ELSEVIER

European Journal of Pharmacology 322 (1997) 173–178

ejp

DCG-IV inhibits synaptic transmission by activation of NMDA receptors in area CA1 of rat hippocampus

Nicholas A. Breakwell [a,*], LingQian Huang [a], Michael J. Rowan [b], Roger Anwyl [a]

[a] *Department of Physiology, Trinity College Dublin, Dublin 2, Ireland*
[b] *Department of Pharmacology and Therapeutics, Trinity College Dublin, Dublin 2, Ireland*

Received 10 October 1996; revised 17 December 1996; accepted 24 December 1996

Abstract

We investigated the synaptic depressant action of the metabotropic glutamate receptor group II agonist, (2*S*,1′*R*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)-glycine (DCG-IV), in area CA1 of rat hippocampus. A brief bath application of DCG-IV (10 μM) caused a rapidly reversible depression to 0.57 ± 0.22 (i.e., 43%) of baseline excitatory postsynaptic potential (epsp) slope. This depression could not be attenuated by the metabotropic glutamate receptor antagonists α-methyl-L-CCGI/(2*S*,3*S*,4*S*)-2-methyl-2-(carboxycyclopropyl)glycine (MCCG), (*RS*)-α-methyl-4-tetrazolyphenylglycine (MTPG) or (*S*)-2-amino-2-methyl-4-phosphonobutanoic acid α-methyl-AP4) (MAP4). However, the DCG-IV-induced depression could be reversed by the NMDA receptor antagonist, D(−)-2-amino-5-phosphonopentanoic acid (AP5; 50 μM), and partially reversed by the adenosine A_1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX; 5 μM). These results strongly suggest that DCG-IV is an agonist at NMDA receptors and provide further evidence against a role for metabotropic glutamate receptor group II in synaptic transmission in area CA1 of rat hippocampus.

Keywords: DCG-IV; Metabotropic glutamate receptor; NMDA receptor; AP5 (D-2-amino-5-phosphonopentanoic acid)

1. Introduction

The synaptic functions of glutamate are mediated through both ionotropic and metabotropic glutamate receptors. Eight metabotropic glutamate receptor subtypes have been classified into three major groups: metabotropic glutamate receptor group I comprising of the phosphoinositide hydrolysis linked metabotropic glutamate receptor subtypes 1 and 5; metabotropic glutamate receptor group II (metabotropic glutamate receptors 2 and 3) and metabotropic glutamate receptor group III (metabotropic glutamate receptors 4, 6, 7 and 8) both linked to inhibition of adenylate cyclase and reduced cyclic AMP formation. Recently a variety of metabotropic glutamate receptor-group and metabotropic glutamate receptor-subtype specific agonists and antagonists have become available, which have enabled investigation of the role of metabotropic glutamate receptors in synaptic transmission and other synaptic processes such as long-term potentiation.

Activation of metabotropic glutamate receptors has frequently been shown to depress synaptic transmission. Baskys and Malenka (1991) demonstrated that (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid ((1*S*,3*R*)-ACPD), a broad-spectrum metabotropic glutamate receptor agonist, presynaptically depressed synaptic transmission between CA3 and CA1, and this observation has been repeated since in several brain areas (see review by Pin and Duvoisin, 1995).

In particular metabotropic glutamate receptor group II agonists have been found to produce presynaptic depression at many synapses (Pook et al., 1992; Ishida et al., 1993a; Kamiya et al., 1996; Jane et al., 1994; Ugolini and Bordi, 1995; Bushell et al., 1996). DCG-IV is the most potent and selective metabotropic glutamate receptor group II agonist so far synthesised (Ishida et al., 1993a). It has been shown to be a potent presynaptic reversible inhibitor of monosynaptic excitatory transmission at motorneurone synapses (Ishida et al., 1993a), corticostriatal synapses (Lovinger and McCool, 1995), lateral perforant path synapses in the dentate gyrus (Bushell et al., 1996) and at mossy fibre-CA3 synapses in the hippocampus (Kamiya et al., 1996). In addition DCG-IV also reduces inhibitory synaptic transmission in hippocampus (Poncer et al., 1995) and in the accessory olfactory bulb (Hayashi et al., 1993).

* Corresponding author.

0014-2999/97/$17.00
PII S0014-2999(97)00015-0

In the present report we describe a depressing action of DCG-IV in area CA1 of rat hippocampus at concentrations higher than are effective in dentate gyrus, and argue that this effect is due not to activation of metabotropic glutamate receptors but to the agonist properties of DCG-IV at NMDA receptors (Wilsch et al., 1994).

2. Materials and methods

All experiments were carried out on hippocampal slices obtained from male Wistar rats (3–4 weeks). Slices were prepared as described previously (Breakwell and Publicover, 1994). Briefly, the brain was rapidly removed and cooled to 4°C or below in 95:5 O_2/CO_2 saturated saline (mmol/l: NaCl 120; KCl 2.5; NaH_2PO_4 1.25; $NaHCO_3$ 26; $MgSO_4$ 2; $CaCl_2$ 2; D-glucose 10; pH 7.4) and hippocampal slices (400 μm) were prepared using a Campden vibroslice (Campden Group Instruments, London, UK). Slices were maintained at 30°C in a holding chamber, before being transferred as required to a submersion type recording chamber at 30–31°C. All drugs were added directly to the perfusate and were purchased from Tocris Cookson (Bristol, UK).

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

Values given in the text are normalised mean ± S.E.M. *P* values refer to paired *t*-tests in which potentials before drug application were compared to potentials during drug application or following washout, and where stated to standard *t*-tests in which different treatment groups were compared.

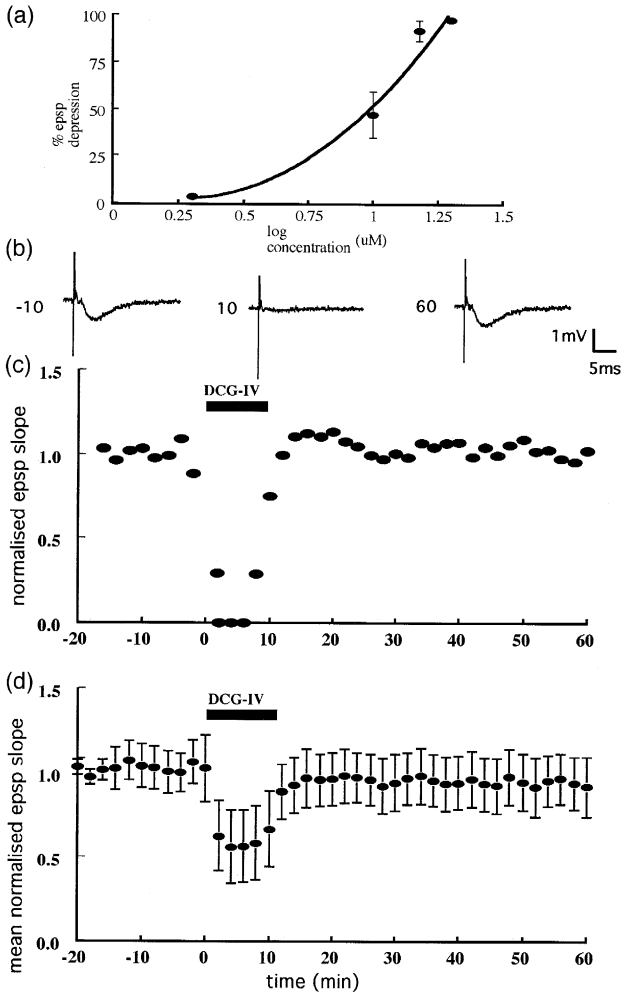

Fig. 1. DCG-IV reversibly depresses test epsp slope. (a) Dose-response curve for DCG-IV. Experimental points (mean ± standard error) represent the percent depression of the test epsp 10 min after addition of the given DCG-IV concentration. (b) Example traces (average of three consecutive traces) taken from the example experiment in (c) at the times indicated to the left of each trace. (c) Single experiment in which brief application (10 min) of DCG-IV (10 μM) (bar) induced a rapid and reversible depression of test epsp. Experimental points represent the average of four consecutive test epsps. (d) Pooled data of seven similar experiments in which DCG-IV (10 μM) (bar) induced a rapid and reversible depression of the test epsp. Data points represent the mean ± standard error of four consecutive test epsps.

3. Results

3.1. High concentrations of DCG-IV depress test epsps

A dose–response curve for the depressant action of DCG-IV on the test epsp was determined. At 2 μM little or no effect on epsp slope was observed, while at 10 μM a significant depression of approximately 50% was seen (Fig. 1a). At concentrations above 15 μM the epsp was almost entirely blocked. The IC_{50} was estimated at 9.6 μM and a concentration of 10 μM was typically used in subsequent experiments. Seven slices were exposed to a brief (10 min) bath application of DCG-IV (10 μM) which induced a rapid depression of synaptic transmission to 0.57 ± 0.22 ($P = 0.041$, df = 6; Fig. 1d) of baseline values. Following washout a rapid reversal of the depression was observed, returning to baseline values within 10 min. At 40 min following washout mean normalised epsp slope was 0.96 ± 0.15, not different from baseline values ($P = 0.196$, df = 6, Fig. 1d).

We further investigated whether the depression of synaptic transmission induced by DCG-IV interfered with processes which are involved in synaptic plasticity. After a stable depression of the test epsp had been established, following DCG-IV application, a series of bursts of high-frequency stimulation (hfs) (8 × 8/200 Hz, 200 ms inter-

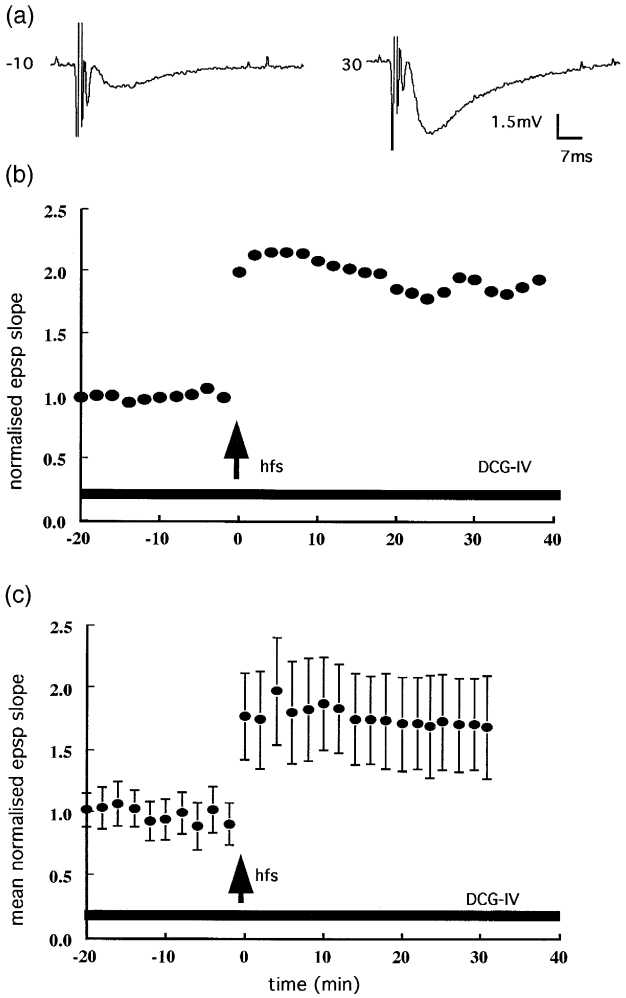

Fig. 2. DCG-IV does not prevent the induction of long-term potentiation. (a) Example traces (mean of three consecutive test epsps) from the single experiment in (b) recorded at the times indicated to the left of each trace. (b) Single experiment in which hfs (8×8/200 Hz, interpulse interval 200 ms; arrow) was given in the presence of DCG-IV (10 μM) (bar). The baseline period in the presence of DCG-IV (10 μM) represents depressed epsp values (approx. 50%) which have been re-normalised. (c) Pooled data from four similar experiments in which hfs (arrow) was delivered in the presence of DCG-IV (10 μM) (bar). Data points represent the mean ± standard error of four consecutive test epsps.

pulse interval, stimulation increased to approx. 70% of maximum) were applied to four slices in the presence of DCG-IV (10 μM). A potentiation of epsp slope was observed in all four slices. At 30 min following hfs mean normalised epsp slope was 1.76 ± 0.36, significantly higher than pre-hfs values ($P = 0.039$, df = 6, Fig. 2).

3.2. The depressant action of DCG-IV is not blocked by metabotropic glutamate receptor group II or metabotropic glutamate receptor group III antagonists

We assessed whether the depressant action of DCG-IV was due to activation of metabotropic glutamate receptor group II or metabotropic glutamate receptor group III with use of the metabotropic glutamate receptor group-specific antagonists MCCG, MTPG and MAP4. MCCG is selective for group II metabotropic glutamate receptors (Jane et al., 1995), MTPG for metabotropic glutamate receptor 2 but not 3 (Jane et al., 1995), and MAP4 is specific for metabotropic glutamate receptor group III, reliably reversing the actions of L-AP4 (Bushell et al., 1995). Having established a stable level of synaptic depression with bath application of DCG-IV (10 μM), MCCG (500 μM) was added to the perfusate. MCCG failed to attenuate the effect of DCG-IV in all four slices tested (0.67 ± 0.17, Fig. 3a). The degree of depression 30 min after introduction of MCCG was not significantly different from the period

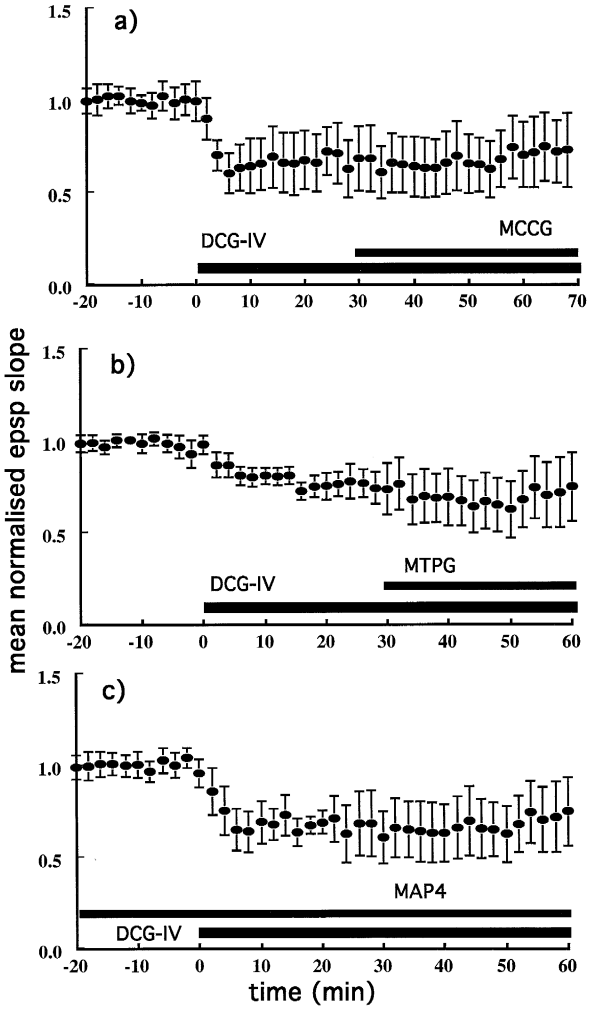

Fig. 3. The depressant effect of DCG-IV is not attenuated by metabotropic glutamate receptor antagonists. (a) Pooled data ($n = 4$) in which DCG-IV (10 μM) (thick bar) induced a stable depression of test epsp slope which was not reversed by addition of the metabotropic glutamate receptor group II-selective antagonist MCCG (500 μM) (thin bar). (b) Pooled data ($n = 4$) in which DCG-IV (10 μM) (thick bar) induced a stable depression of test epsp slope which was not reversed by addition of the metabotropic glutamate receptor subtype 2-selective antagonist MTPG (500 μM) (thin bar). (c) Pooled data ($n = 4$) in which DCG-IV (10 μM) (thick bar) induced a stable depression of test epsp slope in the presence of the metabotropic glutamate receptor group III-selective antagonist MAP4 (500 μM) (thin bar). Data points represent the mean ± standard error of four consecutive test epsps.

immediately before MCCG application ($P = 0.64$, df = 3) or from slices not treated with MCCG ($P = 0.67$, df = 8).

A similar procedure was undertaken for slices treated with MTPG (500 μM). Thirty minutes following MTPG application no reversal of DCG-IV (10 μM) depression was observed (0.72 ± 0.26; Fig. 3b). This was not significantly different from the period immediately before MTPG application ($P = 0.67$, df = 3) or from slices not treated with MTPG ($P = 0.41$, df = 8).

Slices treated with MAP4 (500 μM) were preincubated with MAP4 for at least 30 min before DCG-IV (10 μM) application. The normal depressant effect of DCG-IV was not attenuated by MAP4 40 min after application (0.68 ± 0.06, Fig. 3c), and was not significantly different from slices not treated with MAP4 ($P = 0.39$, df = 8).

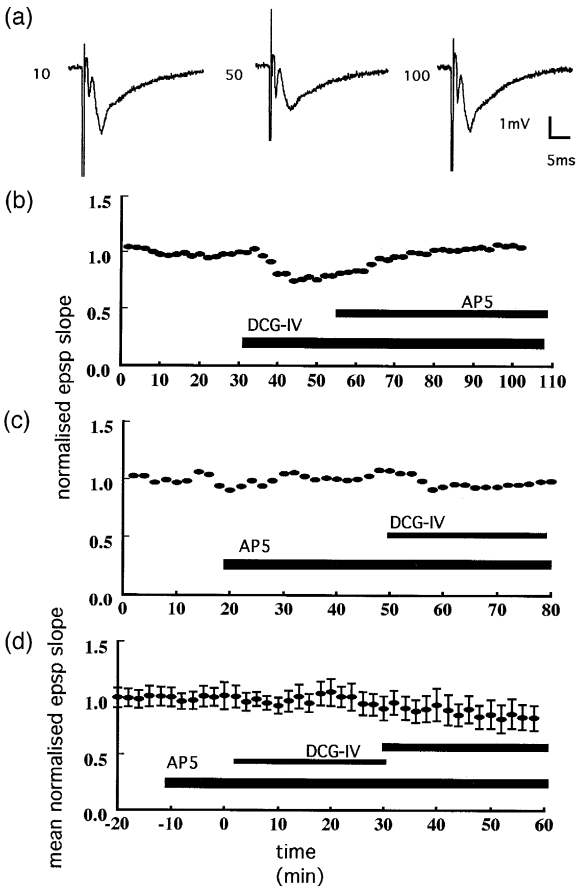

Fig. 4. The depressant action of DCG-IV is reversed by the NMDA receptor antagonist, AP5. (a) Example traces (average of three consecutive traces) from the single experiment in (b) recorded at times indicated to the left of each trace. (b) Single experiment in which the depressant effect induced by DCG-IV (10 μM) (thick bar) was slowly reversed by AP5 (50 μM) (thin bar). (c) Single experiment in which pre-incubation with AP5 (50 μM) (thick bar) prevented the depressant effect seen in control slices following addition of DCG-IV (10 μM) (thin bar). (d) Pooled data ($n = 5$) in which pre-incubation with AP5 (50 μM) (thick bar) prevented the depressant effect seen in control slices following addition of DCG-IV (10 μM) (thin bar). Data points represent the mean ± standard error of four consecutive test epsps. Increasing DCG-IV concentration to 20 μM (medium bar) resulted in a small depression of the test epsp.

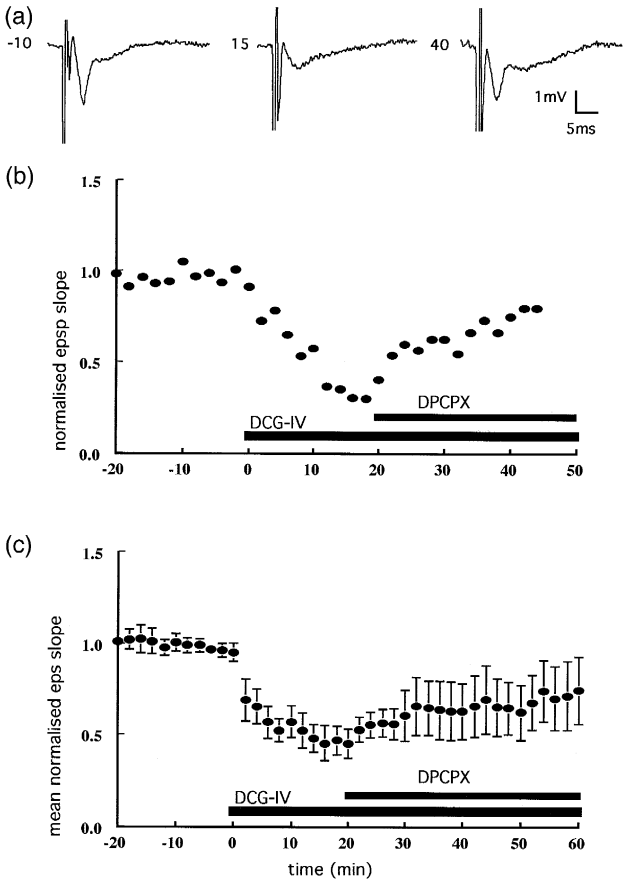

Fig. 5. The depressant action of DCG-IV is partially reversed by the adenosine A_1 antagonist DPCPX. (a) Example traces (average of three consecutive traces) from the single experiment in (b) recorded at times indicated to the left of each trace. (b) Single experiment in which the depressant action of DCG-IV (10 μM) (thick bar) was slowly and partially reversed by addition of DPCPX (5 μM). (c) Pooled data from six similar experiments, three of which demonstrated a clear reversal of the DCG-IV (10 μM) (thick bar) depression by DPCPX (5 μM), as in (b). Data points represent the mean ± standard error of four consecutive test epsps.

3.3. The NMDA receptor antagonist, AP5, blocks the depressing action of DCG-IV

Slices were preincubated with AP5 (50 μM) for at least 15 min. AP5 alone did not affect baseline synaptic transmission. Application of DCG-IV (10 μM) in the presence of AP5 (50 μM) had little or no effect on synaptic transmission (Fig. 4c,d). After 30 min of DCG-IV treatment mean normalised epsp slope was 0.96 ± 0.09, unchanged from values recorded in AP5 alone ($P = 0.60$, df = 4) but significantly higher than values recorded from slices with no AP5 pre-treatment ($P = 0.045$, df = 10). In three slices DCG-IV concentration was increased to 20 μM, following which a small inhibition of the epsp slope was observed (0.84 ± 0.12, Fig. 4d). When slices were first treated with DCG-IV (10 μM) and then exposed to AP5 (50 μM), a slow and complete reversal of the depressed epsp was observed (Fig. 4b).

3.4. The adenosine A_1 antagonist DPCPX partially reverses the depressant action of DCG-IV

Six slices were exposed to DCG-IV (10 μM) and DPCPX (5 μM). DCG-IV was first added to the perfusate and induced a significant depression of baseline (0.53 ± 0.09; $P = 0.005$, df = 5). Following the addition of DPCPX to the perfusate, a slow partial reversal of the DCG-IV-induced depression was observed, in three of the slices tested, typically taking 15 min to reach a stable level (Fig. 5b). Mean normalised epsp ($n = 6$) 30 min after introduction of DPCPX (0.67 ± 0.17, Fig. 5c) was increased relative to the period immediately before addition of DPCPX, but this partial reversal was not significant ($P = 0.23$, df = 5).

4. Discussion

The principal aim of this study was to investigate the depressant action of the metabotropic glutamate receptor group II agonist DCG-IV and to examine the mechanism through which this depression is induced. We demonstrated a fully reversible DCG-IV-induced depression of synaptic transmission in area CA1 of rat hippocampus. We also investigated the effect of DCG-IV on induction of long-term potentiation. Despite a significant effect of DCG-IV on baseline, there was no effect on the induction of long-term potentiation following tetanic stimulation. This suggests that DCG-IV does not interfere with second messenger systems believed to be important in long-term potentiation induction.

Studies in other brain areas such as the lateral perforant path of the dentate gyrus region of the hippocampus (Bushell et al., 1996), mossy fibre synapses (Kamiya et al., 1996) and corticostriatal synapses (Lovinger and McCool, 1995) have described a potent depressant effect of DCG-IV at relatively low concentrations (~ 1 μM). Furthermore, these effects are likely to be mediated by metabotropic glutamate receptors since the non-selective metabotropic glutamate receptor antagonist *R,S*-α-methyl-4-carboxyphenylglycine (MCPG) blocked (Lovinger and McCool, 1995) or greatly attenuated (Kamiya et al., 1996) the depressant effect of DCG-IV. In contrast, in area CA1 of rat hippocampus, low concentrations of DCG-IV (1 μM) failed to affect membrane potential (Gereau et al., 1995), *N*-methyl-D-aspartate (NMDA)-induced depolarisations (Fitzjohn et al., 1996) and failed to elicit NMDA receptor-dependent inward currents in dissociated neurons (Wilsch et al., 1994).

The relatively high estimated IC_{50} value of 9 μM, reported in the present study, suggests either that there is a low concentration of metabotropic glutamate receptor group II in area CA1 or that DCG-IV is an agonist at receptors other than metabotropic glutamate receptors at high concentrations. Several studies have indicated that staining for metabotropic glutamate receptor group II is approximately twice as dense in stratum lucidum of area CA3 than in stratum radiatum of CA3–CA1 (Neki et al., 1996; Petralia et al., 1996). To examine whether high concentrations of DCG-IV depressed synaptic transmission in area CA1 via an agonist action at sparsely distributed metabotropic glutamate receptor group II we used the metabotropic glutamate receptor antagonists MCCG and MTPG. MCCG has been suggested to be a selective antagonist at metabotropic glutamate receptor group II since it antagonised the presynaptic depression induced by (1*S*,3*S*)-ACPD and L-CCG1, selective metabotropic glutamate receptor group II agonists, but failed to affect L-AP4-induced depression in neonatal rat spinal cord (Jane et al., 1994). MTPG is also suggested to be selective for metabotropic glutamate receptor group II, although it also partially reverses the effects of L-AP4 (Bushell et al., 1996). Neither of these antagonists was able to reverse the effect of DCG-IV, suggesting that the depressant effect of DCG-IV described in this study is not due to activation of metabotropic glutamate receptor group II. Since DCG-IV may also activate metabotropic glutamate receptor group III we investigated the effect of the metabotropic glutamate receptor group III-selective antagonist MAP4, which has previously been shown to antagonise the actions of L-AP4 (Bushell et al., 1996). This compound was, similarly, unable to prevent the depressant effect of DCG-IV. These results strongly argue against a metabotropic glutamate receptor agonist action of DCG-IV at the concentrations used in this study in area CA1 of rat hippocampus.

We did find that the depressant actions of DCG-IV were blocked by the NMDA receptor antagonist AP5, suggesting that DCG-IV is an agonist at NMDA receptors. Direct application of NMDA is known to depress synaptic depression (Kauer et al., 1988) and we have previously demonstrated that a depression in CA1 induced by (1*S*,3*R*)-ACPD is significantly reduced in the presence of AP5 (Breakwell et al., 1996). When DCG-IV was applied at concentrations higher than 10 μM, neonatal rat spinal motorneurons displayed an AP5-dependent depolarisation (Ishida et al., 1993b), suggesting that the depolarisation could originate as a result of NMDA receptor activation. The role of DCG-IV as an NMDA receptor agonist has been confirmed with findings that a DCG-IV-induced depolarisation in dissociated hippocampal neurons was blocked by AP5 and 1 mM extracellular Mg^{2+}, and was enhanced by glycine (Wilsch et al., 1994). The data reported here are also very likely to be explained by an action at NMDA receptors. It is also likely that the depressant effect of (1*S*,3*R*)-ACPD (Breakwell et al., 1996) can also be explained by an action at NMDA receptors.

One possible mechanism for the action of DCG-IV is that it activates NMDA receptors leading to a release of adenosine. Application of NMDA resulted in a depression of test epsps in area CAI of rat hippocampus which was shown to be due to a release of adenosine from interneu-

rons or pyramidal cells (Manzoni et al., 1994). The release of adenosine gives rise to a widespread presynaptic inhibition of excitatory synaptic transmission by activating presynaptic adenosine A_1 receptors (Forghani and Krnjevic, 1995). With NMDA receptors blocked this adenosine-mediated inhibition would be at least partially removed.

To test this hypothesis we added the adenosine A_1 antagonist DPCPX to slices in which the epsp slope was already depressed by DCG-IV. We found that the depressant action of DCG-IV could be partially reversed by DPCPX. This suggests that activation of NMDA receptors leading to release of adenosine can explain, at least in part, the depressant effect of DCG-IV. DPCPX at 5 μM is unlikely to be specific for adenosine A_1 receptors but in three experiments (data not shown) we used a lower concentration (1 μM) and observed a similar partial reversal to that seen with 5 μM in two of these slices. The lack of complete reversal by DPCPX suggests that other neurotransmitter substances such as acetylcholine may also be released as a result of NMDA-induced depolarisation.

We conclude that DCG-IV depresses synaptic activity at CA3–CA1 synapses not through an activation of metabotropic glutamate receptors but through an activation of NMDA receptors which may lead to a release of adenosine. This finding indicates that DCG-IV must be used with caution when investigating metabotropic glutamate receptor activity especially in cases where activation of NMDA receptors is also likely to occur.

Acknowledgements

We are grateful to the Wellcome Trust and the Health Research Board of Ireland for financial support.

References

Baskys, A. and R.C. Malenka, 1991, *trans*-ACPD depresses synaptic transmission in the hippocampus, Eur. J. Pharmacol. 193, 131.

Breakwell, N.A. and S.J. Publicover, 1994, Prolonged enhancement of synaptic transmission in area CA1 of rat hippocampal slices induced by $NaF/AlCl_3$ does not require NMDA receptor activation but is suppressed by inhibitors of phosphoinositide-mediated signalling pathways, Brain Res. 633, 72.

Breakwell, N.A., M.J. Rowan and R. Anwyl, 1996, Metabotropic glutamate receptor dependent EPSP and EPSP-spike potentiation in area CA1 of the submerged rat hippocampal slice, J. Neurophysiol. 76, 3126.

Bushell, T.J., D.E. Jane, H.W. Tse, J.C. Watkins, C.H. Davies, J. Garthwaite and G.L. Collingridge, 1995, Antagonism of the synaptic depressant actions of L-AP4 in the lateral perforant path by MAP4, Neuropharmacology 34, 239.

Bushell, T.J., D.E. Jane, H.W. Tse, J.C. Watkins, J. Garthwaite and G.L. Collingridge, 1996, Pharmacological. antagonism of the actions of group II and group III metabotropic glutamate receptor agonists in the lateral perforant path of rat hippocampal slices, Br. J. Pharmacol. 117, 1457.

Fitzjohn, S.M., A.J. Irving, M.J. Palmer, J. Harvery, D. Lodge and G.L. Collingridge, 1996, Activation of group I mGluRs potentiates NMDA responses in rat hippocampal slices, Neurosci. Lett. 203, 211.

Forghani, R. and K. Krnjevic, 1995, Adenosine antagonists have differential effects on induction of long term potentiation in hippocampal slices, Hippocampus 5, 71.

Gereau, R.W., D.G. Winder and P.J. Conn, 1995, Pharmacological differentiation of the effects of co-activation of β-adrenergic and metabotropic glutamate receptors in rat hippocampus, Neurosci. Lett. 186, 119.

Hayashi, Y., A. Momiyama, T. Takahashi, H. Oshishi, R. Ogawameguro, R. Shigemoto, N. Mizuno and S. Nakanishi, 1993, Role of a metabotropic glutamate receptor in synaptic modulation in the accessory olfactory bulb, Nature 366, 687.

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

Ishida, M., T. Saitoh and H. Shinozaki, 1993b, A new metabotropic glutamate receptor agonist – developmental change of its sensitivity to receptors in the newborn rat spinal cord, Neurosci. Lett. 160, 156.

Jane, D.E., P.L. Jones, P. Pook, H. Tse and J.C. Watkins, 1994, Actions of two new antagonists showing selectivity for different sub-types of metabotropic glutamate receptors in the neonatal rat spinal cord, Br. J. Pharmacol. 112, 809.

Jane, D.E., K. Pittaway, D.C. Sunter, N.K. Thomas and J.C. Watkins, 1995, New phenylglycine derivatives with potent and selective antagonist activity at presynaptic glutamate receptors in neonatal rat spinal cord, Neuropharmacology 34, 851.

Kamiya, H., H. Shinozaki and C. Yamamoto, 1996, Activation of metabotropic glutamate receptor type 2/3 suppresses transmission at rat hippocampal mossy fibre synapses, J. Physiol. 493.2, 447.

Kauer, J.A., R.C. Malenka and R.A. Nicoll, 1988, NMDA application potentiates synaptic transmission in the hippocampus, Nature 334, 250.

Lovinger, D. and B. McCool, 1995, Metabotropic glutamate receptor mediated presynaptic depression at corticostriatal synapses involves metabotropic glutamate receptor 2 or 3, J. Neurophysiol. 73, 1076.

Manzoni, O.J., T. Manabe and R.A. Nicoll, 1994, Release of adenosine by activation of NMDA receptors in the hippocampus, Science 265, 2098.

Neki, A., H. Ohishi, T. Kaneko, R. Shigemoto, S. Nakanishi and N. Mizuno, 1996, Pre- and postsynaptic localization of a metabotropic glutamate receptor, metabotropic glutamate receptor2, in the rat brain: an immunohistochemical study with a monoclonal antibody, Neurosci. Lett. 202, 197.

Petralia, R.S., Y.X. Wang, A.S. Niedzielski and R.J. Wenthold, 1996, The metabotropic glutamate receptors, metabotropic glutamate receptor 2 and metabotropic glutamate receptor 3, show unique postsynaptic, presynaptic and glial localisations, Neuroscience 71, 949.

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

Poncer, J.C., H. Shinozaki and R. Miles, 1995, Dual modulation of synaptic inhibition by distinct metabotropic glutamate receptors in rat hippocampus, J. Physiol. 485, 121.

Pook, P.C., D.E. Sunter, P.M. Udvarhelyi and J.C. Watkins, 1992, Evidence for presynaptic depression of monosynaptic excitation in neonatal rat motoneurons by (1*S*,3*S*)- and (1*S*,3*R*)-ACPD, Exp. Physiol. 77, 529.

Ugolini, A. and F. Bordi, 1995, Metabotropic glutamate group II receptors are responsible for the depression of synaptic transmission induced by ACPD in the dentate gyrus, Eur. J. Pharmacol. 294, 403.

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