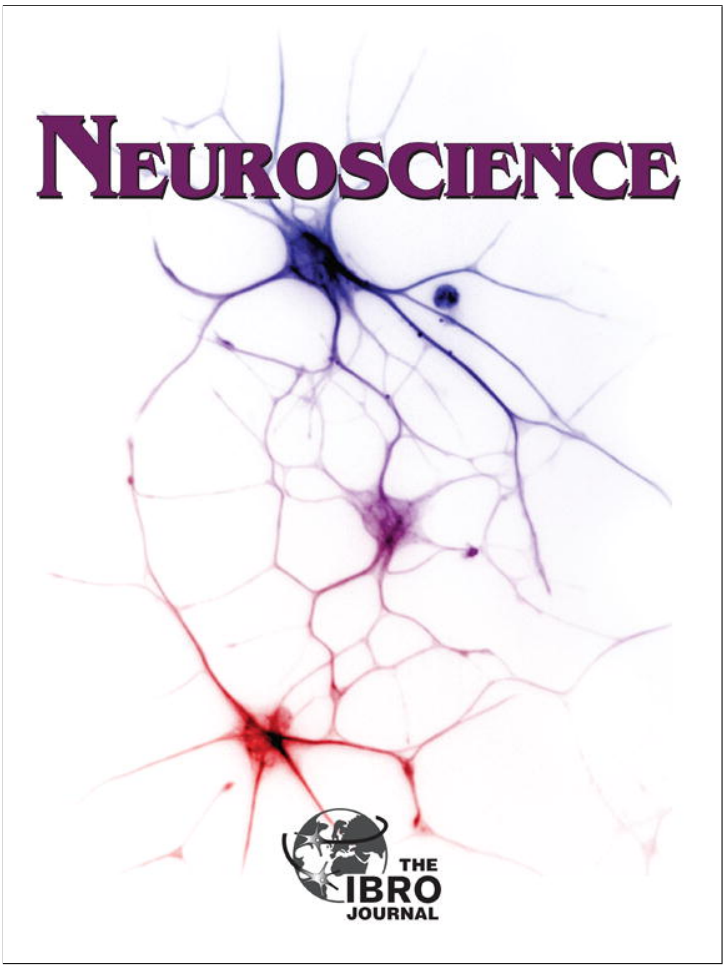

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ACTIVATION OF BOTH GROUP I AND GROUP II METABOTROPIC GLUTAMATERGIC RECEPTORS SUPPRESS RETINOGENICULATE TRANSMISSION

Y.-W. LAM AND S. M. SHERMAN *

University of Chicago, Department of Neurobiology, 947 E. 58th Street, Chicago, IL 60637, United States

Abstract—Relay cells of dorsal lateral geniculate nucleus (LGN) receive a Class 1 glutamatergic input from the retina and a Class 2 input from cortical layer 6. Among the properties of Class 2 synapses is the ability to activate metabotropic glutamate receptors (mGluRs), and mGluR activation is known to affect thalamocortical transmission via regulating retinogeniculate and thalamocortical synapses. Using brain slices, we studied the effects of Group I (dihydroxyphenylglycine) and Group II ((2S,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine) mGluR agonists on retinogeniculate synapses. We showed that both agonists inhibit retinogeniculate excitatory postsynaptic currents (EPSCs) through presynaptic mechanisms, and their effects are additive and independent. We also found high-frequency stimulation of the layer 6 corticothalamic input produced a similar suppression of retinogeniculate EPSCs, suggesting layer 6 projection to LGN as a plausible source of activating these presynaptic mGluRs.

Key words: lateral geniculate nucleus, corticothalamic, thalamus.

INTRODUCTION

Glutamatergic inputs in the thalamus and cortex have been classified into two types: Class 1 and Class 2. Class 1 inputs are thought to provide the main route for information transfer, whereas Class 2 inputs are thought to serve a generally modulatory function (reviewed in Sherman and Guillery (2006) and Sherman (2012)). One of the modulatory properties of these Class 2 inputs is their ability to activate metabotropic glutamate receptors (mGluRs). Several studies of cortical circuitry indicate that Class 2 inputs there can activate mGluRs that act to reduce the amplitude of synaptic transmission from Class 1 inputs (Lee and Sherman, 2009, 2012; DePasquale and Sherman, 2012). Since one of the first defined Class 2 pathways is the layer 6 corticothalamic input to thalamic relay cells (Reichova and Sherman, 2004), and since there is recent evidence that activation of presynaptic mGluRs on retinal terminals can suppress retinogeniculate transmission (Govindaiah et al., 2012; Hauser et al., 2013), we sought to expand on this observation in brain slices from mice by further characterizing the role of mGluRs on retinogeniculate transmission and determining the role layer 6 input might have in this process. A preliminary report of these studies has been made (Lam and Sherman, 2011b).

EXPERIMENTAL PROCEDURES

Preparation of brain slices

Our procedures followed the animal care guidelines of the University of Chicago and closely followed our previously published methodology (Lam and Sherman, 2005, 2012; DePasquale and Sherman, 2012). BALB/c mice (Harlan) of ages 12–21 days postnatal were deeply anaesthetized by inhalation of isoflurane, and their brains were quickly removed and chilled in ice-cold artificial cerebrospinal fluid (ACSF), which contained (in mM): 125 NaCl, 3 KCl, 1.25 NaH_2PO_4, 1 $MgCl_2$, 2 $CaCl_2$, 25 $NaHCO_3$, 25 glucose. Their brains were sliced at 500 μm using a vibrating tissue slicer (Campden Instruments, Loughborough, UK). The slices were cut either coronally (Fig. 1A) or parasagittally at an angle that preserved both corticothalamic and retinogeniculate inputs to the dorsal lateral geniculate nucleus (LGN, Fig. 1B; Turner and Salt, 1998). These slices were then transferred to a holding chamber containing oxygenated ACSF and incubated at 30 °C for at least 1 h before each experiment.

Physiological recording

A few threads of nylon filaments, attached to a platinum wire slice holder, were used to secure the slices in the bath during the experiment. The slice was carefully placed during the experiment so that the nylon threads did not interfere with electrophysiological recording and electrical stimulation.

The LGN was identified in the slice by its location and the presence of the optic tract at its lateral edge.

*Corresponding author. Tel: +1-773-834-2900; fax: +1 773-702-3774.
E-mail addresses: ywlam@uchicago.edu, msherman@bsd.uchicago.edu (Y.-W. Lam).

Abbreviations: ACSF, artificial cerebrospinal fluid; DCG IV, (2S,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine; DHPG, dihydroxy phenylglycine; EGTA, ethylene glycol tetraacetic acid; EPSCs, excitatory postsynaptic currents; GDP-β-S, guanosine 5′-[β-thio]diphosphate; GTP, guanosine triphosphate; HFS, high-frequency stimulation; LGN, lateral geniculate nucleus; mGluRs, metabotropic glutamate receptors.

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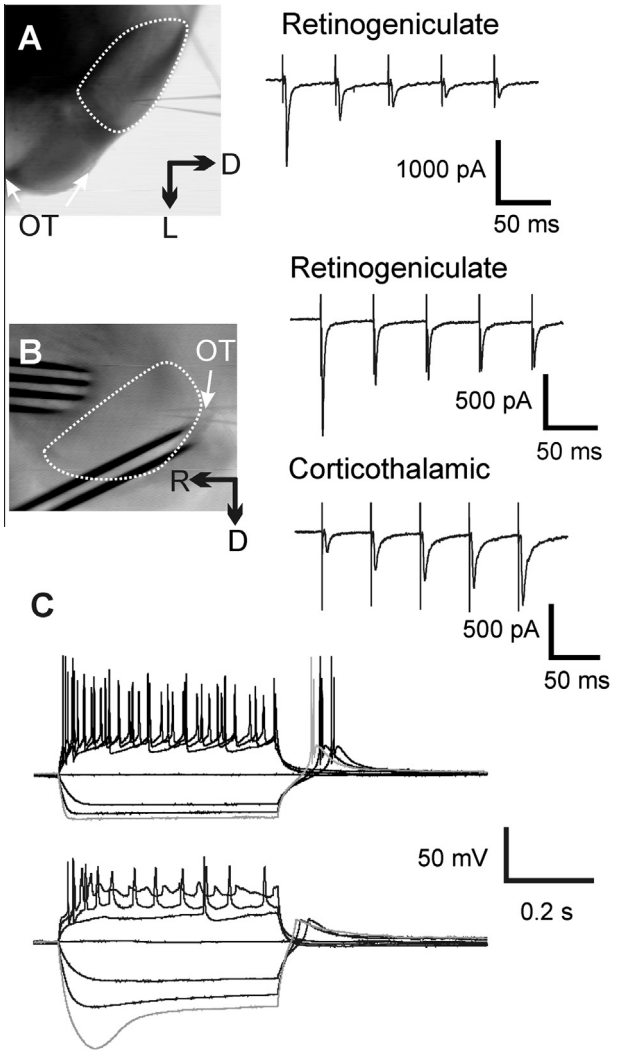

Fig. 1. Experimental setup and methods. (A) Left, photomicrograph taken during a recording from a coronal slice. Right, an example of the EPSC response to optic tract stimulation. (B) Left, photomicrograph taken during a recording from a parasagittal slice. Right, response to optic tract (upper) and corticothalamic axon (lower) stimulation. The dotted line in A and B encircles the LGN and white arrows indicate the location of optic tract (OT). (C) Response of a relay cell (upper) and an interneuron (lower) to current step injection. Interneurons can be distinguished by a distinctive ''sag'' in their response to hyperpolarizing current injection (gray traces).

Retinogeniculate synapses were stimulated using a bipolar electrode straddling the optic tract. For coronal slices, the electrode was placed at a location further ventral to the region shown in Fig. 1A, and so it is not visible in the photomicrograph. The corticothalamic pathway was stimulated by placing a 4×1 electrode array across the incoming corticothalamic axons, near the LGN (Fig. 1B) and the two electrodes with the lowest stimulation response threshold were used for bipolar stimulation. Electric current was generated using a stimulus isolator (A365, World Precision Instrument, Sarasota, FL, USA). Response threshold to optic tract thresholds were determined before each experiment, and the stimulation intensity used was 150–250% above threshold, which turned out to be between 40 and 200 μA.

Whole cell recordings were performed at room temperature (22 °C) using a visualized slice setup (Cox and Sherman, 2000; Lam and Sherman, 2005). Recording pipettes were pulled from borosilicate glass capillaries and had a tip resistance of 3–6 MΩ when filled with a pipette solution containing the following (in mM): 127 K-gluconate, 3 KCl, 1 $MgCl_2$, 0.07 $CaCl_2$, 10 HEPES, 2 Na_2-ATP, 0.3 Na-guanosine triphosphate (Na-GTP), 0.1 EGTA. The pH of the pipette solution was adjusted to 7.3 with KOH or gluconic acid, and the osmolality was 280–290 mOsm.

The experiments were performed in voltage-clamp mode at a holding potential of −60 mV, using an Axopatch 200B (Molecular Devices, Sunnyvale, CA, USA). The access resistance of each cell was constantly monitored throughout the recordings, and experiments were discontinued if the access resistance exceeded 30 MΩ. Gabazine (20 μM, SR95531) was included in the ACSF to prevent any disynaptic IPSCs from contaminating the results.

The LGN of mice contains both relay cells and interneurons (Arcelli et al., 1997), and so we identified interneurons by the presence of a distinctive ''sag'' in their response to hyperpolarization current injection (Fig. 1C, Pape and McCormick, 1995; Zhu et al., 1999; Govindaiah and Cox, 2006).We did not study these cells further, and thus all data reported here are from relay cells.

Photostimulation

Methods for photostimulation have been described by us previously (Lam and Sherman, 2005, 2007, 2010, 2011a) and are briefly outlined here. Data acquisition and photostimulation were controlled by the program Tidalwave (Shepherd et al., 2003). Nitroindolinyl (NI)-caged glutamate (Canepari et al., 2001) was added to the recirculating ACSF to a concentration of 0.39 mM during recording. Focal photolysis of the caged glutamate was accomplished by a 2-ms pulsed UV laser (355-nm wavelength, frequency-tripled Nd:YVO4, 100-kHz pulse repetition rate, DPSS Laser, San Jose, CA, USA). The laser beam was directed into the side port of a double-port tube (U-DPTS) on top of an Olympus microscope (BX50WI) using UV-enhanced aluminum mirrors (Thorlabs, Newton, NJ, USA) and a pair of mirror-galvanometers (Cambridge Technology, Cambridge, MA, USA) and then focused onto the soma of the recording cells using a low-magnification objective (4×0.1 Plan, Olympus).

Chemicals

Various agents were bath applied, including: the Group I mGluR agonist, (R,S)-3,5-dihydroxyphenylglycine (DHPG); the Group II mGluR agonist (2S,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG IV); the $GABA_A$ antagonist gabazine (SR 95531 hydrobromide); and the $GABA_B$ antagonist (3-minopropyl)(cyclohexylmethyl) phosphinic acid (CGP 46381). The G-protein antagonist GDP-β-S (Guanosine 5′-[β-thio]diphosphate) was included in the pipette solution for some cells to block postsynaptic

mGluR responses. All the above reagents were purchased from Tocris (Minneapolis, MN, USA); caged glutamate and chemicals used for the ACSF and intracellular solution were purchased from Sigma (St. Louis, MO, USA).

Data analysis

Data from these experiments were analyzed in Clampfit (Molecular Devices) and Excel (Microsoft). Statistical differences were tested using paired *t*-tests using StatView (SAS Institute) or Origin (Microcal).

RESULTS

Data were obtained from 50 geniculate relay cells, of which 37 were used to study retinogeniculate inputs, and 13, corticothalamic. We assumed that all postsynaptic responses evoked from the stimulation of the optic tract were glutamatergic and monosynaptic, because: with GABA pathways blocked, there are no known multisynaptic inputs to geniculate relay cells that would be evoked, and the responses were smooth and monophasic. Furthermore, as expected, responses at these synapses were very reliable and at the stimulation intensity we used (150–250% of threshold), optic tract stimulation was *always* followed by large excitatory postsynaptic current (EPSC) responses. These retinogeniculate EPSCs could be up to 2 nA and showed paired-pulse depression (Fig. 1A, B, right), whereas corticothalamic EPSCs, evoked from stimulating the corticothalamic fibers, were much smaller (< 500 pA) and showed paired-pulse facilitation (Fig. 1B).

Additive effects for Groups I and II mGluR agonists on retinogeniculate EPSCs

Retinogeniculate EPSCs were evoked in LGN relay cells once every 30 s with optic tract stimulation that consisted of five 0.2-ms stimuli at 20 Hz, and these evoked EPSCs were used as a control against which to test effects of the mGluR agonists added to the bath. Fig. 2A shows the recording trace of an experiment in which we tested the effects of the Group I agonist DHPG (125 μM). Examples of evoked EPSCs (single trial, indicated by black and gray bars underneath the trace in Fig. 2A) to optic tract stimulation before (black) and after (gray) DHPG application are shown in expanded time scale in Fig. 2B. Application of DHPG strongly suppressed the first retinogeniculate EPSCs while having little effect on the subsequent responses to the test stimuli.

Results from five such experiments are combined and shown in Fig. 2C. EPSCs were normalized to the size of the first response to the stimulation trains (P1), and the results were averaged across all five experiments. The average normalized amplitudes of all five EPSCs are then plotted against time. The DHPG application reduced the first evoked EPSC, and evoked responses that are significantly different from the control ($p < 0.05$) are indicated in the graph with open symbols. The DHPG, however, had no discernible effect on the other four evoked EPSCs in each train ($p > 0.05$) (Fig. 2C).

Effects of an mGluR II agonist, DCG IV (12 μM), were tested in five experiments and displayed in Fig. 2D–F in a similar manner with the same conventions. Much like the effects of DHPG, DCG IV strongly suppressed the EPSC response to the first stimulus in the test pulses while leaving subsequent responses unaffected. As in Fig. 2C, responses that are statistically significantly different (Student's *t*-test, $p < 0.05$) from control are indicated with open symbols in Fig. 2F.

Fig. 2G shows an example of a recording from an experiment in which we applied both DCG IV and DHPG, again with conventions as in Fig. 2A–C. Similar experiments were repeated 10 times, four with the $GABA_B$ antagonist CGP 46381 (25 μM) included in the ACSF, and six without; we found no additional effect of adding this $GABA_B$ antagonist, and so we pooled the results of all 10 experiments in Fig. 2I. Application of DCG IV suppressed retinogeniculate EPSCs, similar to that shown in Fig. 2D–F. However, data here also show that subsequent additional DHPG application further suppressed retinogeniculate EPSCs even in the presence of DCG IV (Fig. 2H, I), suggesting that the effects of these two mGluR agonists are independent and additive.

Presynaptic action for mGluR agonists

To determine whether DCG IV and DHPG act pre- or postsynaptically, 0.4 mM GDP-β-S was included in the pipette solution in six experiments during which we bath-applied these agonists (Fig. 3A–C). Fig. 3A shows an example of one such experiment, and Fig. 3B shows the EPSC responses to selected test pulses before (black) and after (darker and lighter gray) drug application in an expanded time scale, showing that inclusion of GDP-β-S, which interrupts the secondary messenger pathway of mGluR activation by inhibiting GTP-binding proteins, did not discernibly affect the reduction of EPSC amplitude caused by application of the mGluR agonists. These data are shown in Fig. 3C as the average normalized results for all six cells, following the format used in Fig. 2C, F and I.

Any effects of DCG IV and DHPG on postsynaptic glutamatergic responses were determined as follows. Synaptic responses were eliminated in these experiments with an ACSF containing 0.2 mM Ca^{2+}/ 3.8 mM Mg^{2+} and 1 μM tetrodotoxin while we used photostimulation to determine any effects of mGluR agonists on direct actions of the uncaged glutamate. This experiment was repeated 6 times for DCG IV and five times for DHPG with the same laser power (24 mW, measured at the back-focal-plane), and Fig. 3D shows that neither mGluR agonist affected the size of evoked responses to uncaged glutamate. Fig. 3E shows the averaged normalized responses for these experiments, indicating that application of the mGluR agonists actually slightly *increased* the size of these responses.

Plausible contribution of corticothalamic inputs

The above experiments indicate that activation of presynaptic mGluRs on retinogeniculate terminals

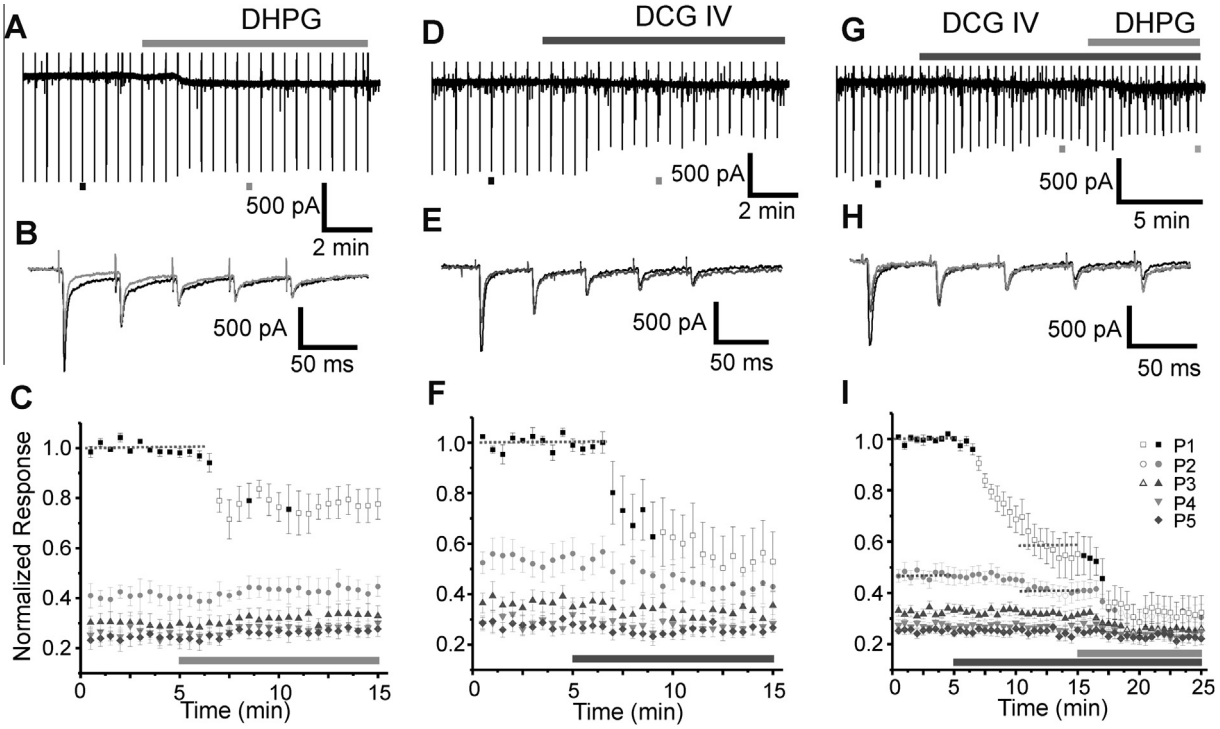

Fig. 2. Effects of mGluR agonists on retinogeniculate EPSCs. (A–C) Effects of Group I agonist, DHPG. (A) Voltage clamp recording during one experiment. The timing of DHPG application is indicated by the gray bar above the trace, and the black and gray bars beneath the trace indicate the EPSCs shown in B. (B) Responses shown in an expanded time scale to the test stimulation of optic tract before (black) and after (gray) DHPG application. (C) Average normalized response of 5 experiments. EPSCs (P1-P5) in the response to a test pulse train are represented with different shades and symbols (see graph legend in I). Application of DHPG is indicated by the gray bar. Responses significantly different from control (horizontal dotted line) are indicated with open symbols. (D–F) Effects of Group II agonist, DCG IV. Conventions as in A–C. (G–I) Independent and additive effects of Group I and Group II mGluR agonists. (G) Recording of an experiment in which both DCG IV and DHPG were applied, with the black bar above the trace showing DCG IV application, and the gray bar, DHPG. (H) In an expanded time scale, selected EPSCs in control condition (black), in the presence of DCG IV (darker gray) and both DCG IV and DHPG (lighter gray). (I) Average normalized EPSCs of 10 experiments, displayed in the same format as C.

reduces the amplitude of the first retinogeniculate EPSC evoked in a train. One possible source of glutamatergic input to relay cells that might produce such modulation is the input from layer 6 of visual cortex. We thus tested for this possibility by determining the effect of evoked corticothalamic input on retinogeniculate EPSCs in 13 cells using parasagittal slices. Unlike the experiments in Figs. 2 and 3, test pulses of the optic tract consisted of only two 20-Hz stimuli delivered at intervals of 5 or 2 s. Effects of the corticothalamic stimulation were tested by delivering high-frequency stimulation (HFS; 125 Hz, 600-ms long) to the corticothalamic axons (arrow in Fig. 4A), and the amplitudes of retinogeniculate EPSCs before and after the HFS were compared. HFS was used in an attempt to maximize the opportunity to evoke mGluR responses (e.g., (Beierlein et al., 2000; Grassi et al., 2002; Rush et al., 2002; Long et al., 2004).

Fig. 4A shows an example experiment, and Fig. 4B (upper) shows in an expanded time scale the averaged responses to optic tract and cortical (lower) stimulation within the 20 s before (black) and after (gray) HFS was applied. In Fig. 4C, the average normalized amplitudes of retinogeniculate responses to both test pulses are plotted against time. These data show that the retinogeniculate EPSC amplitudes in response to both test pulses were significantly decreased after the high-frequency corticothalamic stimulation (Fig. 4D, 1st peak: $t = -5.505$, $p < 0.0001$; 2nd peak: $t = -2.305$, $p = 0.0398$, DF = 12).The reduction of EPSCs from cortical activation is less than that achieved by agonist application (e.g., compare Fig. 2I with Fig. 4D), but this is not unexpected, since the applied agonists presumably can activate all of the mGluRs available, whereas cortical activation is less likely to, because the released glutamate must travel an unspecified distance from the cortical terminals to retinal terminals, and also because in the slice one cannot assume that all relevant cortical axons are activated.

Furthermore, the amplitude of corticothalamic EPSCs was monitored at 5-s intervals in eight such experiments. Their average normalized amplitudes are shown in Fig. 4E. In contrast to retinogeniculate responses, the amplitudes of corticothalamic EPSCs were significantly *increased* after the HFS (Fig. 4F, 1st peak: $t = 5.444$, $p = 0.0009$; 2nd peak: $t = 5.250$, $p = 0.0012$, DF = 7).Given the evidence in Fig. 3D, E that effects on mGluR activation on glutamatergic EPSCs are presynaptic, it follows that these effects on corticothalamic EPSCs must also be presynaptic.

DISCUSSION

We studied the effects Group I (DHPG) and Group II (DCG IV) mGluR agonists on retinogeniculate synapses. We

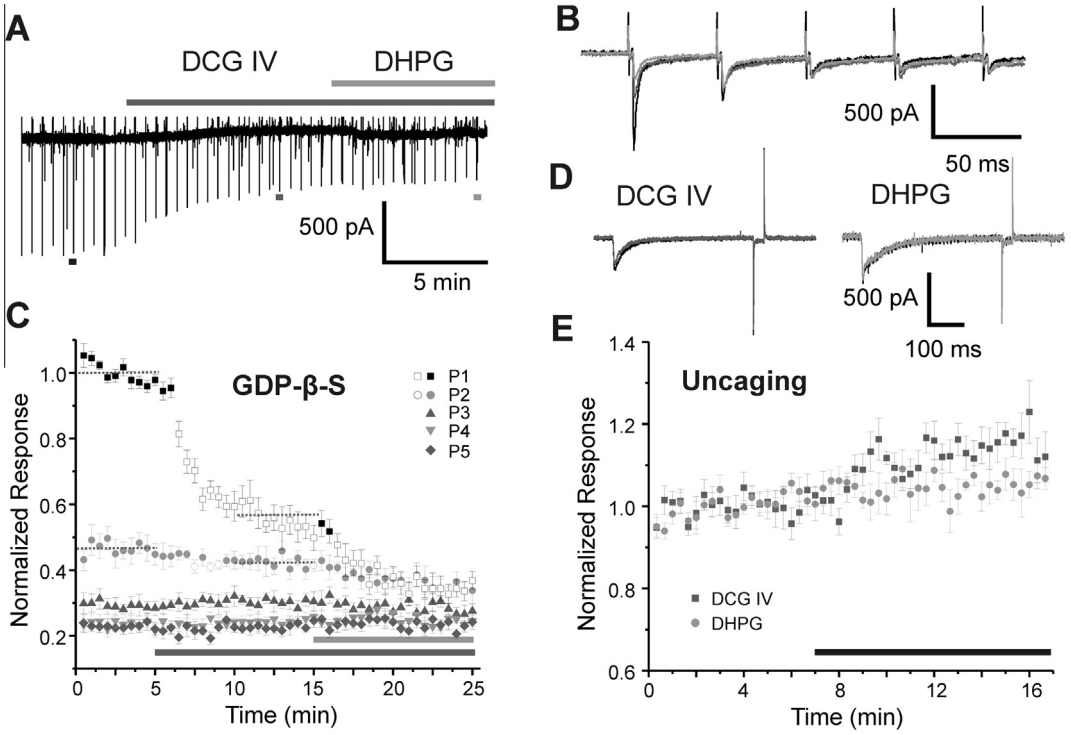

Fig. 3. Presynaptic action of mGluR agonists. (A–C) GDP-β-S did not block the effects of mGluR agonists. (A) Recording in which 0.4 mM GDP-β-S was included in the pipette solution. Application of agonists is shown by the bars (darker gray, DCG IV; lighter gray, DHPG) above the trace. (B) Selected EPSCs from A (indicated with bars in A) in control condition (black), in the presence of DCG IV (darker gray) and in the presence of both DCG IV and DHPG (lighter gray). (C) Average normalized responses of six experiments, displayed using the format shown in Fig. 2C. (D, E) Effects of mGluR agonists on response to photostimulation in a 0.2 mM Ca^{2+}/3.8mM Mg^{2+} ACSF solution containing 1 μM tetradotoxin. (D) Example responses to photostimulation in control condition (black), after DCG IV (darker gray, left) and DHPG (lighter gray, right) application. (E) Effects of DCG IV (N = 6, darker gray squares) and DHPG application (N = 5, lighter gray circles) on average normalized response to photostimulation with agonist application indicated by the black bar.

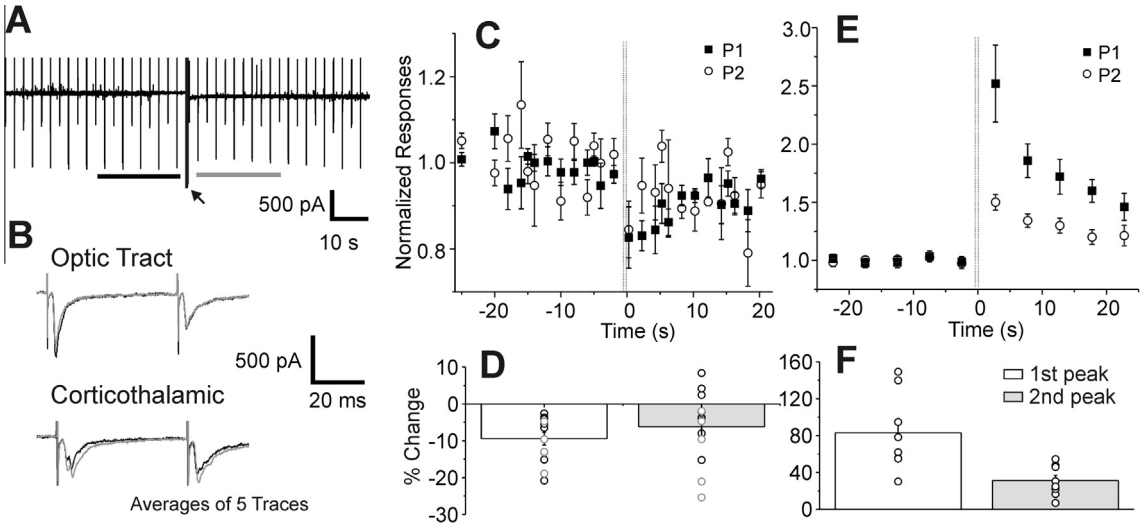

Fig. 4. High-frequency stimulation (HFS) of corticothalamic input suppresses retinogeniculate EPSCs. (A) Recording from one experiment. The black and gray bars beneath the trace indicate periods within which the averages in B are calculated. (B) Reponses to optic tract and corticothalamic stimulation before (black) and after (gray) HFS. Each is the average of five traces within the periods indicated in A. (C) Average normalized responses to optic tract stimulation of 13 experiments. The vertical lines indicate the timing of HFS. (D) Percentage differences between the average responses to optic tract stimulation 20 s before and after HFS (1st peak: $t = -5.505$, $p < 0.0001$; 2nd peak: $t = -2.305$, $p = 0.0398$, DF = 12).Test pulses were delivered every 5 s (black circles) or 2 s (gray circles). (E) Average normalized response to stimulation of corticothalamic axons (N = 8). (F) Percentage differences between the average response to stimulation of corticothalamic input 20 s before and after HFS (1st peak: $t = 5.444$, $p = 0.0009$; 2nd peak: $t = 5.250$, $p = 0.0012$, DF = 7). Test pulses were delivered every 5 s.

showed that these agonists suppress retinogeniculate EPSCs, and their effects are additive and independent (Fig. 2). Moreover, these agonists appear to act through presynaptic mechanisms as determined by the observations that EPSCs in response to the first pulse in a train of test stimulation being suppressed, while leaving the subsequent ones mostly unaffected (Fig. 2C) and that blockage of postsynaptic mGluR effects via inclusion of GTP-β-S in the pipette solution did not ameliorate mGluR suppression of retinogeniculate transmission (Fig. 3B, C). The possibility of a postsynaptic mechanism, such as conductance change, cannot be entirely ruled out, but such a change is not supported by our results since application of mGluR agonists had no effect on postsynaptic responses evoked directly by photostimulation (Fig.3D, E), and our main observations depended on evoked synaptic currents measured in voltage clamp recordings, which would be affected very little if at all by changes in baseline membrane conductance.

Many of our results thus are similar to those recently reported (Govindaiah et al., 2012; Hauser et al., 2013), except that we also show that both Group I and Group II mGluRs affect retinogeniculate transmission. The effects of Groups I and II mGluR agonists are additive, suggesting separate and independent regulatory pathways for both receptor subtypes.

Govindaiah et al. (2012) also showed that HFS of the optic tract mimicked mGluR suppression of retinogeniculate, which they interpreted as the activation of mGluRs by glutamate spillover from retinogeniculate synapses. Our results show that the layer 6 corticothalamic projection to LGN is another plausible source of activating these mGluRs on retinal terminals (Fig. 4).This is somewhat surprising, since it is commonly believed that retinogeniculate synapses are located near the soma, whereas the corticothalamic synapses are distributed further away in the dendritic tree of the relay cells (Wilson et al., 1984), suggesting that glutamate released from cortical terminals must travel quite a distance to affect retinal terminals. However, the evidence for a large separation of these different inputs onto dendrites of relay cells comes from other species, mostly cat (Wilson et al., 1984), and this feature may be different in mice, a point that needs to be determined. Nonetheless, this suggests a novel mechanism that layer 6 projection modulates information flow in the visual system.

We also found mGluR activation may slightly enhance corticothalamic synapses (Fig. 4E, F). It is uncertain how significant this enhancement is since layer 6 neurons also indirectly inhibit thalamic relay cells through the thalamic reticular nucleus – the actual effect would not be known until the combined effect of mGluR activation on neurons of thalamic reticular nucleus and thalamus is determined. However, this observation suggests that firing of corticogeniculate axons sufficient to activate mGluRs (Viaene et al., 2013) could result in greater release of glutamate from these terminals, which in turn could lead to a further reduction of retinogeniculate EPSCs. Such a process is consistent with recent evidence that activation of corticogeniculate axons reduces the gain of receptive fields measured in the visual cortex (Olsen et al., 2012).

Our observations extend the view of the layer 6 cells that make up the corticothalamic pathway, because these cells affect thalamocortical transmission via at least four different mechanisms both in the thalamus and in cortical layer 4: (1) the corticothalamic input activates both a direct EPSP and disynaptic IPSP (via the thalamic reticular nucleus) on relay cells, and in most cases, the IPSP is much stronger and regulated by neuromodulators (Lam and Sherman, 2010); (2) as the present study indicates, it can activate presynaptic mGluRs on retinal terminals to reduce retinogeniculate transmission; (3) it activates postsynaptic mGluRs on thalamorecipient layer 4 cells in cortex, and in many cases, these are Group II mGluRs, which hyperpolarizes the target cells (Lee and Sherman, 2009); and (4) it activates presynaptic mGluRs on thalamocortical terminals, which serves to reduce thalamocortical transmission (Lee and Sherman, 2012). Thus these layer 6 corticothalamic cells have widespread effects on thalamocortical transmission, acting both at its source as well at its target, and overall these effects operate to suppress thalamocortical transmission.

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