Activation of Group I mGluRs Is Necessary for Induction of Long-Term Depression at Striatal Synapses

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Sung, Ki-Wug, Sukwoo Choi, and David M. Lovinger. Activation of group I mGluRs is necessary for induction of long-term depression at striatal synapses. *J Neurophysiol* 86: 2405–2412, 2001. Activation of metabotropic glutamate receptors (mGluRs), which are coupled to G proteins, has important roles in certain forms of synaptic plasticity including corticostriatal long-term depression (LTD). In the present study, extracellular field potential and whole cell voltage-clamp recording techniques were used to investigate the effect of mGluR antagonists with different subtype specificity on high-frequency stimulation (HFS)-induced LTD of synaptic transmission in the striatum of brain slices obtained from 15-to 25-day-old rats. Induction of LTD was prevented during exposure to the nonselective mGluR antagonist (RS)-α-methyl-4-carboxyphenylglycine (500 μM). The group I mGluR-selective antagonists (*S*)-4-carboxy-phenylglycine (50 μM) and (RS)-1-aminoindan-1,5-dicarboxylic acid (100 μM) prevented induction of LTD when applied before and during HFS. The mGluR1-selective antagonist 7-(Hydroxyimino) cyclopropa[b]chromen-1a-carboxylate ethyl ester (80 μM) also blocked LTD induction. Unexpectedly, the mGluR5-selective antagonist 2-methyl-6-(phenylethyl)-pyridine (10 μM) also prevented LTD induction. The group II mGluR antagonist LY307452 (10 μM) did not block LTD induction at corticostriatal synapses, but LY307452 was able to block transient synaptic depression induced by the group II agonist LY314593. None of the antagonists had any effect on basal synaptic transmission at the concentrations used, and mGluR antagonists did not reverse LTD when applied beginning 20 min after HFS. These results suggest that both group I mGluR subtypes contribute to the induction of LTD at corticostriatal synapses.

INTRODUCTION

The neostriatum (caudate and putamen) is involved in the control of movement (Alexander et al. 1986; Chevalier and Deniau 1990; Graybiel et al. 1994; Groves 1983), and it appears that certain forms of learning and memory involve changes in neostriatal function (Jog et al. 1999; Whishaw and Kolb 1984). The major excitatory input to the neostriatum arises from neurons in the neocortex that use glutamate as a neurotransmitter (Graybiel 1990; Parent 1990). Synaptic transmission at corticostriatal synapses is mediated by AMPA receptors with very little involvement of *N*-methyl-D-aspartate (NMDA) receptors (Cherubini et al. 1988; Herrling 1985; Lovinger et al. 1993a). Repetitive activation of corticostriatal glutamatergic synapses produces activity-dependent changes in synaptic efficacy. One such form of synaptic plasticity is long-term depression (LTD) of excitatory synaptic transmission in the striatum. This change in synaptic efficacy has been observed both in vivo (Garcia-Munoz et al. 1996) and in vitro (Calabresi et al. 1992; Lovinger et al. 1993b; Walsh 1993). Synaptic plasticity in the striatum may contribute to long-term behavioral changes, such as those induced by motor learning during neural development, antipsychotic agents, or neurodegenerative diseases including Parkinson's disease and Huntington's disease. Corticostriatal LTD has been shown to be dependent on activation of certain forms of calcium channels (Calabresi et al. 1992; Choi and Lovinger 1997a) as well as dopamine receptors and metabotropic glutamate receptors (Calabresi et al. 1992). However, it is not clear what metabotropic glutamate receptor (mGluR) subtypes participate in LTD induction.

In the striatum, group I mGluRs are particularly highly expressed in the spines and dendrites of medium spiny neurons (Testa et al. 1998). Glutamate can stimulate phosphoinositide (PI) hydrolysis leading to increases in intracellular calcium concentration in striatal neurons through group I mGluR actions (Casabona et al. 1997). This signaling mechanism is one of the essential conditions for corticostriatal LTD induction (Calabresi et al. 1994; Choi and Lovinger 1997a,b). Calabresi et al. (1992) reported that activation of mGluRs is required for the induction of corticostriatal LTD because this induction can be blocked by the mGluR antagonist, 2-amino-3-phosphonopropionic acid (AP3). AP3 is a rather nonselective, low-affinity antagonist for mGluRs, although it has higher affinity for group I mGluRs than for the other receptor subtypes (Saugstad et al. 1995). Thus there is some evidence that group I mGluRs may be involved in LTD induction, but this hypothesis has not been tested with the newer, more potent and selective group I mGluR antagonists. Furthermore, the effect of the mGluR1 and 5 subtype selective antagonists 7-(Hydroxyimino) cyclopropa[b]chromen-1a-carboxylate ethyl ester (CPPCOOEt) and 2-methyl-6-(phenylethyl)-pyridine (MPEP) on striatal LTD has not been examined. In the present study, we tested whether glutamate acting via group I mGluRs might be important for

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the induction of corticostriatal LTD using selective group I and II mGluRs antagonists.

METHODS

Brain slices were prepared from 15- to 25-day-old Sprague-Dawley rats using previously described techniques (Tang and Lovinger 2000). Rats were killed by decapitation, and the brains were removed and placed in ice-cold, modified artificial cerebrospinal fluid (ACSF) containing (in mM) 194 sucrose, 30 NaCl, 4.5 KCl, 1 $MgCl_2$, 26 $NaHCO_3$, 1.2 NaH_2PO_4, and 10 D-glucose adjusted to pH 7.4 by bubbling with 95% O_2-5% CO_2. Coronal slices (400 μm thick) were cut using a manual vibroslice (Campden Instruments, Cambridge, UK). Brain slices were transferred to ACSF containing (in mM) 124 NaCl, 4.5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 26 $NaHCO_3$, 1.2 NaH_2PO_4, and 10 D-glucose adjusted to pH 7.4 by bubbling with 95% O_2-5% CO_2 at room temperature. Slices were used for electrophysiological experiments beginning 1 h after the end of slice preparation. A hemislice containing the cortex and striatum just anterior to the globus pallidus was completely submerged in a recording chamber and continuously superfused (at a flow rate of 2–3 ml/min) with ACSF that was constantly bubbled with 95% O_2-5% CO_2. The temperature of the bath solution was kept at 30–32°C.

Extracellular field potential recordings were performed in the lateral half of the dorsal striatum to record population spikes (PSs) evoked by stimulation of excitatory afferents. Stimuli were delivered by an S88 stimulator and a PSIU6 optical isolation unit (Grass Instruments, Quincy, MA) through a bipolar, Teflon-coated tungsten electrode placed in the white matter dorsal to the striatum. PSs were recorded with a glass micropipette (<1 MΩ tip resistance) filled with 0.9% saline, placed at a site 1–2 mm ventral to the stimulating electrode. The position of the recording electrode was optimized by recording responses to low frequency stimulation (0.02–0.2 ms, 0.5–1.5 mA at 0.1 Hz), and the electrode was set at the depth where the maximal PS amplitude was observed. Stimulus intensity was then adjusted to evoke a PS with amplitude approximately half of the maximum. Once a PS of half-maximal amplitude triggered by 0.05-Hz stimuli had been stably maintained for 10–15 min, receptor agonists or antagonists were delivered, and/or high-frequency stimulation (HFS) was applied. HFS consisted of four 100-Hz trains of 1 s duration delivered at a frequency of one train every 10 s. During HFS, the stimulus intensity was increased to the level producing a maximal PS response. Field potentials were amplified 1,000 times, using a differential AC amplifier (A-M systems, Olympia, WA), and low-pass filtered at 5 kHz. Amplified signals were digitized using a TL-1-125 interface (Axon Instruments, Foster City, CA) or CED 1401 plus interface (Cambridge Electronic Design, Cambridge, UK) and stored on a computer using pClamp6.0 (Axon Instruments) or WCP software (Strathclyde Electrophysiology Software, version 3.1.4, Glasgow, UK).

Whole cell voltage-clamp recordings were performed to record the stimulus-induced excitatory postsynaptic currents (EPSCs) at glutamatergic striatal synapses. Slices were placed in the recording chamber and superfused with ACSF as described in the preceding text. Tight-seal whole cell recordings were obtained using pipettes made from borosilicate glass capillaries pulled on a Flaming-Brown micropipette puller (Sutter Instruments, Novato, CA). Pipette resistance ranged from 2.5 to 3 MΩ, when filled with internal solution containing (in mM) 120 $CsMeSO_3$, 5 NaCl, 10 tetraethylammonium chloride, 10 HEPES, 5 lidocaine N-ethyl bromide (QX-314) (Br^{2+} salt), 1.1 EGTA, 4 ATP (Mg^{2+} salt), and 0.3 GTP (Na^{+} salt), pH adjusted to 7.2 with CsOH, osmolarity adjusted to 290–300 mOsm with sucrose. Recordings from medium-sized neurons within two or three layers below the surface of slices were made under differential interference contrast-enhanced visual guidance.

Neurons were voltage-clamped at −60 or −70 mV during the whole cell recording period before and after application of HFS. Stimuli were delivered to the white matter dorsal to the striatum as described for field potential recordings. The series resistance, which was not compensated and was typically between 5 and 10 MΩ, was monitored during the recording. Once a stable EPSC of 100–300 pA amplitude triggered by 0.05-Hz stimuli had been recorded for 10–15 min, drugs were delivered and/or LTD induction was attempted by pairing HFS and depolarization. HFS consisted of four 100-Hz trains of 1 s duration delivered at a frequency of one train every 10 s, with simultaneous 1-s depolarization of postsynaptic neurons to −10 or 0 mV. Whole cell currents recorded with an Axopatch 1D amplifier (Axon Instruments) were filtered at 5 kHz, digitized at ≤20 kHz using a DigiData 1200 interface (Axon Instruments) and stored on computer using pClamp 6.0 software (Axon Instruments). Changes in PS and EPSC amplitude after HFS or drug treatment are expressed as the percentage of the baseline response. The magnitude of LTD was defined as the ratio of the average PS amplitude 20–30 min (30 episodes) following HFS to the average response amplitude during a 10-min baseline pre-HFS recording period (30 episodes) in all experiments. The representative PS and EPSC waveforms shown in the text are the average of 15–30 consecutive individual responses during a given recording. LTD was defined as a decrease in the amplitude of PS or EPSC after HFS of >2 SDs below the baseline PS. All averaged values are presented as means ± SE. The statistical significance of changes in synaptic responses relative to baseline response amplitude was determined using a two-tailed paired *t*-test. The statistical criterion for significance was $P < 0.05$.

(RS)-1-Aminoindan-1,5-dicarboxylic acid (AIDA), (*S*)-4-carboxyphenylglycine (4-CPG), CPCCOEt, (RS)-3,5-dihydroxyphenylglycine (DHPG), (RS)-α-methyl-4-carboxyphenylglycine (MCPG), and MPEP were purchased from Tocris Cookson (Ballwin, MO). LY307452 and LY314593 were obtained as a gift from Dr. D. D. Shoepp (Lilly Research Laboratories). All other chemicals used in this experiment were ACS grade and purchased from Sigma (St. Louis, MO). Drugs tested in slice experiments were diluted with ACSF immediately before use from stock solutions prepared according to the manufacturers' instructions. Drug solutions were delivered into the recording chamber by gravity flow.

RESULTS

As a control experiment to determine the frequency of LTD induction at excitatory synapses in dorsolateral striatum, we examined the induction rate of LTD in 36 hemislices from 18 coronal slices at the same range of anterior-posterior positions. We found that 52% of the hemislices tested showed long-lasting decreases in PS amplitude (as defined in METHODS), 31% exhibited no change (PSs changed <20%), and 17% showed long-term potentiation (LTP, increase in PS amplitude of >20% of baseline 20 min after HFS). When one hemislice showed LTD in response to HFS, application of the same HFS protocol in the other hemislice from the same coronal brain slice resulted in LTD in 78% of the paired slices, no change in 11% of the slices, and LTP in 11% of the slice. Because of the high concordance of paired hemislices with respect to LTD expression, we tested mGluR antagonist effects on LTD induction using hemislices in which the paired control hemislice had been shown to express LTD when HFS was given in the absence of antagonist.

The nonselective mGluR antagonist MCPG (500 μM) prevented LTD when applied before and during HFS. Field potential recordings revealed that HFS failed to induce LTD (108.8 ± 6.8% of baseline PS amplitude) in the presence of MCPG. After HFS in MCPG, we removed the antagonist from the bath and delivered a second set of HFS stimuli. In four of

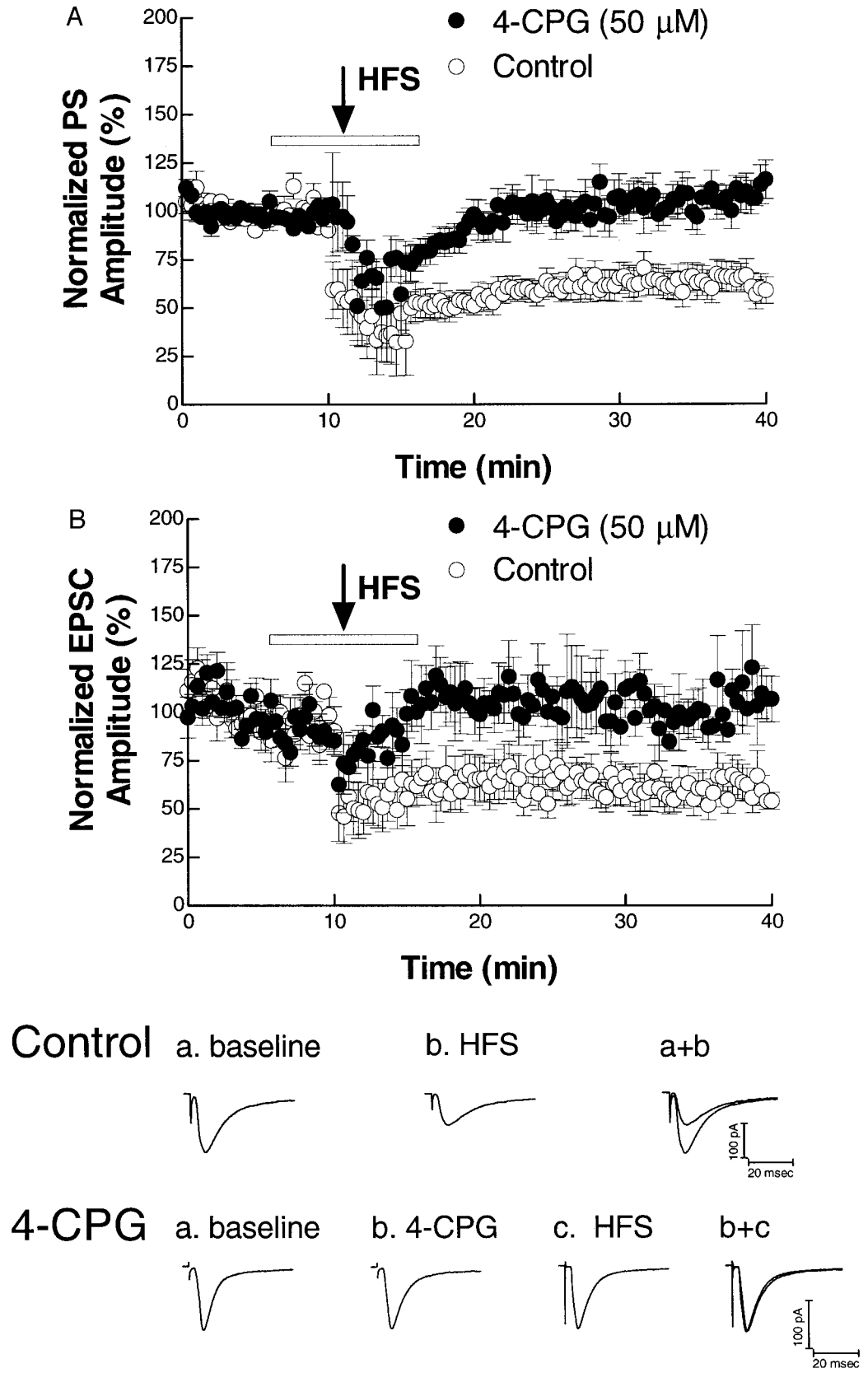

FIG. 1. Inhibition of corticostriatal long-term depression (LTD) induction by the selective group I metabotropic glutamate receptor (mGluR) antagonist, (*S*)-4-carboxyphenylglycine (4-CPG). Superimposed are the average normalized population spikes (PSs, *A*) and excitatory postsynaptic currents (EPSCs, *B*) in the presence (●) and absence (○) of 4-CPG (50 M). Averaged EPSC traces from 15 to 30 episodes are shown on the *bottom*. □, the duration of 4-CPG application, and ↓, application of high-frequency stimulation (HFS).

the six slices examined, we observed a decrease in PS amplitude of >20% (59.5 ± 0.7% of baseline PS) after removal of MCPG. In slices that were not exposed to MCPG, the PS amplitude decreased to 58.4 ± 9.2% of baseline PS following HFS. This finding supported earlier studies indicating the necessity for activation of an mGluR in the induction of striatal LTD but did not clarify which mGluR was involved.

To determine the mGluR subtype(s) involved in LTD induction, we examined the effect of group I and II selective mGluR antagonists on striatal LTD induction in 35 paired hemislices from 32 animals. We applied each antagonist for a total of 10 min, 5 min prior to HFS, and an additional 5 min during and after HFS. The effects of the group I mGluR antagonists 4-CPG, AIDA, MPEP, and CPCCOEt were examined first. Pretreatment with the group I mGluR antagonist 4-CPG (50 μM) prevented the induction LTD by HFS (Fig. 1*A*, −3.2 ± 11.1% decrease in PS amplitude relative to baseline, $P = 0.66$ paired *t*-test, $n = 8$). Application of 4-CPG (50 μM) did not alter the PS amplitude during the recording period prior to HFS (Fig. 1, *A* and *B*). HFS resulted in a long-lasting decrease in PS amplitude in paired control hemislices (37.8 ± 6.7% decrease in PS amplitude, $P < 0.001$, paired *t*-test, $n = 8$). The effect of 4-CPG on LTD induction was also examined using whole cell recording. In the absence of antagonist, HFS induced a long-lasting decrease of 39.7 ± 8.3% in EPSC amplitude ($P < 0.05$, paired *t*-test, $n = 5$), but HFS did not alter EPSC amplitude in the presence of 50 μM 4-CPG (amplitude decreased by 3.7 ± 13.6%, $P = 0.9429$, paired *t*-test, $n = 5$; Fig. 1*B*).

We also examined the effect of other group I mGluR selective antagonists on induction of corticostriatal LTD in field potential recording experiments. AIDA prevented depression of PSs by HFS. LTD could be induced in control slices (41.1 ± 6.8% decrease in PS amplitude, $P < 0.05$, paired *t*-test, $n = 5$) but not in the presence of AIDA (100 μM, 14.15 ± 12% decrease in PS amplitude, $P = 0.3083$, paired *t*-test, $n = 5$, Fig. 2). The recently developed antagonists CPCCOEt and MPEP have been shown to selectively block activation of mGluRs1 and 5, respectively. We thus examined the effect of these compounds on induction of striatal LTD to determine which of these group I mGluRs was involved in this form of synaptic plasticity. Pretreatment with CPCCOEt (80 μM) blocked the induction of corticostriatal LTD by HFS (4.5 ± 6.4% decrease in PS amplitude, $P = 0.3663$, paired *t*-test, $n = 5$) when compared with control slices (36.6 ± 4.1% decrease in PS amplitude, $P < 0.01$, paired *t*-test, $n = 5$, Fig. 3*A*). Pretreatment with MPEP (10 μM) also prevented induction of LTD by HFS. Indeed, when HFS was delivered in the presence of MPEP, we observed an increase of >20% in PS amplitude in

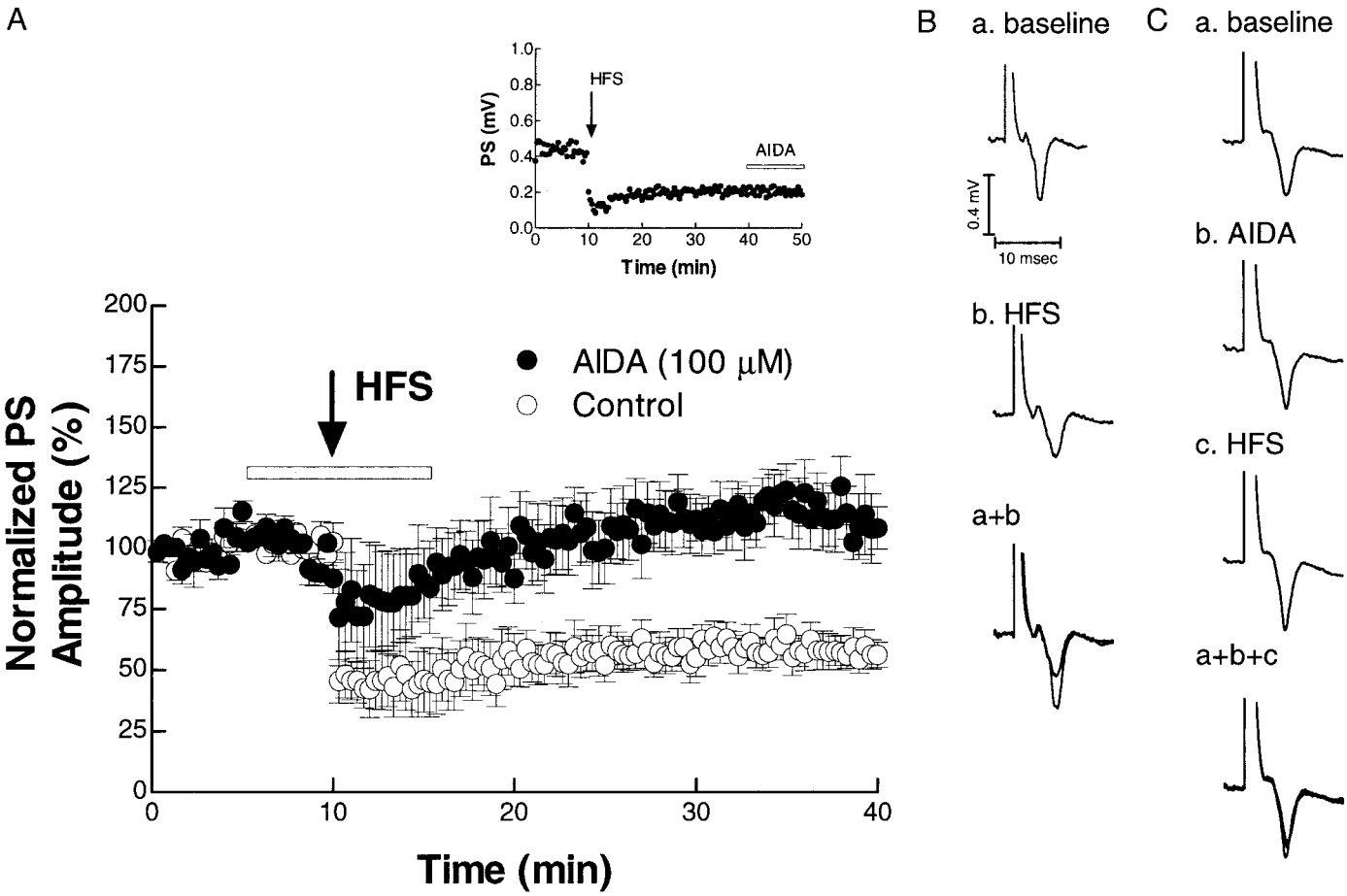

FIG. 2. Inhibition of corticostriatal LTD induction by the selective group I mGluR antagonist, (RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA). *A*: superimposed are the average normalized PSs in the presence (●) and absence (○) of AIDA (100 μM). PS amplitude plots from a representative experiment showing that AIDA treatment 30 min after HFS did not alter evoked PS amplitude are shown in the *inset*. Averaged PSs for 15–30 episodes are shown in *B* and *C*. □, the duration of application of AIDA, and ↓, the application of HFS.

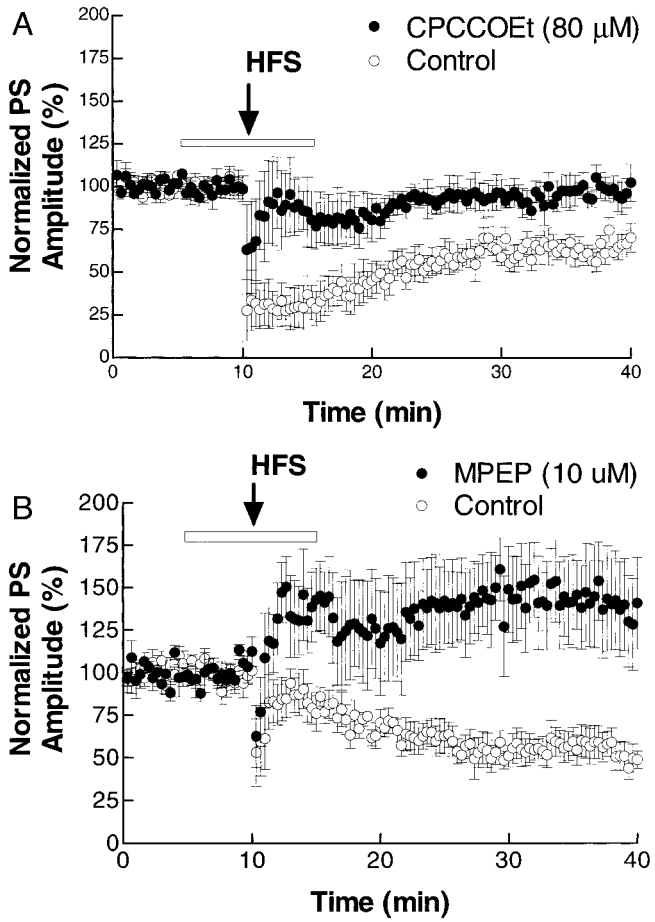

FIG. 3. Inhibition of corticostriatal LTD induction by the selective group I mGluR antagonists, 7-(Hydroxyimino) cyclopropa[b]chromen-1a-carboxylate ethyl ester (CPCCOEt, *A*) and 2-methyl-6-(phenylethyl)-pyridine (MPEP, *B*). Superimposed are the average normalized PSs in the presence (●) and absence (○) of CPCCOEt (80 μM) or MPEP (100 μM). □, the duration of application of CPCCOEt or MPEP, and ↓, application of HFS.

three of six tested slices. The remainder of the MPEP-treated slices showed no LTD induction. The average change in amplitude after PS was not statistically significant (42.9 ± 24.9% increase in PS amplitude, $P = 0.1454$, paired *t*-test, $n = 6$). In control slices, LTD could be induced by HFS (44.4 ± 7.6% decrease in PS amplitude, $P < 0.005$, paired *t*-test, $n = 6$, Fig. 3*B*).

The findings reported in the preceding text suggested involvement of group I mGluRs in induction of striatal LTD. However, it is also possible that group II receptors participate in synaptic plasticity, and it is known that this class of mGluRs can influence transmission at glutamatergic striatal synapses (Lovinger and McCool 1995). We thus examined the effect of a group II mGluR selective antagonist LY307452 on LTD induction. This antagonist did not block LTD induction. In slices pretreated with LY307452 (10 μM), LTD could be induced by HFS (34.6 ± 12.9% decrease in PS amplitude, $P < 0.05$, paired *t*-test, $n = 5$, Fig. 4*A*). To ensure that the LY307452 was active in our striatal slice preparation, we examined the ability of this compound to antagonize synaptic depression produced by acute exposure to a group II mGluR agonist. Previously we have shown that mGluR2,3-selective agonists inhibit the synaptically driven PS evoked by afferent stimulation during field potential recording in striatal slices (Lovinger and McCool 1995). In agreement with this result, we observed that the group II mGluR selective agonist LY314593 (10 μM) inhibited the PS evoked by afferent stimulation in striatal slices ($n = 3$). As expected, LY307452 (7 μM) completely reversed the synaptic depressant actions of LY314593 (Fig. 4*B*). The group I mGluR agonist DHPG (100 μM) did not alter PSs evoked by low-frequency stimuli as we have previously observed (data not shown).

Synaptic responses produced by low-frequency afferent stimulation were not altered by either group I or group II mGluR antagonists (as can be seen in Figs. 1–3 during the pre-HFS drug application period). We measured PS amplitude in response to low-frequency stimulation in the presence and absence of each of the mGluR antagonists before HFS, and the amplitude was not significantly altered by any of the antagonists (paired *t*-test, $P > 0.1$, data not shown). Application of both groups of antagonists 30 min after HFS did not alter the PS amplitude (data not shown, but representative PS amplitude plot is shown in the Fig. 2*A* and Fig. 4*A insets*). We also examined the effect of applying MCPG beginning 20 min after cessation of HFS. Application of the antagonist at this time did not alter PS amplitude (data not shown). This observation suggests that blocking mGluR function cannot reverse LTD once it has been established for 10 s of minutes. This finding also indicates that maintained mGluR activation is not likely to be the mechanism underlying maintained expression of LTD at these post-HFS time points.

DISCUSSION

We have observed that antagonism of group I mGluRs prevents the induction of striatal long-term synaptic depression. In contrast, antagonists of group II mGluRs did not block LTD induction, but these antagonists were able to prevent acute synaptic depression produced by application of a group II mGluR agonist. Thus the lack of effect of this group II antagonist is not due to the inability of the compound to block striatal mGluRs in the slice preparation. Our results are most consistent with the idea that group I mGluRs play a crucial role in the induction of striatal LTD.

Our findings confirm and extend the previous work of Calabresi et al. (1992), who observed that the mGluR antagonist, 2-amino-3-phosphonopropionic acid significantly reduced corticostriatal LTD, suggesting that mGluR activation is required for long-term changes in synaptic transmission in the striatum. There is ample evidence for the expression of both pre- and postsynaptic mGluRs in the striatum (Calabresi et al. 1993; Lovinger and McCool 1995; Testa et al. 1998). Testa et al. (1998) reported that group I mGluRs and group II mGluRs have distinct cellular localizations in different components of the basal ganglia. These investigators suggested that group I mGluRs appear to be postsynaptic receptors present on the dendrites of striatal medium spiny neurons, and also suggest the presence of group II mGluRs on the terminals of corticostriatal afferents, where they may regulate glutamate release. Our observations, both past and present, agree with this anatomical distribution of mGluRs. Several group II mGluR agonists produce a transient depression of glutamatergic transmission that appears to involve a decrease in presynaptic glutamate release (Lovinger and McCool 1995). In contrast, group I agonists such as DHPG, do not produce presynaptic depression

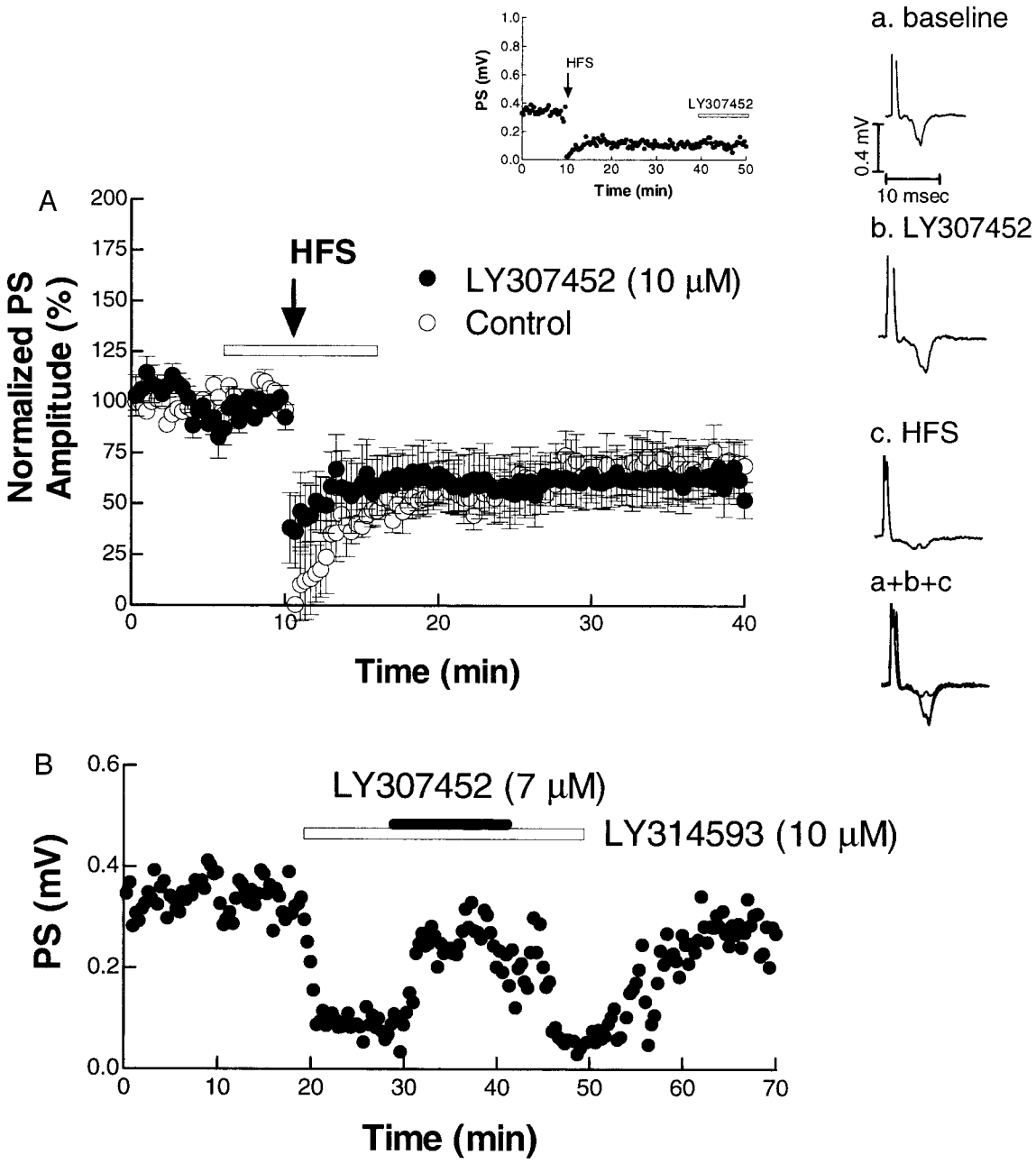

FIG. 4. Effects of the selective group II mGluR antagonist, LY307452 on corticostriatal LTD induction. *A*: effects of LY307452 on LTD induction. *Left*: superimposed are the average normalized PSs in the presence (●) and absence (○) of LY307452 (10 μM). *Right*: representative field potentials recorded before treatment (*a*), during application of LY307452 (*b*), and after HFS in the presence of antagonist (*c*). Each waveform is the average of 15–30 individual field potentials. A PS amplitude plot from a representative experiment indicating that LY307452 treatment 30 min after HFS did not evoke changes in PS amplitude is shown in the *inset*. *B*: inhibition of corticostriatal synaptic transmission by the selective group II mGluR agonist LY314593 (10 μM) and antagonism of the effect of LY314593 by LY307452 (7 μM), a selective group II mGluR antagonist. PS amplitude plotted as a function of time during the course of an experiment examining the effect of these compounds on synaptic transmission in striatum. □ and ■, time from switching on to switching off agonist and antagonist application. Note that depression of synaptic transmission by agonist is completely reversed in the presence of antagonist and reversible when washing with artificial cerebrospinal fluid.

when applied to striatal slices. However, the antagonist data in the present study indicates that group I mGluRs do have important roles in long-lasting depression of striatal synaptic transmission and that group II mGluRs do not participate in this form of synaptic plasticity. These anatomical and functional data support the idea that mGluRs have an important role in synaptic transmission and synaptic plasiticity through distinct receptor subtypes in the striatum.

A publication that appeared after submission of the present paper also presented evidence for a crucial role of group I mGluRs in striatal LTD induction (Gubellini et al. 2001). For the most part, our findings agree quite well with this report, especially with respect to the important role of mGluR1 in LTD. However, while we found that MPEP blocked LTD induction, Gubellini et al. (2001) did not observe any effect of MPEP. The reason for this discrepancy is unclear. However,

the difference may relate to the age of the animals used in the two studies. We have used animals in the postnatal 15–25 day range, a time when striatal LTD is quite robust, while fully adult rats were used by Gubellini and coworkers. It will be interesting to determine if changes in the functional role of mGluR5 take place as a consequence of early postnatal development. Interestingly, both mGluR1 and -5 contribute to activation of striatal cholinergic interneurons (Pisani et al. 2001). Thus it is possible that one or both of these group I mGluRs might contribute to LTD via alterations in cholinergic synaptic transmission.

Several postsynaptic mechanisms are required for induction of striatal LTD. Among these mechanisms are depolarization and increased intracellular calcium in the medium spiny neurons (Calabresi et al. 1992). The postsynaptically localized group I mGluRs are well positioned to contribute to these important LTD induction mechanisms. Indeed, recent studies from Calabresi and coworkers suggest that activation of group I mGluRs on medium spiny neurons enhances increases in intracellular calcium (Pisani et al. 2000).

It is well known that glutamate can stimulate PI hydrolysis in the brain, mainly through activation of group I mGluRs (Knöpfel et al. 1995; Pin and Duvoisin 1995; Riedel and Reymann 1996; Schoepp et al. 1999). Casabona et al. (1997) reported expression and coupling to polyphosphoinositide hydrolysis of group I mGluRs in several brain areas including striatum. Increased intracellular Ca^{2+} concentration resulting from signaling mechanisms initiated by mGluR activation and PI has been suggested to be an important mediator of the induction of synaptic plasticity in the hippocampus (Anwyl 1999). Previous reports indicated that application of calcium chelators in the intracellular solution prevents the induction of corticostriatal LTD (Calabresi et al. 1992; Choi and Lovinger 1997a,b). These results suggest that increased intracellular Ca^{2+} concentration in the postsynaptic neuron is one essential factor for the induction of LTD in the striatum. Thus it is quite probable that group I mGluRs act through PI hydrolysis and increased intracellular Ca^{2+} to contribute to the induction of striatal LTD.

It is difficult to determine which of the two group I mGluRs (mGluR1 or 5) has a more important role in striatal LTD induction based on the present findings. The antagonist 4-CPG has actions on mGluR1a but is not specific for this receptor type, having either weak agonist (Hayashi et al. 1994) or weak antagonist (Thomsen et al. 1994) actions at mGluR2. AIDA has been reported to selectively antagonize rat mGluR1a compared with mGluR5a and mGluR2 (Moroni et al. 1997; Pellicciari et al. 1995). The observation that CPCCOEt blocks LTD induction is certainly consistent with the idea that mGluR1 is involved in this process. However, MPEP, at a concentration that appears to be selective for mGluR5 among the mGluRs, also blocked induction of striatal LTD. These results are unexpected because MPEP has a selectivity for mGluR5 that is not seen with the other antagonists we used. We do not believe that MPEP blockade of striatal LTD involves inhibition of NMDA receptors because it has been clearly demonstrated that striatal LTD is not blocked by specific NMDA receptor antagonists (Calabresi et al. 1992; Choi and Lovinger 1997b). It is not clear why more than one type of group I mGluR would need to be involved in corticostriatal LTD. However, it is tempting to speculate that both mGluR1 and 5 must be activated for LTD induction to occur. This is not unreasonable because both of these receptors are present at glutamatergic synapses on medium spiny neurons (Standaert et al. 1999; Testa et al. 1998). Perhaps the two receptors act in concert to promote increases in intracellular calcium in the medium spiny neuron during high-frequency activation of glutamatergic synapses with neither receptor on its own producing calcium rises of a magnitude sufficient to exceed a threshold needed for LTD induction. Another potential explanation for our findings is that a novel group I-like mGluR sensitive to both antagonists is present in striatum and participates in LTD induction. However, no such receptor has been identified to date. Despite the fact that we were not able to implicate only one mGluR subtype in striatal LTD induction, our results do strongly indicate that the mGluR involved in LTD has the pharmacological features of a group I receptor based on the relative specificities of the antagonists used.

It should be noted that none of the four group I antagonists reduced synaptic responses produced by low-frequency afferent stimulation either before or after induction of LTD. This finding suggests that group I mGluRs do not play a prominent role in the induction of synaptic responses during low-frequency afferent input. Furthermore, application of the group I mGluR agonist DHPG did not induce a change in synaptic responses, indicating that activation of group I mGluRs is not sufficient to produce striatal LTD. Rather, these receptors likely act in concert with other proteins, such as dopamine receptors and L-type voltage-gated calcium channels, to initiate the mechanisms required for LTD induction.

In conclusion, the present data show that group I mGluRs are involved in the induction of striatal LTD. In contrast, transmission at these synapses is strongly modulated on an acute time scale by group II mGluRs.

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