Differential Regulation of Synaptic Inputs to Dentate Hilar Border Interneurons by Metabotropic Glutamate Receptors

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INTRODUCTION

Inhibitory interneurons in the dentate gyrus limit synaptic input to the hippocampus by regulating the output of dentate granule cells. Pharmacological disruption of this inhibitory control leads to synchronous firing of hippocampal neurons (Miles and Wong 1987), and therefore transient reductions in synaptic inhibition may contribute to the initiation or propagation of seizures in epilepsy. Although synaptic inhibition can be readily reduced by a variety of pharmacological agents, physiological conditions that produce such a state in the untreated animal are less well understood. Receptor- (Doherty and Dingledine 1996) or agent- (Doherty and Dingledine 1997) mediated modulation of synaptic input to interneurons from both CA3 and the granule cell layer. We conclude that multiple pharmacologically distinct mGluRs presynaptically regulate synaptic transmission at two excitatory inputs to hilar border interneurons. Further, the degree of mGluR-mediated depression of excitatory drive is greater at synapses from dentate granule cells onto interneurons than at synapses from CA3 pyramidal cells.

METHODS

Thin (250 μm) hippocampal slices were prepared from immature (10–16 day) male Sprague-Dawley rats in oxygenated (95% O2-5% CO2), ice-cold artificial cerebrospinal fluid (ACSF), as previously described (Doherty and Dingledine 1997). Slices were incubated at 30°C for at least 60 min, then transferred to a submerged recording chamber and immobilized with a nylon mesh-covered platinum frame. Slices were continuously perfused (2–3 ml/min) with room temperature ACSF (in mM: 130 NaCl, 3.5 KCl, 1.5 CaCl2·2 H2O, 1.5 MgSO4·7 H2O, 24 NaHCO3, 1.25 NaH2PO4, and 10 glucose, pH 7.4, 295–305 mosM).
Individual hilar border interneurons were visually selected under Hoffman modulation contrast optics (×600). Whole cell patch recordings were performed using an Axopatch 1D electrometer (Axon Instruments). Recordings were made in voltage-clamp mode at a holding potential of −70 mV. Both spontaneous and evoked excitatory postsynaptic currents (EPSCs) were filtered at 3 kHz with an 8-pole bessel filter and digitized at 10–30 kHz on an IBM-compatible Pentium computer using pClamp and Axotape data acquisition software (Axon Instruments). Patch electrodes (5–6 MΩ) were filled with 130 mM CsOH, 140 mM methanesulfonic acid, 10 mM N-2-hydroxyethylpiperazine-N’-2-ethanesulfonic acid (HEPES), 2 mM MgCl₂, and 1% biocytin. Intracellular solution was buffered to pH 7.3 with CsOH and adjusted to 275–280 mosM with H₂O. All experiments were performed in the presence of bicuculline methobromide (10 μM).

ACSF-filled glass pipettes were used to deliver electrical stimulation (0.3 Hz, 10–80 μA; 200–300 μs) to sites within the dentate granule cell layer (GCL) and the area CA3b-c. In some experiments, stimuli were delivered to both the GCL and CA3. The interpulse interval between stimuli at the two sites was 80–120 ms in these experiments.

Both minimal and more conventional higher intensity stimulations were employed to explore the effects of mGluRs on synaptic input to hilar border interneurons. In 23 experiments, minimal stimulation (Dobrunz and Stevens 1997; Raastad et al. 1992; Stevens and Wang 1994) was employed to isolate a single synaptic input. Careful positioning of the stimulating pipette and adjustment of the stimulus intensity to the minimum necessary to evoke a postsynaptic response resulted in EPSCs with amplitudes and shapes similar to those of spontaneous miniature EPSCs, each event presumably representing transmitter release from a single synaptic terminal. To guard against counting spontaneous EPSCs as evoked inputs or evoked single short-latency EPSCs or resulted in a failure of synaptic transmission. Synaptic reliability and EPSC amplitude remained stable for each input (bottom). Arrow denotes application of electrical stimulus. B: minimal stimulation of the stratum granulosum evoked short-latency EPSCs. Synaptic reliability and EVSC amplitude remained stable for each input (bottom). C: individual traces of minimal EPSCs evoked following stimulation of both the CA3 and the granule cell layer in the same interneuron. An interpulse interval of 80 ms separated the 2 stimuli in each trial. Transmission rates calculated for each input in experiments where both inputs were evoked were not significantly different from those observed when only 1 input was stimulated. GCL, granule cell layer.

Drugs

Bicuculline methobromide (10 μM), DHPG (20–100 μM), DCG-IV (1 μM), and L-AP4 (3–500 μM) were all obtained from Tocris Cookson, dissolved in known quantities of ACSF and delivered by bath perfusion. DCG-IV was the kind gift of Tocris Cookson.

RESULTS

We examined the effects of several mGluR agonists on excitatory synaptic transmission at two different excitatory inputs onto hilar border interneurons. Visually guided, whole cell patch recordings were made from 60 interneurons located at the border between the stratum granulosum and the hilus in thin slices of rat hippocampus. In addition to their position at the hilar border, other morphological criteria used for visual selection of interneurons included a large diameter soma (>20 μm) and, often, a thick apical dendrite traversing the stratum granulosum into the stratum radiatum. Patterns of axonal ramification indicated that these neurons included basket cells (Ribak 1992; Seress and Ribak 1990), as well as interneurons that projected to the molecular layer (Han et al. 1993; Mott et al. 1997; Scharfman 1995). Whole cell recordings made from hilar border interneurons had a resting membrane potential of −49 ± 0.9 (SE) mV, a series resistance of 14.9 ± 0.4 MΩ, and an input resistance of 270 ± 7 MΩ (n = 60).

The use of minimal stimulation allows the measurement of synaptic reliability, the proportion of stimuli that evokes a postsynaptic response (Raastad et al. 1992; Stevens and Wang 1994). We measured the reliability of synaptic transmission at minimal inputs to hilar border interneurons over windows of 20 consecutive trials, an interval long enough to minimize the potential for errors introduced by moment-to-moment variations in transmitter release (Doherty and Dingledine 1997).

Minimal stimulation delivered either at the border of stratum pyramidale and stratum oriens in CA3 (Fig. 1A) or in the stratum granulosum of the dentate gyrus (Fig. 1B) evoked glutamatergic EPSCs from hilar border interneurons, as previously described (Doherty and Dingledine 1997). In 23 experiments in which minimal stimulation was employed, the transmission rate of evoked input from CA3 was 43 ± 5%, whereas granule cell layer—evoked inputs produced minimal EPSCs in 58 ± 6% of stimulus trials. In nine experiments, minimal evoked EPSCs were obtained from both inputs onto the same interneuron during the same trial (Fig. 1C). The mean amplitude of EPSCs evoked by minimal stimulation was −15 ± 3 pA (n = 13) for CA3-evoked responses and −14 ± 2 pA for GCL-evoked responses (n = 13).
Significant effect on the amplitude of spontaneous EPSCs consistent with a presynaptic site of action, DCG-IV had no effect of GCL-evoked EPSCs was mediated through a presynaptic C (●), suggesting that the effect of DCG-IV on the reliability C of minimal EPSCs evoked from either CA3 or GCL inputs (Fig. 2). The transmission rate of minimal EPSCs evoked by GCL stimulation was reduced to 41 ± 4% of control (n = 11), whereas the transmission rate of minimal CA3-evoked EPSCs remained above 85 ± 8% of control (n = 9; Fig. 2B).

DCG-IV did not alter the amplitude of the remaining minimal EPSCs evoked from either CA3 or GCL inputs (Fig. 2C), suggesting that the effect of DCG-IV on the reliability of GCL-evoked EPSCs was mediated through a presynaptic suppression of transmitter release by group II mGluRs. Consistent with a presynaptic site of action, DCG-IV had no significant effect on the amplitude of spontaneous EPSCs (-13.3 ± 1.8 pA vs. -13.9 ± 2.7 pA; n = 4 experiments); however, the frequency of sEPSCs was significantly (paired t-test, P = 0.02) reduced in the presence of DCG-IV (from 5.4 ± 1.1 to 3.1 ± 0.8 Hz) in seven interneurons. Thus excitatory synaptic input to hilar border interneurons from dentate granule cells, but not from CA3 pyramidal cells, appears to be presynaptically depressed by group II mGluRs.

Because DCG-IV activates both mGluR2 and mGluR3 with similar potencies (EC50 = 0.2–0.3 μM) (Hayashi et al. 1993), either one or both group II mGluRs may be involved in depressing synaptic reliability at granule cell inputs to hilar border interneurons. At high concentrations, DCG-IV can act as an N-methyl-d-aspartate (NMDA) receptor agonist (EC50 = 144 μM) (Wilisch et al. 1994). However, at the concentration of DCG-IV utilized in these experiments (1 μM), significant activation of NMDA receptors would not be expected. Consistent with this prediction, no inward currents were detected in hilar border interneurons after treatment with DCG-IV.

Although DCG-IV did not usually depress the synaptic reliability of CA3-evoked inputs, in two experiments CA3-evoked inputs were depressed. Addition of these two DCG-IV-sensitive inputs to the group data for CA3-evoked inputs (Fig. 2B) did not cause a statistically significant decrease in the mean transmission rate for that input (P = 0.12; 1-way ANOVA). The mean latencies of these DCG-IV-sensitive CA3 EPSCs were 6.5 and 7 ms. Such relatively long latency inputs were often observed after CA3 stimulation, although not all longer latency inputs were depressed by DCG-IV. The long latency of these inputs suggests that they may have been evoked through a multisynaptic pathway, perhaps including a DCG-IV-sensitive hilar interneuron. Hilar border interneurons can be activated through a polysynaptic pathway involving the hilar interneurons in response to CA3 stimulation (Scharfman 1995). Alternatively, a minor population of hilar border interneurons may receive CA3 afferents that bear group II mGluRs.

**Group III mGluRs**

Unlike DCG-IV, the group III selective agonist, L-AP4, usually depressed excitatory input to hilar border interneurons from both CA3 and the granule cell layer. Because several group III mGluRs are present in the hippocampal formation and can be activated by different L-AP4 concentrations, L-AP4 was applied at 3, 20, 50, and 500 μM. The depression of minimal transmission rates by L-AP4 was independent of the control transmission rate for either GCL- or CA3-evoked inputs (Fig. 3A). At 3 μM, L-AP4 depressed synaptic transmission equally from CA3 and GCL inputs. Thus the transmission rate of minimal GCL-evoked EPSCs was reduced to 24 ± 9% of control (n = 5), whereas transmission rate of minimal CA3-evoked EPSCs inputs was reduced to 29 ± 7% of control (n = 5).

**Input-selective effect of group II mGluRs**

![Fig. 2](http://jn.physiology.org/). A: (2S,1R*,2R*,3R*)-2,3-dicarboxyloxyethyl) glycine (DCG-IV; 1 μM) increased the incidence of synaptic failures at minimal granule cell layer (GCL) inputs (right), but not CA3 inputs (left) to hilar border interneurons. B: DCG-IV (1 μM) significantly depressed the transmission rate of minimal GCL-evoked (●), but not CA3-evoked EPSCs (○). Each point represents the value of the transmission rate (mean ± SE) calculated from 8 CA3 (○) or GCL (●) inputs. C: DCG-IV did not significantly depress the amplitude of minimal CA3-evoked EPSCs or the remaining minimal EPSCs evoked with GCL stimulation.

**Group III mGluRs**

![Fig. 3](http://jn.physiology.org/). A: effects of L-(-)2-amino-4-phosphonobutyric acid (L-AP4) on minimal inputs evoked from either the GCL (●, ○, □, and ▲) or CA3 (▲, ●, and ■) did not depend on the control transmission rate. Control transmission rate is plotted against the maximal effect of L-AP4 presented as a percentage of the control transmission rate. The maximal effect of L-AP4 on transmission rates was determined at 4 concentrations of L-AP4: 3 μM [GCL: 24 ± 9% of control (n = 5), ○; CA3: 29 ± 7% of control (n = 3), ▬]; 20 μM [GCL: 39 ± 7% of control (n = 5); ▲; 50 μM [GCL: 167 ± 4% of control (n = 3), □; and 500 μM [GCL: 25 ± 10% of control (n = 3), ▪; CA3: 5 ± 3% of control (n = 3), ▼]. Note the potentiation of GCL-evoked transmission rates in 5 experiments with 20 or 50 μM L-AP4. B: transmission rate of minimal GCL-evoked EPSCs was reduced to 39 ± 7% of control by 20 μM L-AP4. Each point represents the value of the transmission rate (mean ± SE) calculated from 5 GCL inputs. C: L-AP4 did not significantly depress the amplitude of minimal CA3- or GCL-evoked EPSCs at 3–500 μM (n = 15).
control (n = 3). To directly compare the effects of L-AP4 on both minimal inputs and conventionally evoked ensemble EPSCs, amplitudes of minimal EPSCs were recalculated to all concentrations of agonist tested, results from all three mGluRs. amplitudes of minimal EPSCs were reduced to 25 ± 5% of control amplitude (n = 4). As expected, these values were in good agreement with the effect of L-AP4 on the transmission rates of minimal inputs.

In five of seven experiments, 20 μM L-AP4 reduced the transmission rates of minimal GCL inputs (Fig. 3B) to a level that was not significantly (P = 0.22; unpaired t-test) greater than that caused by 3 μM L-AP4. The amplitude of ensemble EPSCs, including synaptic failures, was reduced to 42 ± 5% of control (n = 6), again not significantly different (P = 0.12) from the reduction cause by 3 μM L-AP4. In contrast to the depressant effect of L-AP4 in the majority of experiments, an increase in either minimal transmission rate (Fig. 3A) or ensemble EPSC amplitudes (191 ± 39% of control; n = 5) was observed in 5 of 10 experiments at 20–50 μM L-AP4. Increases in either transmission rate or ensemble EPSC amplitude were not observed with 3 μM (n = 13 experiments) or 500 μM (n = 10 experiments) L-AP4 (Fig. 3A).

L-AP4 at 500 μM was not significantly (P = 0.95; unpaired t-test) more effective than 3 μM at depressing transmission at minimal GCL-evoked EPSCs. However, the depression of transmission rates at CA3 inputs by 500 μM L-AP4 (Fig. 3A) was significantly (P = 0.03; unpaired t-test) greater than that evoked by 3 μM L-AP4. Similarly, the reduction in the amplitude of ensemble GCL-evoked EPSCs caused by 500 μM L-AP4 (26 ± 7% of control amplitude; n = 5) was not significantly (P = 0.87; unpaired t-test) greater than that caused by 3 μM L-AP4, whereas the reduction of CA3-evoked EPSC amplitudes (10 ± 4% of control amplitude; n = 6) was significantly (P = 0.04; unpaired t-test) greater than that caused by 3 μM L-AP4. Despite changes in the transmission rates at both excitatory inputs, L-AP4 had no significant effect on the amplitudes of minimally evoked EPSCs when synaptic failures were not counted (Fig. 3C), suggesting that, similar to DCG-IV, L-AP4 exerts its effect on synaptic input to hilar border interneurons at a presynaptic site.

These data indicate that 3 μM L-AP4 was equally effective in depressing synaptic inputs to hilar border interneurons from dentate granule cells or CA3 pyramidal cells. A concentration of 3 μM L-AP4 appears to generate maximal depression of GCL inputs; however, we cannot rule out the possibility that an additional depression of CA3 inputs occurs at 500 μM L-AP4.

**Group I mGluRs**

We tested the ability of three concentrations (20, 50, and 100 μM) of the Group I selective agonist, DHPG, to reduce the reliability of synaptic transmission at excitatory inputs to hilar border interneurons. The transmission rate of GCL-evoked EPSCs was maximally depressed by these three concentrations of DHPG to 36, 28, and 30% of control, respectively (n = 5). For CA3 inputs, DHPG depressed the transmission rate to 45, 26, and 30% of control (n = 5). Because a similar peak reduction of transmission was observed at all concentrations of agonist tested, results from all three concentrations were pooled. Thus DHPG (20–100 μM) significantly and reversibly reduced the synaptic reliability of both CA3 and granule cell inputs (Fig. 4A). As with DCG-IV and L-AP4, the maximal reduction in synaptic reliability of minimal inputs was achieved within 5 min after the start of agonist perfusion, and recovery to control transmission rates occurred at both synapses within 10–25 min after wash out of agonist. The amplitudes of one minimal CA3-evoked and three minimal GCL-evoked EPSCs were not significantly depressed by 20 μM DHPG (Fig. 4B).

DHPG (20–100 μM) increased the frequency of spontaneous EPSCs (sEPSCs; Fig. 5A). Despite the increase in sEPSC frequency, evoked EPSCs were readily discriminated from spontaneous events (Fig. 5B). DHPG also induced small inward currents in hilar border interneurons (-19 ± 5 pA; n = 4), an effect not observed during the application of either the group II agonist, DCG-IV or the group III agonist, L-AP4. They were however, similar to currents observed in hilar border interneurons after treatment with ACPD (Doherty and Dingledine 1997).

**Discussion**

Two major findings can be derived from this study. First, the pharmacology of mGluR-mediated depression of synaptic transmission at two excitatory inputs to hilar border interneurons from dentate granule cells or CA3 pyramidal cells appears to be consistent. A concentration of 3 μM L-AP4 appears to generate maximal depression of GCL inputs; however, we cannot rule out the possibility that an additional depression of CA3 inputs occurs at 500 μM L-AP4.

![Figure 4](http://jn.physiology.org/)

**Figure 4.** A: (RS)-3,5-dihydroxyphenylglycine (DHPG) (20–100 μM) significantly depressed the transmission rate of minimal CA3-evoked (P = 0.002; ○) and GCL-evoked (P = 0.04; ▲) EPSCs. Each point represents the value of the transmission rate (mean ± SE) calculated from 4 CA3 inputs or 3 GCL inputs. B: DHPG (20 μM) had no significant effect on the amplitudes of minimal EPSCs evoked with stimulation of either CA3 (n = 1) or the GCL (n = 3).
neurons matches that observed for other targets of the same afferents. This finding suggests that the mGluR complement in presynaptic axon terminals, rather than the nature of the postsynaptic targets, determines the characteristics of mGluR-mediated synaptic depression in these interneurons. The second major finding of the study is that synaptic transmission at both excitatory inputs to hilar border interneurons that we examined is regulated by multiple mGluRs. This result indicates that activation of mGluRs at these synapses can provide interneurons with significant plasticity in their responsiveness to afferent input. Taken together, these observations suggest that, under appropriate conditions, activation of mGluRs may enhance the activity of dentate granule cells via a reduction in synaptic inhibition, thus contributing to the generation of hyperexcitability in the hippocampus.

The finding that inputs to interneurons are regulated in a manner similar to principal neuron targets of the same afferents is most clearly illustrated by the effects of the group II mGluR agonist, DCG-IV on evoked inputs to hilar border interneurons. Excitatory input from dentate granule cells to hilar border interneurons is depressed by DCG-IV, whereas synaptic input to hilar border interneurons from CA3 pyramidal cells is generally not affected. Transmitter release from granule cell mossy fiber axons onto CA3 pyramidal cells is presynaptically regulated by group II mGluRs (Kamiya et al. 1996; Manzoni et al. 1995; Yokoi et al. 1996; Yoshino et al. 1996). Most reports suggest that Schaffer collateral input of CA3 pyramidal cells to CA1 pyramidal cells is not depressed by DCG-IV (Gereau and Conn 1995; Kamiya et al. 1996; Yoshino and Kamiya 1995; but see Vignes et al. 1995). mRNA for group II mGluRs are present in dentate granule cells, but absent from CA3 pyramidal cells (Fotuhi et al. 1994; Oshini et al. 1993). Similarly, immunohistochemical analyses indicate that mossy fiber terminals in CA3 contain group II mGluRs (Neki et al. 1996; Petralia et al. 1996; Shigemoto et al. 1997; Yokoi et al. 1996), but that Schaffer collateral terminals do not (Neki et al. 1996; Shigemoto et al. 1997). These observations, combined with our results, suggest that granule cell inputs to both of its major targets are regulated presynaptically by group II mGluRs, whereas synapses made by CA3 pyramidal cells are not regulated by group II mGluRs.

Which group III mGluRs account for the depression of excitatory input onto hilar border interneurons by L-AP4? In this study, 3 μM L-AP4 was capable of depressing synaptic transmission at both synaptic inputs to hilar border interneurons. L-AP4 activates both mGluR4a and mGluR8 with relatively high potency (EC$_{50}$ = 0.4–1.2 μM), but is much less potent at mGluR7 (EC$_{50}$ = 160–1,000 μM) (Conn and Pin 1997; Suzdak et al. 1994). Whereas mRNA for mGluR6 is not strongly expressed in the adult hippocampus (Testa et al. 1994), mRNA encoding mGluRs 4, 7, and 8 have all been observed in CA3 pyramidal cells and dentate granule cells by in situ hybridization (Kinzie et al. 1995; Saugstad et al. 1997; Testa et al. 1994). Immunostaining for mGluR7 is found throughout the adult hippocampus (Bradley et al. 1996; Shigemoto et al. 1997), whereas both mGluR4 and mGluR8 appear to be restricted to the molecular layer (Shigemoto et al. 1997). L-AP4–sensitive (group III) mGluRs presynaptically depress synaptic transmission at many glutamatergic hippocampal synapses, including mossy fiber input to CA3 (Manzoni et al. 1995; Yoshino et al. 1996), perforant path input to granule cells (Kahle and Cotman 1993; Macek et al. 1996), and Schaffer collateral input to CA1 (Baskys and Malenka 1991; Gereau and Conn 1995; Vignes et al. 1995). However, the potency of L-AP4–mediated suppression of synaptic transmission at these hippocampal synapses appears to be dependent on both species and developmental stage. For example, Baskys and Malenka (1991) reported that 50 μM L-AP4 caused an ~30% reduction in transmission at Schaffer collateral–CA1 synapses in neonatal rats and suggested that responsiveness to L-AP4 at these synapses is downregulated during development, with 50 μM L-AP4 having no effect on slices taken from adult (80–150 days) rats. Gereau and Conn (1995) found that higher concentrations of L-AP4 (1 mM) were capable of suppressing transmission at Schaffer collateral–CA1 synapses in older rats and suggested that different group III mGluRs mediate this effect in neonatal and adult hippocampus. Because the rats in this study were neonatal (12–16 days), it is perhaps unsurprising that L-AP4 suppressed transmission at low micromolar concentrations. We therefore conclude that the depression of synaptic input to hilar border interneurons by L-AP4 is likely to be mediated primarily by mGluR4a or mGluR8, although we cannot, of course, rule out the possibility that L-AP4 exerts its effects on inputs to hilar border interneurons through an as yet unidentified group III–like mGluR. Because L-AP4 more completely depressed CA3 inputs at the highest concentration tested (500 μM), it is possible that...
mGluR7 contributes to the regulation of these synapses in the neonatal rat. The distribution of group III mGluRs in the neonatal hippocampus has not been reported. The potentiation of GCL inputs by 20–50 μM L-AP4 in a minority of experiments recalls the observation that 100 μM ACPD potentiates synaptic input to some, but not all, CA1 stratum oriens interneurons (McBain et al. 1994). These data suggest that significant heterogeneity in responsiveness to mGluRs among different classes of interneurons remains to be explored.

The observation that minimal EPSC amplitudes are not affected by either DCG-IV (Fig. 2C) or L-AP4 (Fig. 3C), whereas transmission rates are depressed, suggests that these agonists act primarily on presynaptic mGluRs at these synapses. However, the direct effect of the group I agonist, DHPG, on membrane potential of hilar border interneurons makes it difficult to determine whether DHPG depresses synaptic transmission solely through a postsynaptically mediated reduction in transmitter release or also as a consequence of its direct effects on the interneuron. It has been suggested that group I mGluRs depress transmission at Schaffer collateral inputs to CA1 as a result of an interaction with postsynaptic NMDA receptors (Harvey et al. 1996). It is also possible that an mGluR-mediated depolarization of hilar border interneurons could lower evoked EPSC amplitudes to the point that they could not be distinguished from baseline noise levels, resulting in a perceived reduction in the transmission rate, if such depolarization occurs in a poorly clamped portion of the dendritic arbor.

Multiple mGluRs are capable of regulating both of the excitatory synapses to hilar border interneurons examined in this study. mGluRs from all three mGluR subgroups are capable of depressing excitatory synaptic input from granule cells to hilar border interneurons, but only groups I and III regulate CA3 inputs. L-AP4–sensitive mGluRs are not activated by ACPD at the concentrations previously used to depress synaptic inputs to hilar border interneurons (Doherty and Dingledine 1997). Taken together, these results suggest that groups I and III mGluRs act in concert to depress excitability at these synapses.

**Functional implications**

Under what conditions do mGluRs participate in synaptic transmission in the hippocampus? Elevations in extracellular glutamate levels following repetitive synaptic stimulation are thought to activate presynaptic mGluRs. Scanziani et al. (1997) have demonstrated that 1-Hz stimulation or block of glutamate reuptake at mossy fiber synapses result in a rapid block of transmitter release onto CA3 pyramidal cells, a process mediated by presynaptic mGluRs. It is believed that mGluRs contribute to both short- (Brown and Reymann 1995; Kahle and Cotman 1993) and long- (Reidel et al. 1995; Tong et al. 1996) term plastic changes in the strength of synaptic circuitry within the dentate gyrus. Although many of these changes have been attributed to effects of mGluRs on excitatory synapses to principal neurons, mGluR-induced reduction in the strength of excitatory drive onto interneurons may also contribute to the observed effects of mGluR agonists on the output of hippocampal synaptic circuitry.

mGluR-mediated reductions in synaptic inhibition may also contribute to the generation of hyperexcitability. Suppression of GABAergic synaptic transmission is epileptogenic in many animal models, whereas enhancement of GABAergic transmission is used in the clinical management of many types of epilepsy (Mattson et al. 1995; Petroff et al. 1996). Elevated extracellular glutamate levels have been associated with both acute epileptiform activity (Lucke et al. 1996; Ueda and Tsuru 1995) and chronic epilepsies (During and Spencer 1993). Functional disconnection of excitatory input to inhibitory interneurons due to increased mGluR-mediated presynaptic inhibition could contribute to reduced inhibition observed in a variety of seizure models.

In summary, we conclude that excitatory input to hilar border interneurons in juvenile rats is regulated by multiple mGluRs, although experiments with selective agonists indicate that mGluRs do not completely depress synaptic input to hilar border interneurons. The two synaptic inputs that we examined are regulated by different combinations of mGluRs, suggesting that mGluR-mediated inhibition of synaptic input provides a flexible mechanism for moment-to-moment regulation of inhibition in the dentate gyrus.

The authors thank Dr. Y. Ohfune and Tocris Cookson for the gift of DCG-IV and Dr. P. J. Conn for helpful comments on the manuscript. This work was supported by an American Epilepsy Society Research Training Fellowship to J. Doherty and National Institute of Neurological Disorders and Stroke Grant NS-17771. Address for reprint requests: J. Doherty, Dept. of Pharmacology, Rollins Bldg., Rm. 5010, Emory University Medical School, Atlanta, GA 30322. Received 10 September 1997; accepted in final form 18 February 1998.

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