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The role of group II metabotropic glutamate receptors in hippocampal CA1 long-term potentiation in vitro

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Abstract

The role of group II metabotropic glutamate receptors (mGlu receptors) in mechanisms of long-term potentiation was investigated by analysis of excitatory postsynaptic field potentials of the CA1 region in rat hippocampal slices. The application of the group II agonists (2*S*,1′*S*,2′*S*)-2-(carboxycyclopropyl) glycine (L-CCG-I) and (2*S*,1′*R*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl) glycine (DCG IV) resulted in a dose-dependent reduction of long term potentiation in the concentration range 3–50 μM. In contrast to the effects of group II agonists on long-term potentiation, the group II antagonists (*RS*)-α-methyl-3-carboxy-4-hydroxy-phenylglycine (M3C4HPG) and (*RS*)-α-methylserine-*O*-phosphate monophenyl ester (MSOPPE) elicited a dose-dependent enhancement of long-term potentiation (50–100 μM or 20–50 μM, respectively). We conclude that group II mGlu receptors are not essential for the induction of long-term potentiation; however, they may be involved in feedback mechanisms in long-term potentiation. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Long-term potentiation; Metabotropic glutamate receptors group II; Hippocampus; (Rat)

1. Introduction

Investigations of neuronal synaptic plasticity have provided information that co-activation of ionotropic receptors and second messenger cascades is necessary for mechanisms of synaptic plasticity (Bliss and Collingridge, 1993). Experiments have shown that hippocampal CA1 long-term potentiation, requires the influx of Ca^{2+} through (NMDA) receptors and additional activation of phospholipase C- and adenylate cyclase-dependent signal cascades (Frey et al., 1993; Reymann and Staak, 1994; Blitzer et al., 1995; Collingridge and Bliss, 1995). Metabotropic glutamate (mGlu) receptors are linked to the phospholipase C and the adenylate cyclase via G-proteins (Cartmell et al., 1994). These pathways modulate, among other effects, the excitability of neurons (see for review Gereau and Conn, 1995; Conn and Pin, 1997). Until now, eight heterogeneously distributed metabotropic glutamate receptor (mGlu receptor) subtypes have been described and divided into three groups according to their sequence homologies, the second messenger systems to which they are coupled and their pharmacological properties (Tanabe et al., 1992, 1993; Genazzani et al., 1993; Nakanishi, 1994; Pin and Duvoisin, 1995; Blumcke et al., 1996). Group I mGlu receptors comprise $mGlu_1$ and $_5$ receptors, which are coupled to the phospholipase C, and group II and III include the receptors 2, 3 and 4, 6, 7, 8 respectively, which are coupled to the adenylate cyclase pathway, but have a different agonist preference for L-2-amino-4-phosphonobutyrate.

The current knowledge of the role of mGlu receptors in hippocampal long-term potentiation is based on investigations of non-selective group I compounds. Although, several studies investigating the effects of non-specific group I mGlu receptor antagonists on long-term potentiation proved their importance (Bashir et al., 1993; Behnisch and Reymann, 1993; Izumi and Zorumski, 1994; Little et al., 1995), other investigations did not confirm their necessity for long-term potentiation induction (Chinestra et al., 1993; Manzoni et al., 1994; Selig et al., 1995). Experiments with group I mGlu receptor-knockout mice indicated the necessity of activation of the $mGlu_5$ receptor subtype during tetanization for CA1 long-term potentiation (Lu et al., 1997), but yielded ambiguous results concerning the in-

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volvement of $mGlu_1$ receptors in CA1 long-term potentiation (Aiba et al., 1994; Conquet et al., 1994). With the non-specific mGlu receptor agonist 1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) it was clarified that activation of mGlu receptors during long-term potentiation induction enhances long-term potentiation or induces a slow-onset potentiation (McGuinness et al., 1991; Bortolotto and Collingridge, 1992; Behnisch and Reymann, 1993; Manahan-Vaughan and Reymann, 1995). For presynaptically localized group III mGlu receptors, it was shown that activation of these receptors leads to a reduction of CA1- and dentate gyrus-long-term potentiation and to a long-lasting depression of synaptic transmission (Reymann and Matthies, 1989; Manahan-Vaughan and Reymann, 1995). Little is known regarding the role of group II mGlu receptors in CA1 long-term potentiation. It has been shown that application of the group II and partial group I mGlu receptor agonist (1*S*,3*S*)-1-aminocyclopentane-1,3-dicarboxylic acid (1*S*,3*S*-ACPD) inhibited the induction of long-term potentiation and depotentiation in the CA1 area in vivo (Hölscher et al., 1997). Additionally, it has been reported that group II mGlu receptor agonists prevent long-term potentiation in the dentate gyrus (Huang et al., 1997a,b), and that group II mGlu receptor antagonists do not affect long-term potentiation in the CA1 region in vivo (Manahan-Vaughan, 1997).

The aim of our study was to investigate whether selective group II mGlu receptor agonists or antagonists modulate long-term potentiation in the CA1 region in vitro. To investigate the effects of an additional activation of group II mGlu receptors on long-term potentiation we applied the mGlu receptor group II agonists (2*S*,1′*R*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl) glycine (DCG IV) (Ishida et al., 1993; Wilsch et al., 1994; Breakwell et al., 1997) and (2*S*,1′*S*,2′*S*)-2-(carboxycyclopropyl) glycine (L-CCG-I), that acts as a mGlu receptor group I and III agonists (Hayashi et al., 1992; Cartmell et al., 1994). The antagonists (*RS*)-α-methyl-3-carboxy-4-hydroxy-phenylglycine (M3C4HPG) and (*RS*)-α-methylserine-*O*-phosphate monophenyl ester (MSOPPE), which have a greater selectivity for group II mGlu receptors (Thomas et al., 1996), were used to test the involvement of group II mGlu receptors in long-term potentiation induction.

2. Materials and methods

Hippocampal slices were prepared from male rats (7–8 weeks old) of the Wistar outbred strain MOL:WIST (SHOE). After decapitation and dissection of the hippocampus, 400-μm transverse slices were cut in ice-cold oxygenated artificial cerebrospinal fluid (ACSF in mM: NaCl 124, KCl 4.9, $MgSO_4$ 1.3, $CaCl_2$ 2.5, KH_2PO_4 1.2, $NaHCO_3$ 25.6, D-glucose 10, saturated with 95% O_2, 5% CO_2, pH 7.3). Hippocampal slices were transferred to a submerged slice chamber and permanently perfused with 32°C ACSF (2.5 ml/min).

Synaptic responses were elicited by stimulation of the Schaffer collateral-commissural fibers in the *stratum radiatum* of hippocampal CA1-region, using lacquer-coated stainless steel stimulating electrodes. Glass electrodes (filled with ACSF, 1–4 MΩ) were placed in the apical dendritic layer to record excitatory postsynaptic field potentials (fEPSPs). The analysis of the fEPSP slope was used as a parameter of the synaptic efficacy. After an analysis of a fEPSP input/output curve, the test stimulation strength was adjusted to elicit a response 35% of the fEPSP slope maximum. During the baseline recording four single stimuli (10-s intervals) were averaged every 5 min. After stabilization of the fEPSP values, long-term potentiation was induced by a tetanization consisting of four pairs of stimuli with a 10-ms inter-stimulus interval (100 Hz) and with a 200-ms pair-interval (double biphasic test pulse width). Only in the experiments which are presented in Fig. 2B was long-term potentiation induced with a single 400-ms 100 Hz tetanization. fEPSP values were analyzed every 5 min over the whole field potential recording period.

Substances were applied by bath-application 10 min before and up to 5 min after the tetanization. All drugs were dissolved in ACSF and the solutions were adjusted to a pH of 7.3. M3C4HPG, MSOPPE and L-CCG-I were obtained from Tocris Cookson, England. DCG IV was kindly donated by Ohfune, Japan (Ishida et al., 1993). For the interpretation of the significance of differences between control long-term potentiation and drug long-term potentiation the values of both groups were analyzed with the Mann-Whitney *U* test (independent samples), using a significance level of $P \leq 0.05$. IC_{50} and EC_{50} were calculated according to the four-parameter logistic equation, using the GraFit computer programme (Erithacus Software, England).

3. Results

3.1. Activation of group II mGlu receptors inhibits long-term potentiation in vitro

No effect on synaptic transmission was observed when the effect of the group II agonist L-CCG-I (10 μM) was monitored for 180 min following a 10-min drug application ($n = 6$, data not shown). Application of L-CCG-I (10 μM) from 10 min before, until 5 min after tetanization caused a significant inhibition of fEPSP potentiation in comparison with that of the long-term potentiation control experiments (Fig. 1A). The initial potentiation was 193 ± 7% for control ($n = 9$) and 180 ± 12% for the L-CCG-I experiments ($n = 7$). The fEPSP slope recovered to baseline levels within 80 min after tetanization. The fEPSP potentiation in the control experiments decreased within 110 min to 115 ± 3%. Three slices treated with L-CCG-I

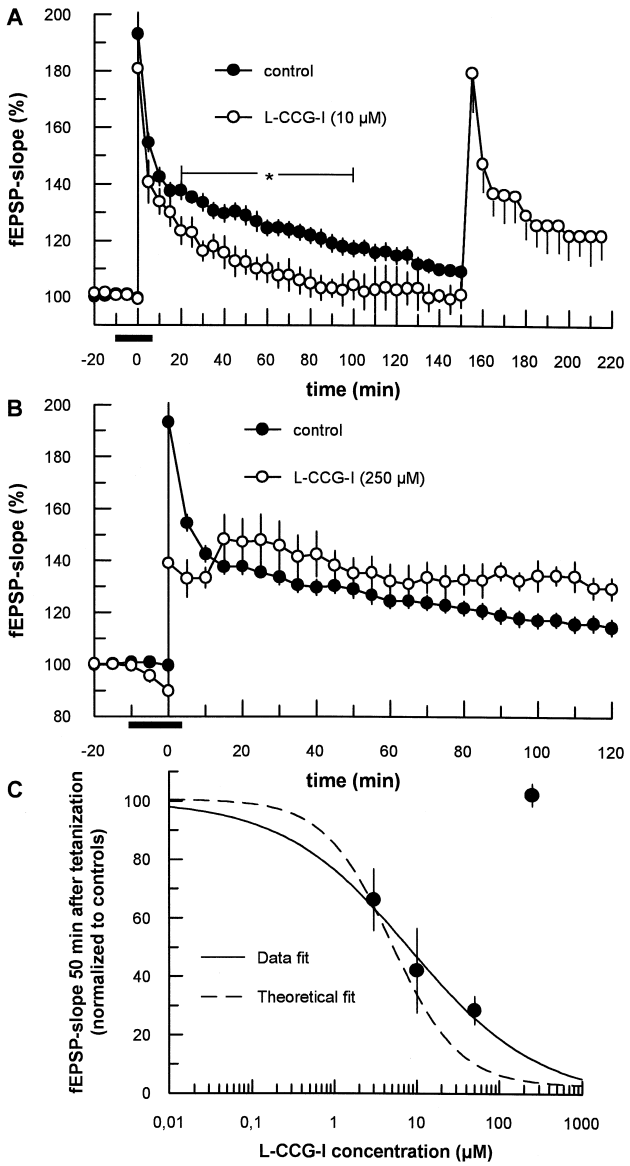

Fig. 1. The group II mGluR agonist L-CCG-I inhibited the induction of long-term potentiation. (A) Application (black line) of 10 μM L-CCG-I ($n = 7$) leads to a significant reduction of long-term potentiation in comparison with the control group ($n = 9$). The significance interval is indicated by a bracket with an asterisk ($P < 0.05$). Three slices of the drug-treated slice group were tetanized again with the same stimulus 150 min post-tetanization. (B) Increasing the L-CCG-I concentration up to 250 μM ($n = 6$) had the opposite effect on long-term potentiation. Additionally, at this concentration a decrease of the baseline fEPSP slopes was obtained during drug application (88 ± 1.5%). (C) The effects of L-CCG-I on long-term potentiation are presented with the dose–response curve (3 μM [$n = 5$], 10 μM [$n = 7$] and 50 μM [$n = 5$], 250 μM [$n = 6$]). With a Hill-coefficient of 1 the experimental data fitted the theoretical curve up to a drug concentration of 10 μM. Higher drug concentrations, however, led to a decrease of inhibitory effect of the L-CCG-I on long-term potentiation. Finally, the drug was ineffective at a concentration of 250 μM. The data fit yielded an estimate of the EC_{50} of 8.2 ± 3.7 μM with a Hill-coefficient of 0.5 ± 0.1. Data points were analyzed 50 min after tetanization and normalized to data for the corresponding control group (potentiation drug-experiment$_{50\ min}$ × 100%/potentiation control$_{50\ min}$).

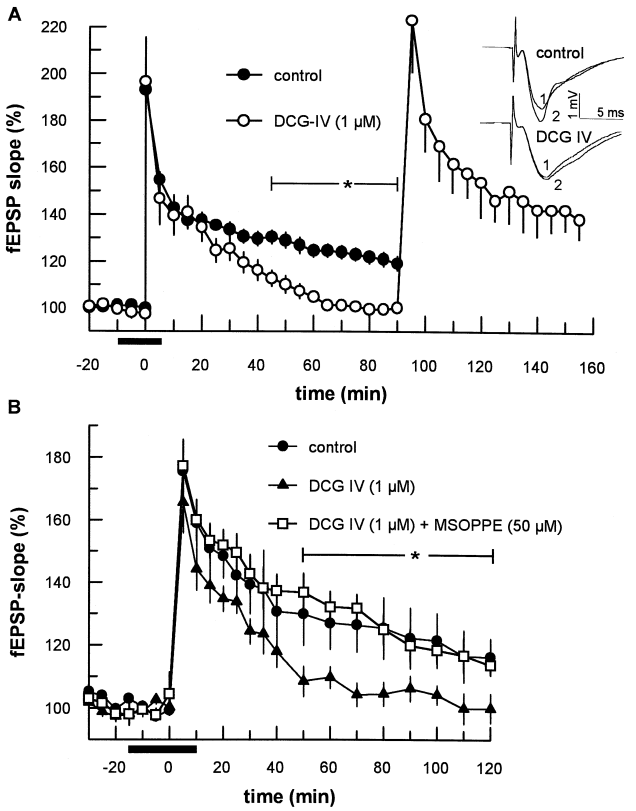

Fig. 2. The effects of DCG IV, a group II mGlu receptor agonist, on the induction of long-term potentiation. (A) Application (black line) of 1 μM DCG IV ($n = 7$) led to a reduction of fEPSP potentiation, in comparison to control experiments ($n = 9$). Three slices of the drug-treated slice group were tetanized with the same stimulus again 90 min after tetanization. Analogue traces on the right site represent typical recorded fEPSPs taken before (1) and 80 min after tetanization (2). (B) If long-term potentiation was induced with a 400-ms 100 Hz tetanization, the application (black line) of 1 μM DCG IV ($n = 6$) caused a decrease of potentiation in comparison to control experiments ($n = 6$). The effect of DCG IV on long-term potentiation was abolished by co-application with 50 μM MSOPPE ($n = 6$).

were tetanized 150 min after the initial tetanization, to show that further potentiation was still possible (Fig. 1A). When the concentration of L-CCG-I was raised to 250 μM, a reduction of basal fEPSPs and the post-tetanic potentiation was elicited during drug application ($n = 6$; Fig. 1B). The initial potentiation was 193 ± 7% in controls ($n = 9$) and only 138 ± 6% in the L-CCG-I experiments ($n = 6$). After wash-out of L-CCG-I, the potentiation tended to increase and remained at a higher level as compared to the potentiation of controls, which displayed a faster decay. The difference became statistically significant 90 min after tetanization ($n = 6$; Fig. 1B).

The dose dependence of the L-CCG-I effect in blocking long-term potentiation was studied at the concentrations of 3, 10 and 50 μM ($n = 5$, 7 and 5, respectively; Fig. 1C). A curve fit of the data resulted in an EC_{50} estimate of 8.2 ± 3.7 μM with a Hill-coefficient of 0.5 ± 0.1. Moreover, a theoretical fit with the Hill-coefficient of 1 (Fig. 1C, dotted line), indicated a noticeable decrease of L-

CCG-1 efficacy at concentrations higher than 10 μM. Although the calculated EC_{50} for L-CCG-I was about 10-folds greater than that previously published data (Bedingfield et al., 1995), this difference is most likely due to methodical constraints in constructing dose–response curves from long-term potentiation-experiments.

To verify the findings obtained with L-CCG-I the action of another group II agonist, DCG IV, on long-term potentiation was examined. Owing to its agonistic effect on the NMDA receptor/channel complex at higher concentrations, the concentration of DCG IV was restricted to 1 μM (Wilsch et al., 1994; Breakwell et al., 1997). The administration of DCG IV during tetanization led to a significant inhibition of long-term potentiation (Fig. 2A). The initial values of fEPSP potentiation were unaffected by DCG-IV ($193 \pm 18\%$; $n = 7$) in comparison to long-term potentiation control ($195 \pm 5\%$; $n = 9$). The fEPSP potentiation returned to baseline within 40 min after tetanization, being $115 \pm 4\%$ after DCG-IV compared with $129 \pm 3\%$ in the controls ($P < 0.05$). A second tetanization delivered 90 min after the first revealed that the long-term potentiation induction was not affected (Fig. 2A). To clarify, whether the effect of DCG IV is mediated through desensitization of NMDA receptors, additional experiments were designed (Fig. 2B). Long-term potentiation was induced by a 400-ms 100 Hz tetanization. Application of 1 μM DCG IV ($n = 6$) led to an inhibition of potentiation in comparison to control experiments ($n = 6$). Co-application of DCG IV and 50 μM MSOPPE abolished the effect of DCG IV on long-term potentiation.

3.2. Antagonists of group II mGlu receptors enhance long-term potentiation

In order to further clarify the role of group II mGlu receptors in long-term potentiation induction, the group II mGlu receptors antagonists M3C4HPG and MSOPPE were tested. Application of 100 μM M3C4HPG did not affect the initial potentiation ($181 \pm 20\%$, $n = 6$) in comparison to that of the control experiments ($183 \pm 11\%$; $n = 8$), but from the first hour after tetanization, a significant difference between control and drug experiments was observed ($106 \pm 2\%$ for controls and $123 \pm 4.4\%$ for experiments; Fig. 3A). Administration of 50 μM M3C4HPG during tetanization was ineffective in modifying long-term potentiation (Fig. 3A). The initial potentiation in control experiments ($n = 8$) amounted to $183 \pm 11\%$ and was $208 \pm 12\%$ in M3C4HPG experiments ($n = 6$).

Since M3C4HPG has been suggested to act in high concentrations as an antagonist at group III mGlu receptors (Bedingfield et al., 1995), additionally we applied MSOPPE, an antagonist with higher selectivity towards group II mGlu receptors (Thomas et al., 1996). The results obtained with MSOPPE resemble the findings with M3C4HPG. A concentration of MSOPPE of 50 μM led to a significant enhancement of long-term potentiation al-

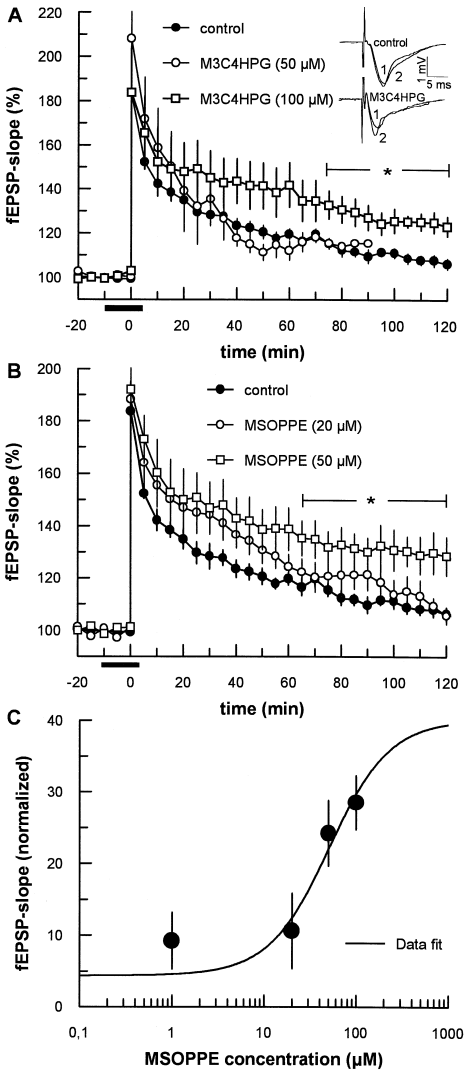

Fig. 3. The mGluR group II antagonist M3C4HPG influenced long-term potentiation only at a higher concentration. (A) After application of 50 μM M3C4HPG (small horizontal black line), no difference between controls ($n = 8$, black circles) and drug-treated slices ($n = 6$, open circles) was detected. The application of 100 μM M3C4HPG ($n = 6$, white squares) led to a long-term potentiation enhancement which was significant different 75 min after tetanization (bracket with asterisk, $P < 0.05$). Analogue traces represent fEPSP recordings immediately before (1) and 80 min after tetanization (2). (B) MSOPPE had similar effects on long-term potentiation as M3C4HPG. After application (black line) of 20 μM MSOPPE no enhancement of long-term potentiation in drug-treated slices ($n = 7$, white circles) compared with the controls ($n = 8$, black circles) was detected. At a concentration of 50 μM an enhancement of long-term potentiation was observed ($n = 6$, white squares). (C) The dose–response curve for the effect of MSOPPE on long-term potentiation (data points taken 50 min after tetanization). The IC_{50} was 50 ± 20 μM with a Hill-coefficient of 1.3 ± 0.7, however, there was no significant difference between the effect of adjacent concentrations (1 and 100 μM; $n = 6$).

though the magnitude of long-term potentiation immediately after tetanization was not significantly different in drug ($128 \pm 7\%$; $n = 6$) and control ($183 \pm 11\%$; $n = 8$) groups. One hour after tetanization, a significant enhancement of long-term potentiation had occurred in the

MSOPPE group compared with controls ($P < 0.05$) (see Fig. 3B). These effects were dose-dependent and the dose–response curve is presented in Fig. 3C. With 20 μM MSOPPE there was no difference between controls ($n = 8$) and MSOPPE-treated slices ($n = 7$). The initial potentiation amounted to 183 ± 11% for the controls and to 188 ± 12% for the MSOPPE-treated slices and declined within 2 h to 106 ± 2.5% and 105 ± 3%, respectively (Fig. 3B). The IC_{50} was 50.9 ± 17 μM with a Hill-coefficient of 1.3 ± 0.5.

4. Discussion

Our results indicate that activation of group II mGlu receptors during tetanization is not required for the induction of long-term potentiation, but rather has detrimental consequences. These findings are in agreement with reports by others that activation of group II mGlu receptors reduces CA1- and dentate gyrus-long-term potentiation in vivo and in vitro (Hölscher et al., 1997; Huang et al., 1997b; Breakwell et al., 1998). The facilitatory effect of the mGlu receptor group II antagonists M3C4HPG and MSOPPE on long-term potentiation is in contrast to data obtained in vivo, where application of group II mGlu receptor antagonists did not affect long-term potentiation (Hölscher et al., 1997; Manahan-Vaughan, 1997). This could imply that basal group II mGlu receptor activation is altered in in vitro preparations compared to in the intact animal.

A striking result was the U-shaped dose–response curve for the group II agonist L-CCG-I, which may be due to the agonist activity of L-CCG-I at group I mGlu receptors at higher concentrations (Cartmell et al., 1994; Davies et al., 1995; Conn and Pin, 1997). The latter assumption is supported by the temporary depression of baseline followed by a facilitation of potentiation during and shortly after infusion of high L-CCG-I concentrations. This finding resembles that for the group I agonist (*S*)-3,5-dihydroxyphenylglycine (Cohen et al., 1998). The action of L-CCG-I in higher concentrations at group I mGlu receptors, which are able to facilitate potentiation (McGuinness et al., 1991; Bortolotto and Collingridge, 1992; Behnisch and Reymann, 1993; Manahan-Vaughan et al., 1996), can probably overcome the inhibitory action of L-CCG-I on long-term potentiation which is mediated by group II mGlu receptors. In contrast, at lower concentrations of L-CCG-I no baseline effects were observed, supporting an action at group II mGluRs in this concentration range. The DCG IV experiments corroborated the findings obtained with L-CCG-I, i.e., the application of DCG IV (1 μM) resulted in an impairment of long-term potentiation. This effect was due to a specific action at group II mGluRs since it could be prevented by the selective group II antagonist MSOPPE (Thomas et al., 1996).

On the basis of the above data, a plausible mechanism for the decrease of long-term potentiation by activation of group II mGlu receptors may involve inhibition of the cAMP pathway because inhibitors of this pathway cause a decrease of early or late long-term potentiation (Frey et al., 1993; Matthies and Reymann, 1993; Blitzer et al., 1995). It is known that activation of group II mGlu receptors in rat hippocampus or of $mGlu_{2,3}$ receptors expressed in transfected cell lines inhibits the forskolin-stimulated cAMP accumulation (Genazzani et al., 1993; Schoepp and Johnson, 1993). The possible inhibition of tetanization-linked stimulation of cAMP formation by activation of group II mGlu receptors, may lead to a reduction or block of long-term potentiation. Indeed, both agonists, L-CCG-I and DCG IV, were able to reduce long-term potentiation. Conversely, elimination of this negative control of the cAMP pathway should result in a facilitation of long-term potentiation. Exactly such long-term potentiation promoting effects were observed after application of the group II antagonists M3C4HPG and MSOPPE. The weak tetanization used in our study allowed the detection of the facilitatory effects of drugs, whereas strong tetanization protocols which result in a saturated potentiation may well mask the facilitatory actions of group II antagonists on long-term potentiation (Hölscher et al., 1997; Manahan-Vaughan, 1997).

Since the effects of cAMP pathway inhibitors on long-term potentiation are mainly thought to occur postsynaptically, it would require the postsynaptic presence of group II mGlu receptors, those subcellular localization is still a matter of discussion (Fotuhi et al., 1994; Ohishi et al., 1994; Neki et al., 1996; Petralia et al., 1996; Shigemoto et al., 1997). However, at present it is impossible to rule out that the influence of group II mGlu receptors antagonists or agonists influence on long-term potentiation by interacting with glia cells, or interneurones, cell types in which group II mGlu receptors are highly expressed (Petralia et al., 1996). Notwithstanding the cellular and subcellular localization of group II mGlu receptors, they may specifically limit the long-term potentiation under physiological conditions.

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References

Aiba, A., Chen, C., Herrup, K., Rosenmund, C., Stevens, C.F., Tonegawa, S., 1994. Reduced hippocampal long-term potentiation and context-specific deficit in associative learning in mGluR1 mutant mice. Cell 79, 365–375.

Bashir, Z.I., Bortolotto, Z.A., Davies, C.H., Berretta, N., Irving, A.J.,

Seal, A.J., Henley, J.M., Jane, D.E., Watkins, J.C., Collingridge, G.L., 1993. Induction of LTP in the hippocampus needs synaptic activation of glutamate metabotropic receptors. Nature 363, 347–350.

Bedingfield, J.S., Kemp, M.C., Jane, D.E., Tse, H.W., Roberts, P.J., Watkins, J.C., 1995. Structure–activity relationships for a series of phenylglycine derivatives acting at metabotropic glutamate receptors (mGluR). Br. J. Pharmacol. 116, 3323–3329.

Behnisch, T., Reymann, K.G., 1993. Co-activation of metabotropic glutamate and *N*-methyl-D-aspartate receptors is involved in mechanisms of long-term potentiation maintenance in rat hippocampal CA1 neurons. Neuroscience 54, 37–47.

Bliss, T.V., Collingridge, G.L., 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361, 31–39.

Blitzer, R.D., Wong, T., Nouranifar, R., Iyengar, R., Landau, E.M., 1995. Postsynaptic cAMP pathway gates early LTP in hippocampal CA1 region. Neuron 15, 1403–1414.

Blumcke, I., Behle, K., Malitschek, B., Kuhn, R., Knopfel, T., Wolf, H.K., Wiestler, O.D., 1996. Immunohistochemical distribution of metabotropic glutamate receptor subtypes mGluR1b, mGluR2/3, mGluR4a and mGluR5 in human hippocampus. Brain Res. 736, 217–226.

Bortolotto, Z.A., Collingridge, G.L., 1992. Activation of glutamate metabotropic receptors induces long-term potentiation. Eur. J. Pharmacol. 214, 297–298.

Breakwell, N.A., Huang, L., Rowan, M.J., Anwyl, R., 1997. DCG-IV inhibits synaptic transmission by activation of NMDA receptors in area CA1 of rat hippocampus. Eur. J. Pharmacol. 322, 173–179.

Breakwell, N.A., Rowan, M.R., Anwyl, R., 1998. MCPG blocks LTP via an agonist action at mGluR II in CA1 of rat hippocampus. J. Neurophysiol. 79, 1270–1276.

Cartmell, J., Kemp, J.A., Alexander, S.P.H., Shinozaki, H., Kendall, D.A., 1994. Modulation of cyclic-AMP formation by putative metabotropic receptor agonists. Br. J. Pharmacol. 111, 364–369.

Chinestra, P., Aniksztejn, L., Diabira, D., Ben-Ari, Y., 1993. (*RS*)-alpha-methyl-4-carboxyphenylglycine neither prevents induction of LTP nor antagonizes metabotropic glutamate receptors in CA1 hippocampal neurons. Neurophysiology. 70, 2684–2689.

Collingridge, G.L., Bliss, T.V., 1995. Memories of NMDA receptors and LTP. Trends Neurosci. 18, 54–62.

Cohen, A.S., Raymond, C.R., Abraham, W.C., 1998. Priming of long-term potentiation induced by activation of metabotropic glutamate receptors coupled to phospholipase C. Hippocampus 8, 160–170.

Conn, P.J., Pin, J.P., 1997. Pharmacology and functions of metabotropic glutamate receptors. Annu. Rev. Pharmacol. Toxicol. 37, 205–237.

Conquet, F., Bashir, Z.I., Davies, C.H., Daniel, H., Ferraguti, F., Bordi, F., Franzbacon, K., Reggiani, A., Matarese, V., Conde, F., Collingridge, G.L., Crepel, F., 1994. Motor deficit and impairment of synaptic plasticity in mice lacking mGluR1. Nature 372, 237–243.

Davies, C.H., Clarke, V.R., Jane, D.E., Collingridge, G.L., 1995. Pharmacology of postsynaptic metabotropic glutamate receptors in rat hippocampal CA1 pyramidal neurones. Br. J. Pharmacol. 116, 1859–1869.

Fotuhi, M., Standaert, D.G., Testa, C.M., Penney, J.B., Young, A.B., 1994. Differential expression of metabotropic glutamate receptors in the hippocampus and entorhinal cortex of the rat. Mol. Brain Res. 21, 283–292.

Frey, U., Huang, Y.Y., Kandel, E.R., 1993. Effects of cAMP simulate a late-stage of LTP in hippocampal CA1 neurons. Science 260, 1661–1664.

Genazzani, A.A., Casabona, G., L'Episcopo, M.R., Condorelli, D.F., Dell'Albani, P., Shinozaki, H., Nicoletti, F., 1993. Characterization of metabotropic glutamate receptors negatively linked to adenylyl cyclase in brain slices. Brain Res. 622, 132–138.

Gereau, R.W., Conn, J.P., 1995. Roles of specific metabotropic glutamate receptor subtypes in regulation of hippocampal CA1 pyramidal cell excitability. J. Neurophysiol. 74, 122–129.

Hayashi, Y., Tanabe, Y., Aramori, I., Masu, M., Shimamoto, K., Ohfune, Y., Nakanishi, S., 1992. Agonist analysis of 2-(carboxycyclopropyl) glycine isomers for cloned metabotropic glutamate receptor subtypes expressed in Chinese hamster ovary cells. Br. J. Pharmacol. 107, 539–543.

Hölscher, C., Anwyl, R., Rowan, M.J., 1997. Activation of group-II metabotropic glutamate receptors blocks induction of long-term potentiation and depotentiation in area CA1 of the rat in vivo. Eur. J. Pharmacol. 322, 155–163.

Huang, L., Breakwell, N.A., Rowan, M.J., Anwyl, R., 1997a. PCCG-IV inhibits the induction of long-term potentiation in the dentate gyrus in vitro. Eur. J. Pharmacol. 332, 161–165.

Huang, L.Q., Rowan, M.J., Anwyl, R., 1997b. mGluR II agonist inhibition of LTP induction, and mGluR II antagonist inhibition of LTD induction, in the dentate gyrus in vitro. Neuroreport 8, 687–693.

Ishida, M., Saitoh, T., Shimamoto, K., Ohfune, Y., Shinozaki, H., 1993. A novel metabotropic glutamate receptor agonist: marked depression of monosynaptic excitation in the newborn rat isolated spinal cord. Br. J. Pharmacol. 109, 1169–1177.

Izumi, Y., Zorumski, C.F., 1994. Developmental changes in the effects of metabotropic glutamate receptor antagonists on CA1 long-term potentiation in rat hippocampal slices. Neurosci. Lett. 176, 89–92.

Little, Z., Grover, L.M., Teyler, T.J., 1995. Metabotropic glutamate receptor antagonist, (*R,S*)-alpha-methyl-4-carboxyphenylglycine, blocks two distinct forms of long-term potentiation in area CA1 of rat hippocampus. Neurosci. Lett. 201, 73–76.

Lu, Y.M., Jia, J.Z., Janus, C., Henderson, J.T., Gerlai, R., Wojtowicz, J.M., Roder, J.C., 1997. Mice lacking metabotropic glutamate receptor 5 show impaired learning and reduced CA1 long-term potentiation (LTP) but normal CA3 LTP. J. Neurosci. 17, 5196–5202.

Manahan-Vaughan, D., 1997. Group 1 and 2 metabotropic glutamate receptors play differential roles in hippocampal long-term depression and long-term potentiation in freely moving rats. J. Neurosci. 17, 3303–3309.

Manahan-Vaughan, D., Reymann, K.G., 1995. Regional and developmental profile of modulation of hippocampal synaptic transmission and LTP by AP4-sensitive mGluRs in vivo. Neuropharmacology 34, 991–1001.

Manahan-Vaughan, D., Reiser, M., Pin, J.P., Wilsch, V., Bockaert, J., Reymann, K.G., Riedel, G., 1996. Physiological and pharmacological profile of *trans*-azetidine-2,4-dicarboxylic acid: metabotropic glutamate receptor agonism and effects on long-term potentiation. Neuroscience 72, 999–1008.

Manzoni, O.J., Weisskopf, M.G., Nicoll, R.A., 1994. MCPG antagonizes metabotropic glutamate receptors but not long-term potentiation in the hippocampus. Eur. J. Neurosci. 6, 1050–1054.

Matthies, H., Reymann, K.G., 1993. Protein kinase-A inhibitors prevent the maintenance of hippocampal long-term potentiation. Neuroreport 4, 712–714.

McGuinness, N., Anwyl, R., Rowan, M., 1991. *trans*-ACPD enhances long-term potentiation in the hippocampus. Eur. J. Pharmacol. 19, 231–232.

Nakanishi, S., 1994. Metabotropic glutamate receptors: synaptic transmission, modulation, and plasticity. Neuron 13, 1031–1037.

Neki, A., Ohishi, H., Kaneko, T., Shigemoto, R., Nakanishi, S., Mizuno, N., 1996. Pre- and postsynaptic localization of a metabotropic glutamate receptor, mGluR2, in the rat brain: an immunohistochemical study with a monoclonal antibody. Neurosci. Lett. 202, 197–200.

Ohishi, H., Ogawa-Meguro, R., Shigemoto, R., Kaneko, T., Shigetada, N., Mizuno, N., 1994. Immunohistochemical localization of metabotropic glutamate receptors, mGluR2 and mGluR3, in rat cerebellar cortex. Neuron 13, 55–66.

Petralia, R.S., Wang, Y.X., Niedzielski, A.S., Wenthold, R.J., 1996. The metabotropic glutamate receptors, mGluR2 and mGluR3, show unique postsynaptic, presynaptic and glial localizations. Neuroscience 71, 949–976.

Pin, J.P., Duvoisin, R., 1995. The metabotropic glutamate receptors: structure and functions. Neuropharmacology 34, 1–26.

Reymann, K.G., Matthies, H., 1989. 2-Amino-4-phosphonobutyrate selectively eliminates late phases of long-term potentiation in rat hippocampus. Neurosci. Lett. 98, 166–171.

Reymann, K.G., Staak, S., 1994. Molecular mechanism underlying long-term potentiation: postsynaptic glutamate receptors and protein kinase C. In: Canonico, P.L., Scapgnini, U., Pamparana, F., Routtenberg, A. (Eds.), Protein Kinase C in the CNS Focus on Neuronal Plasticity (Proceedings), Masson, Milano, p. 31.

Schoepp, D.D., Johnson, G., 1993. Pharmacology of metabotropic glutamate receptor inhibition of cyclic AMP formation in the adult rat hippocampus. Neurochem. Int. 22, 277–283.

Selig, D.K., Lee, H.K., Bear, M.F., Malenka, R.C., 1995. Reexamination of the effects of MCPG on hippocampal LTP, LTD, and depotentiation. J. Neurophysiol. 74, 1075–1082.

Shigemoto, R., Kinoshita, A., Wada, E., Nomura, S., Ohishi, H., Takada, M., Flor, P.J., Neki, A., Abe, T., Nakanishi, S., Mizuno, N., 1997. Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus. J. Neurosci. 17, 7503–7522.

Tanabe, Y., Masu, M., Ishii, T., Shigemoto, R., Nakanishi, S., 1992. A family of metabotropic glutamate receptors. Neuron 8, 169–179.

Tanabe, Y., Nomura, A., Masu, M., Shigemoto, R., Mizuno, N., Nakanishi, S., 1993. Signal transduction, pharmacological properties, and expression patterns of two rat metabotropic glutamate receptors, mGluR3 and mGluR4. J. Neurosci. 13, 1372–1378.

Thomas, N.K., Jane, D.E., Tse, H.W., Watkins, J.C., 1996. α-Methyl derivatives of serine-*O*-phosphate as novel, selective competitive metabotropic glutamate receptor antagonists. Neuropharmacology 35, 637–642.

Wilsch, V.W., Pidoplichko, V.I., Opitz, T., Shinozaki, H., Reymann, K.G., 1994. Metabotropic glutamate receptor agonist DCG IV as NMDA receptor agonist in immature rat hippocampal neurons. Eur. J. Pharmacol. 262, 287–291.