceptionally high levels of neuronal activity as occur during epileptic activity may result in synaptic activation of these

receptors. Similarly, none of these antagonists had any effect on high-frequency stimulation-induced long-term potentiation or low-frequency stimulation-induced depotentiation. This does not preclude the involvement of metabotropic glutamate receptors which are sensitive to these antagonists having a role in phases of long-term potentiation or depotentiation later than the time window which was examined in the present studies (30 min). Equally, synaptic plasticity induced using other stimulation protocols may prove sensitive to some of these agents. In particular, it is not yet known which electrical stimulation protocols might optimally activate metabotropic glutamate receptors.

1*S*,3*S*-ACPD did not block long-term potentiation or depotentiation by reducing the synaptic responses, as the dose used for the plasticity studies produced only a transient baseline reduction, with no evidence of a baseline change at the time when the high-frequency stimulation was applied. Similarly, although high doses of MAP4 and MCCG produced a significant reduction of baseline transmission, the doses used in the antagonist studies were without baseline effect. These results support similar findings found previously in vitro which suggest that both MAP4 and MCCG may have mixed agonist/antagonistic properties at certain concentrations (Bushell et al., 1996; Kemp et al., 1994, 1996).

Since mRNA for cloned group-II metabotropic glutamate receptors have not been detected in the CA1 region (Ohishi et al., 1993a,b) and only low binding of antibodies to these receptors was found (Petralia et al., 1996), our results may be taken to imply that other metabotropic glutamate receptor group-II-like receptors which have not been cloned yet are involved in the effects of 1*S*,3*S*-ACPD observed here. This is consistent with the findings of other authors who described prominent effects of metabotropic glutamate receptor group-II agonists in the CA1 region of the hippocampus (Davies et al., 1995; Vignes et al., 1995).

The present results on the ability of activation of group-II metabotropic receptors to inhibit depotentiation are not consistent with a recent report on genetic knockout of subtype-2 metabotropic glutamate receptors (Yokoi et al., 1996). In mice lacking these receptors, low-frequency stimulation failed to induce long-term depression at mossy fibre synapses with CA3 neurones. The discrepancy may be due to a difference in the induction mechanisms for depotentiation and long-term depression in the CA1 and CA3 areas, respectively.

It is concluded that activation of group-II metabotropic glutamate receptors can block both high-frequency stimulation-induced long-term potentiation and low-frequency stimulation-induced depotentiation in the CA1 area of the rat hippocampus in vivo. However, 1*S*,3*S*-ACPD-sensitive metabotropic glutamate receptors do not appear to be of importance for synaptic mechanisms that underlie learning of spatial and non-spatial tasks in rats (Hölscher et al., 1997).

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