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Antagonists reversibly reverse chemical LTD induced by group I, group II and group III metabotropic glutamate receptors

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ABSTRACT

Metabotropic glutamate (mGlu) receptors are implicated in many neurological and psychiatric diseases and are the targets of therapeutic agents currently in clinical development. Their activation has diverse effects in the central nervous system (CNS) that includes an involvement in synaptic plasticity. We previously reported that the brief exposure of hippocampal slices to dihydroxyphenylglycine (DHPG) can result in a long-term depression (LTD) of excitatory synaptic transmission. Surprisingly, this LTD could be fully reversed by mGlu receptor antagonists in a manner that was itself fully reversible upon washout of the antagonist. Here, 15 years after the discovery of DHPG-LTD and its reversible reversibility, we summarise these initial findings. We then present new data on DHPG-LTD, which demonstrates that evoked epileptiform activity triggered by activation of group I mGlu receptors can also be reversibly reversed by mGlu receptor antagonists. Furthermore, we show that the phenomenon of reversible reversibility is not specific to group I mGlu receptors. We report that activation of group II mGlu receptors in the temporo-ammonic pathway (TAP) and mossy fibre pathway within the hippocampus and in the cortical input to neurons of the lateral amygdala induces an LTD that is reversed by LY341495, a group II mGlu receptor antagonist. We also show that activation of group III mGlu8 receptors induces an LTD at lateral perforant path inputs to the dentate gyrus and that this LTD is reversed by MDCPG, an mGlu8 receptor antagonist. In conclusion, we have shown that activation of representative members of each of the three groups of mGlu receptors can induce forms of LTD than can be reversed by antagonists, and that in each case washout of the antagonist is associated with the re-establishment of the LTD.

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1. Introduction

Glutamate receptors comprise three main ionotropic subtypes, AMPA, NMDA and kainate (Collingridge et al., 2009), and a family of G-protein coupled metabotropic (mGlu) receptors (Pin and Duvoisin, 1995). The eight known mGlu receptors are further subdivided into three groups based on structural and functional criteria: group I (mGlu1 and mGlu5), group II (mGlu2 and mGlu3) and group III (mGlu4, mGlu6, mGlu7 and mGlu8). There is currently considerable interest in mGlu receptors as targets for therapeutic agents (Nicoletti et al., 2011; Niswender and Conn, 2010). For example, negative allosteric modulators (NAMs) acting at mGlu5 receptors are being explored as potential treatments for epileptogenesis, Fragile-X syndrome, tardive dyskinesias and autism spectrum disorders (Bianchi et al., 2012; Gürkan and Hagerman, 2012; Michalon et al., 2012; Rylander et al., 2009). In addition, agonists acting at group II mGlu receptors have shown efficacy in man as therapies for anxiety and schizophrenia (Dunayevich et al., 2008; Grillon et al., 2003; Patil et al., 2007). Furthermore, mGlu5 receptors have been linked to the aetiology of Alzheimer's disease (Hu et al., 2012). Therefore understanding both the functions of

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Abbreviations

1*S*,3*R*-ACPD (*1S*,*3R*)-1-aminocyclopentane-1,3-dicarboxylic acid
DCG-IV (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine
DCPG (*S*)-3,4-dicarboxyphenylglycine
DHPG (*RS*)-3,5-dihydroxyphenylglycine
L-AP4 L-(+)-2-amino-4-phosphonobutyric acid
L-689,560 *trans*-2-carboxy-5,7-dichloro-4-phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline
LY341495 (2*S*,1′*S*,2′*S*)-2-(9-xanthylmethyl)-2-(2′-carboxycyclopropyl)glycine
LY367385 (*S*)-(+)-α-amino-4-carboxy-2-methylbenzeneacetic acid
LY379268 (1*R*,4*R*,5*S*,6*R*)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid
LY395756 (1*SR*,2*SR*,4*RS*,5*RS*,6*SR*)-2-amino-4-methylbicyclo[3.1.0]-hexane-2,6-dicarboxylic acid
MCPG α-Methyl-4-carboxyphenylglycine
MDCPG (*RS*)-α-methyl-3,4-dicarboxyphenylglycine
MPEP 2-methyl-6-(phenylethynyl)-pyridine hydrochloride

mGlu receptors and the actions of ligands that affect these receptors is of relevance to the development of therapeutic agents active against these, and other, disorders.

Fifteen years ago we described a form of LTD following the selective activation of group I mGlu receptors using the agonist, DHPG (Fitzjohn et al., 1998; Palmer et al., 1997). This form of synaptic plasticity, referred to hereafter as DHPG-LTD, has been extensively studied by many groups (e.g. Huang and Hsu, 2006; Huber et al., 2000; Massey and Bashir, 2007; Watabe et al., 2002; Xiao et al., 2001) A similar form of LTD has also been seen using the less selective mGlu receptor agonist, 1S,3R-ACPD, (O'Mara et al., 1995; Overstreet et al., 1997) although this is not invariably the case (Palmer et al., 1997).

DHPG-LTD is mechanistically different from the other major form of chemical LTD that can be induced by activation of NMDA receptors (NMDA-LTD) (see Collingridge et al., 2010). However, there is still disagreement over some aspects of the pharmacology and biochemistry of the induction and expression mechanisms. For example, which group I receptor mediates the DHPG-LTD (Faas et al., 2002; Gladding et al., 2009; Kumar and Foster, 2007; Moult et al., 2006; Volk et al., 2006), which kinases and phosphatases are involved (Gallagher et al., 2004; Hou and Klann, 2004; Mockett et al., 2011; Moult et al., 2008; Schnabel et al., 1999) and the relative contributions of pre- and post-synaptic mechanisms (Fitzjohn et al., 2001; Moult et al., 2006; Qian and Noebels, 2006; Tan et al., 2003; Upreti et al., 2013; Watabe et al., 2002; Waung et al., 2008; Xiao et al., 2001) are all subject to controversy. These aspects of LTD are, however, not the subject of the present article but rather we concentrate on the pharmacology of the maintenance phase of LTD induced by the pharmacological activation of mGlu receptors.

More specifically, at the same time as reporting DHPG-LTD, we noted the curious phenomenon that mGlu receptor antagonists, such as α-methyl-4-carboxyphenylglycine (MCPG), can reverse this plasticity long after it has been induced and that the plasticity is restored after washout of the antagonist (Fitzjohn et al., 1998; Palmer et al., 1997). Here we summarise these historical findings and present a series of new observations concerning the antagonist reversal of the maintained phase of group I mGlu receptor-triggered LTD (mGlu receptor-LTD). We also demonstrate similar phenomena for other mGlu receptor subtypes in groups II (mGlu2 and mGlu3) and III (mGlu8).

2. Materials and methods

2.1. Animals and slice preparation

Experiments were performed according UK Scientific Procedures Act, 1986 and EU Guidelines for Animal Care and conducted as described in previous publications (Ceolin et al., 2011; Fitzjohn et al., 1999; Hanna et al., 2012; Lucas et al., 2012; Mercier et al., 2013; Sherwood et al., 2012). Briefly, electrophysiological recordings were obtained from slices prepared from rats and mice. Extracellular and whole cell experiments were performed as described in the text. Stimulating electrodes were placed in the Schaffer collaterals, the temporo-ammonic pathway, mossy fibre pathway, the external capsule or the lateral perforant path and recordings were made in the CA1 *stratum radiatum*, the CA1 *stratum lacunosum moleculare*, the CA3 *stratum lucidum*, the lateral amygdala or the outer third of the dentate gyrus *stratum moleculare*, respectively.

2.2. Analyses of electrophysiological recordings

Data were captured and analysed using the WinLTP program (Anderson and Collingridge, 2007).

In extracellular experiments, the effects of compounds on AMPA receptor-mediated synaptic transmission were quantified by measuring either initial slopes or peak amplitudes of AMPA receptor-mediated field excitatory post-synaptic potentials (fEPSPs) and normalised to baseline. Similarly, peak excitatory postsynaptic currents (EPSCs) were quantified in whole cell experiments. Changes in excitability due to DHPG application were quantified using coastline analyses, which are built into WinLTP (www.winltp.com).

Data are presented both as single experiments and as mean values of experimental groups (±S.E.M).

2.3. Chemicals

Compounds were purchased from Tocris Cookson, Bristol, U.K.:-(2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV) and *trans*-2-carboxy-5,7-dichloro-4-phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline (L-689,560), or from Abcam, Cambridge, U.K.:- picrotoxin (PTX), (*S*)-3,4-dicarboxyphenylglycine (DCPG), (2*S*,1′*S*,2′*S*)-2-(9-xanthylmethyl)-2-(2′-carboxycyclopropylglycine (LY341495), (*RS*)-3,5-dihydroxyphenylglycine (DHPG), D-2-amino-5-phosphono-pentanoate (D-AP5), (*S*)-(+)-α-amino-4-carboxy-2-methylbenzeneacetic acid (LY367385), α-methyl-4-carboxyphenylglycine (MCPG) and 2-methyl-6-(phenylethynyl)-pyridine hydrochloride (MPEP). (1*R*,4*R*,5*S*,6*R*)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268) and (1*SR*,2*SR*,4*RS*,5*RS*,6*SR*)-2-amino-4-methylbicyclo[3.1.0]-hexane-2,6-dicarboxylic acid (LY395756) were kind gifts of Dr James Monn, Eli Lilly & Co. and (*RS*)-α-methyl-3,4-dicarboxyphenylglycine (MDCPG) was synthesized in house. All other fine chemicals were purchased from Fisher Scientific or Sigma.

3. Results

3.1. Group I mGlu receptor-mediated LTD

The original observation that MCPG (Palmer et al., 1997), and other mGlu receptor antagonists (Fitzjohn et al., 1998, 1999; Palmer et al., 1997), can reverse DHPG-LTD in a reversible manner is illustrated in Fig. 1. Fig. 1A shows a single example time-course plot. MCPG alone had little effect on the synaptic response when applied during baseline recording but, when applied after the induction of DHPG-LTD, it was able to fully reverse the synaptic depression. Significantly, DHPG-LTD was fully restored upon washout of MCPG. The consistency of this observation can be seen in the pooled time-course data plot (Fig. 1B). The effect is extremely unlikely to be due