RAPID REPORT

Metabotropic glutamate receptors modulate feedback inhibition in a developmentally regulated manner in rat dentate gyrus

James J. Doherty, Sudar Alagarsamy, Kristopher J. Bough, P. Jeffrey Conn, Raymond Dingledine and David D. Mott

Department of Pharmacology, Emory University Medical School, Atlanta, GA 30322, USA

We investigated group II metabotropic glutamate receptor (mGluR) modulation of glutamatergic input onto hilar-border interneurones and its regulation of feedback inhibition in the dentate gyrus. Selective activation of group II mGluRs with (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV) depressed mossy fibre (MF)-evoked excitatory drive to these interneurones with significantly greater depression in juvenile than adult rats. During 20 Hz MF stimulus trains, EPSCs became depressed. Depression during the early, but not later part of the train was significantly greater in juvenile than adult rats and was blocked by the mGluR antagonist (2*S*)-2-amino-2-[(1*S*,2*S*)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid (LY341495). In dentate granule cells from juvenile rats polysynaptic feedback IPSCs, but not monosynaptic IPSCs, were strongly suppressed by DCG-IV. DCG-IV also suppressed feedback inhibition of perforant path-evoked population spikes. In contrast, in adult animals DCG-IV did not significantly depress feedback inhibition. During 20 Hz stimulus trains in juvenile animals the summation of polysynaptic, but not monosynaptic IPSCs was suppressed by synaptically activated group II mGluRs. Blockade of these mGluRs with LY341495 significantly increased the area and duration of the summated IPSC, causing greater feedback inhibition of granule cell firing. In contrast, in adult animals LY341495 did not alter feedback inhibition following the stimulus train. These findings indicate that group II mGluRs modulate excitatory drive to interneurones in a developmentally regulated manner and thereby modulate feedback inhibition in the dentate gyrus.

(Received 31 August 2004; accepted after revision 22 October 2004; first published online 28 October 2004)
Corresponding author D. D. Mott: Department of Pharmacology, Emory University Medical School, Atlanta, GA 30322, USA. Email: dmott@emory.edu

At glutamatergic inputs onto principal neurones, presynaptic mGluRs are important mediators of short-term plastic changes in synaptic efficacy (Conn, 2003). Similar to other presynaptic receptors, the activation of group II (mGluR2 and mGluR3) mGluRs depresses the release of glutamate in the hippocampus and in other parts of the brain (Conn & Pin, 1997; Conn, 2003). Less is known about how mGluRs contribute to short-term plasticity at interneurone inputs or how mGluR-mediated short-term regulation of excitatory drive onto interneurones affects the strength of GABAergic inhibition in cortical networks. Because individual GABAergic interneurones typically inhibit the activity of large numbers of principal neurones (Sik *et al.* 1994; Freund & Busáki, 1996), regulation of excitatory synaptic drive onto individual interneurones could have a disproportionately large effect on local cortical activity (Cobb *et al.* 1995; Miles *et al.* 1996). Glutamatergic synapses onto GABAergic interneurones are likely to be important points for regulatory control of network behaviour. We have examined group II mGluR-mediated regulation of excitatory drive to interneurones. We demonstrate that presynaptic group II mGluRs contribute to activity-dependent short-term depression (STD) of excitatory inputs onto hilar border interneurones in a developmentally regulated manner and that this regulation controls the strength of feedback inhibition in the dentate gyrus.

 DOI: 10.1113/jphysiol.2004.074930

Methods

Whole cell patch clamp recordings

Hippocampal slices from juvenile (12–16 days old) or adult (36–60 days old) Sprague-Dawley rats were prepared as described previously (Doherty & Dingledine, 1998, 2001). Briefly, rats were anaesthetized with isoflurane and decapitated according to the protocol approved by the Emory University Animal Care and Use Committee. Thin (225–250 μm) hippocampal slices were prepared using a vibratome and incubated at 30°C in artificial cerebrospinal fluid (ACSF) containing (mM): 130 NaCl, 3.5 KCl, 1.5 $CaCl_2$, 1.5 $MgSO_4$, 24 $NaHCO_3$, 1.25 NaH_2PO_4 and 10 glucose (pH 7.3, 295–305 mosmol l^{-1}) before being transferred to a submerged recording chamber. Slices were then perfused (2–3 ml min^{-1}) with room temperature ACSF.

Hilar border interneurones were visually selected under Hoffman modulation contrast optics. Interneurones selected for recording had somata located near the hilar border of the granule cell layer, were distinctively larger than granule cells and exhibited basilar dendrites entering the hilus (Mott *et al.* 1997).

Whole cell patch recordings were acquired using an Axopatch 1D electrometer and pCLAMP 8.0 software (Axon Instruments, Union City, CA, USA). Only neurones in which series and input resistance did not change by more than 10% were included for study. EPSCs were recorded at −70 mV and were evoked using glass micropipettes to deliver stimuli (0.3 Hz, 10–80 μA; 300–400 μs) in stratum granulosum 10–50 μm from the recording site. For EPSCs, bicuculline was added to the ACSF and the pipette solution contained (mM): 130 CsOH, 140 methanesulphonic acid, 10 Hepes, 2 MgATP and 0.3 NaGTP (pH 7.3; 270 mosmol l^{-1}). $GABA_A$ IPSCs were recorded at 0 mV using a pipette solution containing (mM): 130 caesium gluconate, 7 KCl, 10 Hepes, 2 MgATP, 0.3 TrisGTP and 3 QX-314 (pH 7.3).

Field potential recordings

Standard electrophysiological procedures were used to record field potentials from the dentate gyrus of hippocampal slices prepared from juvenile or adult rats (Mott *et al.* 1993). ACSF contained (mM): 130 NaCl, 3.5 KCl, 1.25 NaH_2PO_4, 24 $NaHCO_3$, 10 glucose, 1.5 $CaCl_2$ and 1.5 $MgCl_2$.

Assay for cAMP formation

The dentate gyrus was microdissected from 500 μm thick hippocampal slices from juvenile or adult rats and equal numbers (3–4) of slices were added to separate tubes. A protocol modified from Shimizu *et al.* (1969) was used to determine the effect of group II mGluRs on forskolin-stimulated [^{3}H]cAMP accumulation. Briefly, for each age group 30 μCi of [8-^{3}H]adenine (American Radiolabelled Chemicals, St Louis, MO, USA) was added to each tube in the presence or absence of 10 μM DCG-IV. Following forskolin exposure (30 μM for 15 min), the reaction was stopped with 50 μl 77% trichloroacetic acid and 25 μl unlabelled cAMP and the samples were sonicated and centrifuged. The supernatant was isolated by sequential elution through Dowex (50W 200–400 mesh; Sigma Chemical Co., St Louis, MO, USA) and then Alumina columns. cAMP was eluted from the alumina with 2 ml Tris-HCl, pH 8.0 and the samples counted with a Beckman (LS 6500) liquid scintillation counter.

Analysis

Data were analysed using Clampfit 9.0 (Axon Instruments). All results are expressed as mean ± S.E.M. Statistical significance was determined using Student's *t* test and one-way ANOVA with *post hoc* Bonferroni test, as appropriate. In all figures a significant effect of drug treatment is indicated using asterisks ($^*P < 0.05$, $^{**}P < 0.01$), whereas a significant difference between juvenile and adult is indicated using # (#$P < 0.05$, ##$P < 0.01$).

Drugs

Bicuculline methobromide (10 μM), (2*S*)-2-amino-2-[(1*S*,2*S*)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid (LY341495; 500 nM), (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV; 1 μM), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 10 μM), D(−)-2-amino-5-phosphonopentanoic acid (D-APV; 50 μM) and *N*-(2,6-dimethylphenylcarbamoylmethyl)triethylammonium bromide (QX-314; 3 mM) were obtained from Tocris Cookson (Ellisville, MO, USA). All other salts were purchased from Sigma Chemical Company (St. Louis, MO). All drugs were used at the concentrations indicated above unless otherwise specified.

Results

Developmental regulation of group II mGluRs

We have previously observed that group II mGluRs suppress glutamate release from MF inputs onto hilar border interneurones in juvenile rats (Doherty & Dingledine, 1998). We have now evaluated developmental regulation of mGluR function at this synapse by comparing depression of the MF-evoked EPSC produced by the selective group II agonist DCG-IV in adult and juvenile rats. While DCG-IV depressed the MF-evoked EPSC in adult animals, it produced a significantly greater depression in juvenile rats (Fig. 1*A*). In both adult and juvenile animals the group II mGluR antagonist LY341495 (Kingston *et al.* 1998) reversed the DCG-IV-induced depression (Fig. 1*B*).

To determine whether the mechanism of DCG-IV-induced depression of the MF-evoked EPSC was similar in adult and juvenile animals we examined the effect of DCG-IV on the failure rate and amplitude of minimally evoked MF-EPSCs (Fig. 1*C* and *D*). DCG-IV significantly increased the EPSC failure rate in both adult and juvenile animals, but the effect in juvenile animals was significantly greater (Fig. 1*E*). In contrast, DCG-IV had no effect on the amplitude of minimally evoked EPSCs in either adult or juvenile animals. To confirm this developmental change in group II mGluR activity, we compared DCG-IV (3 μM)-evoked inhibition of forskolin-stimulated cAMP formation in slices of dentate gyrus from adult and juvenile rats. There was no difference in the percentage stimulation of cAMP formation by forskolin in adult ($875 \pm 105\%$; $n = 6$) and juvenile ($816 \pm 116\%$; $n = 6$) animals. However, as with inhibition of evoked EPSCs, DCG-IV inhibited forskolin-stimulated cAMP formation in the juvenile dentate significantly more than in the adult (Fig. 1*F*). Thus, the difference in the extent of DCG-IV-induced depression appears to be caused by a developmental decrease in group II mGluR suppression of glutamate release from MF terminals onto hilar border interneurones in the adult animal.

mGluR-mediated STD is greater in juvenile than adult rats

Brief (350–1000 ms) stimulus trains were delivered to MF inputs onto hilar border interneurones to examine short-term plasticity. The amplitude of the first EPSC of the train was similar in juvenile (30 ± 6 pA) and adult animals (35 ± 7 pA). MF stimulation at 20 Hz evoked synaptic depression of EPSCs during the train (Fig. 2*A* and *B*). This STD was well fitted to a single exponential function in both the adult and juvenile animals ($r^2 = 0.991$ adult; 0.995 juvenile) and reached a similar plateau level of depression within 400–500 ms (adult $43 \pm 4\%$ of control, $n = 8$; juvenile $42 \pm 2\%$ of control, $n = 8$). Recovery from STD following a 500 ms, 20 Hz train was rapid, with EPSC amplitudes fully returning to control levels within 3 s ($n = 9$; data not shown).

In the juvenile EPSC depression was greatest on the second pulse of the train, whereas in the adult the greatest depression occurred on either the second or third pulse of the train. However, both the second and third EPSCs, but not the plateau EPSC amplitude, were significantly more depressed in juvenile than adult animals (Fig. 2*B*), suggesting an additional mechanism for depression early in the train in juvenile animals that was diminished or absent in adults.

To determine the frequency dependence of EPSC depression, we delivered MF stimulus trains at frequencies ranging from 5 to 50 Hz and measured the second EPSC as well as the plateau EPSC amplitude as a percentage of the first EPSC of the train (Fig. 2*C*). In juvenile animals the second EPSC of the train was depressed at all frequencies tested with the greatest depression at 20 Hz. In adult animals the second EPSC was also depressed at all frequencies tested, but the extent of depression was less than the juvenile at each tested frequency and this difference was significant at both 10 and 20 Hz. In contrast, the plateau level of depression increased with increasing frequency and was not different between adult and juvenile animals.

Given the greater DCG-IV-induced depression of MF-evoked EPSCs in juvenile than adult rats, we

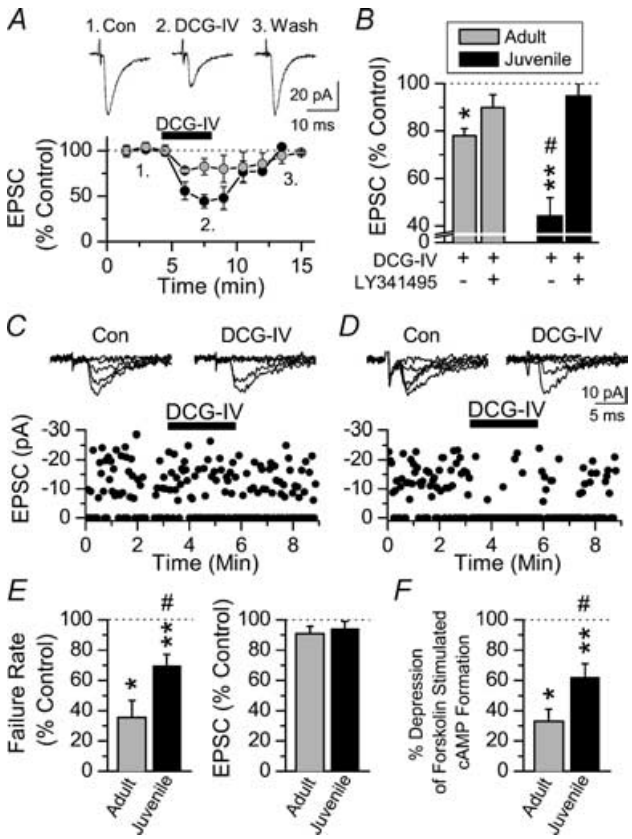

Figure 1. Depression of MF-evoked EPSCs in hilar border interneurones by group II mGluRs is developmentally regulated
A, time course of the depression of MF-evoked EPSCs by DCG-IV in juvenile (black circles, $n = 10$) and adult (grey circles, $n = 5$) interneurones. *B*, DCG-IV depressed MF-evoked EPSCs significantly more in juvenile than adult animals. LY341495 reversed DCG-IV effects. *C*, in an adult animal DCG-IV caused a small increase in the failure rate of minimally evoked EPSCs and did not affect their amplitude. *D*, in a juvenile animal DCG-IV markedly increased the failure rate of minimally evoked EPSCs with no effect on their amplitude. *E*, averaged effect of DCG-IV on failure rate (left) and amplitude (right) of minimally evoked EPSCs from adult ($n = 5$) and juvenile ($n = 10$) animals. *F*, DCG-IV (3 μM) inhibited forskolin-stimulated cAMP formation significantly more in dentate slices from juvenile than adult rats ($n = 6$ independent experiments done in triplicate).

used LY341495 to test whether the difference in EPSC depression early in the train in adult and juvenile animals was caused by synaptic activation of group II mGluRs. LY341495 had no significant effect ($95 \pm 5\%$ of control EPSC amplitude, $n = 4$) on the amplitude of MF-evoked EPSCs at a low (0.3 Hz) stimulus frequency. However, during a 20 Hz MF stimulus train, LY341495 completely blocked depression of the second EPSC and significantly reduced depression of the third EPSC in both the adult and juvenile (Fig. 2*D*). The effect of LY341495 was significantly greater on the juvenile animal. In contrast, LY341495 had no effect on the plateau EPSC amplitude. Thus, in the presence of LY341495 there was no longer any difference in STD during the stimulus train in the juvenile and adult (Fig. 2*D* and *E*). These results indicate that the difference in EPSC depression during a 20 Hz stimulus train can be entirely explained by the increased activation of group II mGluRs early in the train in the juvenile animal. However, a non-mGluR-mediated mechanism, possibly transmitter depletion (Dobrunz & Stevens, 1997) governs the plateau level of depression in a similar manner in the juvenile and adult animal.

mGluR activation regulates feedback inhibition of granule cells

These experiments suggest that group II mGluRs may regulate feedback inhibition of granule cells in the juvenile dentate by transiently reducing excitatory synaptic input to hilar border interneurones. We tested this hypothesis by examining whether DCG-IV would reduce polysynaptic feedback IPSCs in juvenile dentate granule cells. Polysynaptic feedback IPSCs were evoked in granule cells by MF stimulation (Fig. 3*A*). Monosynaptic IPSCs were evoked by direct stimulation of inhibitory fibres in the dentate molecular layer in the presence of CNQX and D-APV. As predicted, DCG-IV significantly depressed polysynaptic IPSC amplitude, while having no effect on monosynaptic IPSCs (Fig. 3*B*). LY341495 significantly ($P < 0.01$) attenuated the effect of DCG-IV.

Group II mGluR regulation of feedback inhibition in juvenile and adult animals was then compared by measuring feedback inhibition of perforant path (PP)-evoked population spikes (PS) produced by a MF conditioning stimulus, delivered 5–10 ms prior to stimulation of the perforant path (Mott *et al.* 1993). The perforant path stimulus intensity was adjusted to

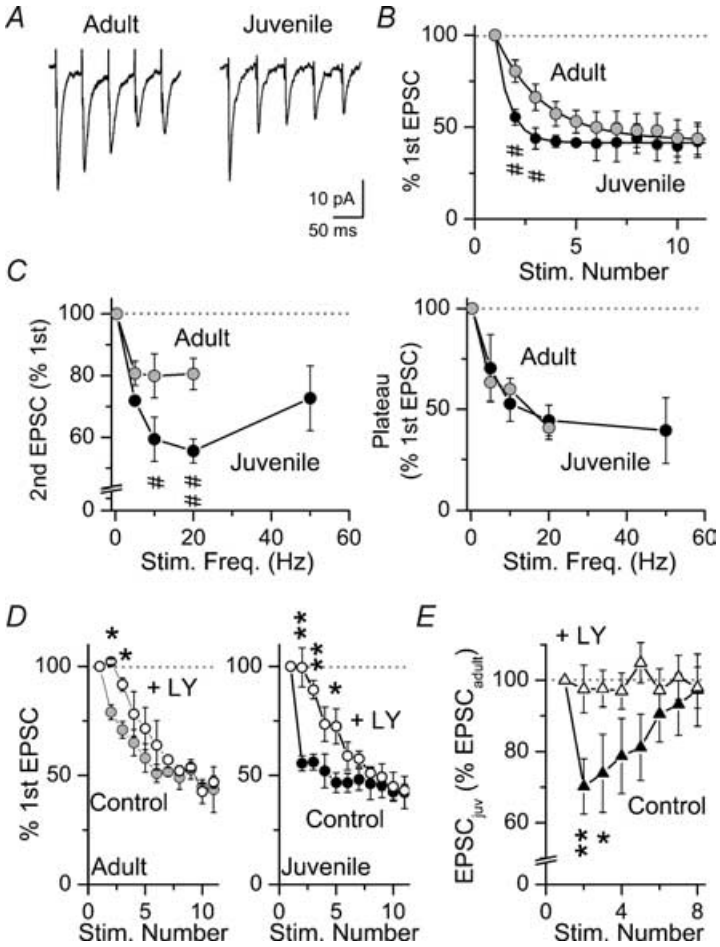

Figure 2. mGluR regulation of short-term depression at MF synapses onto hilar border interneurones
A, waveforms depicted are the combined average from 4 adult and 4 juvenile animals showing short-term depression of the MF-evoked EPSC amplitude in response to a 20 Hz stimulus train. *B,* averaged EPSC amplitude on each pulse of a 20 Hz MF stimulus train in an adult ($n = 8$) and juvenile ($n = 8$) animal. Short-term depression of MF-evoked EPSCs was fitted to a single exponential decay (continuous lines; τ_{decay}: adult: 117 ± 35; juvenile: 34 ± 8 ms). *C,* effect of MF train frequency on the average amplitude of the second EPSC (left) or the plateau EPSC amplitude (right) of the train in adult ($n = 3$–8) or juvenile ($n = 6$–9) animals. *D,* LY341495 significantly reduced EPSC depression early, but not late, in the train in adult ($n = 4$) and juvenile ($n = 5$) rats. *E,* averaged EPSC amplitude during the train in the juvenile expressed as a percentage of the corresponding EPSC amplitude in the adult. In control the juvenile exhibited significantly greater depression early in the train. In LY341495 the adult and juvenile are not different.

produce a PS of half-maximal amplitude (Fig. 3*C*, top left). The MF conditioning stimulus inhibited the PP-evoked PS by 81 ± 6% in the juvenile animal ($n = 6$; Fig. 3*C*, bottom left) and by 84 ± 8% in the adult. In the juvenile animal DCG-IV produced a significant reduction in the strength of this feedback inhibition that was completely blocked by LY341495 (Fig. 3*C* and *D*). In contrast, in the adult animal DCG-IV had little effect on inhibition, a significant difference from its marked effect on the juvenile animal. As previously reported (Kilbride *et al.* 1998), addition of DCG-IV reduced the slope of PP-evoked field EPSPs (26 ± 2% reduction; $n = 7$), but did not alter the antidromic spike amplitude. Therefore, when DCG-IV was added PP stimulation intensity was adjusted to produce a PS of control amplitude (Fig. 3*C*, top centre) prior to measurement of feedback inhibition (Fig. 3*C*, bottom centre).

To determine whether synaptic activation of mGluRs can suppress feedback IPSPs we delivered a brief stimulus train (400 ms; 20 Hz) to either the polysynaptic or monosynaptic pathway. Repetitive stimulation of either pathway resulted in summation of IPSCs primarily over the first two to three pulses of the train until a plateau amplitude was reached (Fig. 4*A*). Despite summation of the overall IPSC, individual IPSCs during the train were depressed. As predicted, LY341495 significantly increased summation of polysynaptic, but not monosynaptic IPSCs during the train (Fig. 4*A*). In the presence of LY341495 both the amplitude of the summated IPSC 200 ms after the last stimulus of the train (Fig. 4*B*) and the IPSC area (Fig. 4*C*) were significantly greater in the polysynaptic pathway. Combined with our previous results, these findings strongly suggest that by regulating the strength of excitatory drive to hilar border interneurones group II mGluRs can modulate feedback inhibition in granule cells.

To confirm that the LY341495-induced increase in the polysynaptic IPSC was capable of increasing feedback inhibition, we compared the amplitude of the conditioned PS evoked by PP stimulation 200 ms after the last pulse of the stimulus train with that of an unconditioned PP response (Fig. 4*D*). We found that in the juvenile animal inhibition of the conditioned PP-evoked PS was significantly increased by LY341495 (Fig. 4*E*). In contrast,

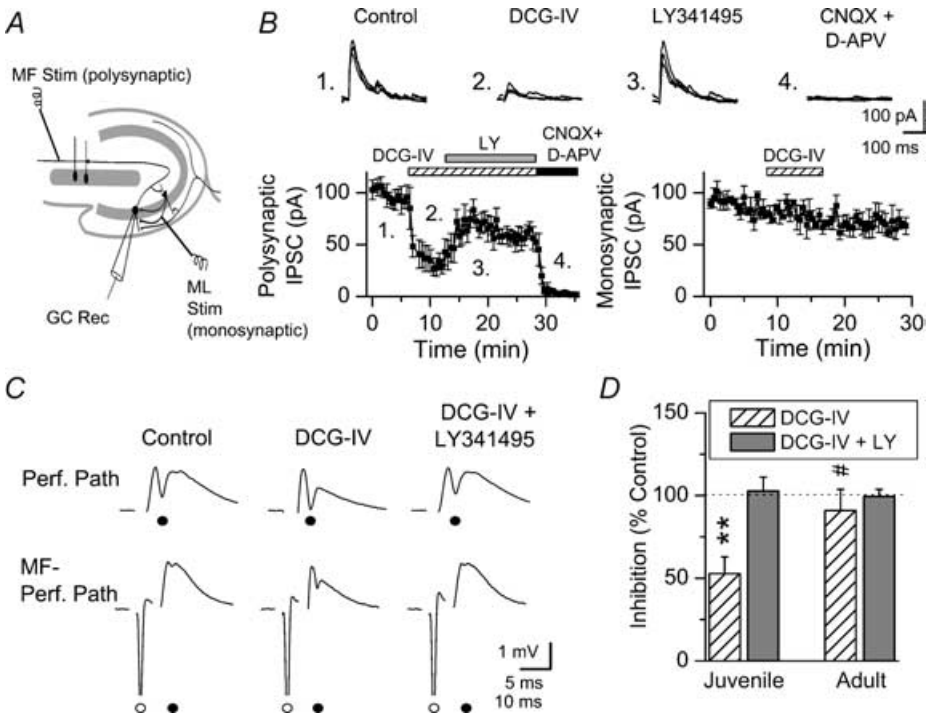

Figure 3. DCG-IV depresses feedback inhibition of dentate granule cells
A, schematic diagram indicating the positions of the stimulating and recording electrodes. *B,* averaged time course of depression of MF-evoked polysynaptic IPSCs by DCG-IV and reversal of this depression by LY341495 (LY). IPSCs were subsequently blocked by CNQX and D-APV, indicating that they were polysynaptic (lower left; $n = 5$). IPSCs from a sample experiment are shown (top). DCG-IV did not depress the monosynaptic IPSC (lower right; $n = 3$). *C,* in a juvenile animal the perforant path-evoked PS (●; upper left) was inhibited when preceded by a MF stimulus (10 ms interval; lower left). DCG-IV (300 nM) reduced inhibition of the PP-evoked PS (bottom centre), but had no effect on the antidromic PS (○). LY341495 (bottom right) antagonized the effect of DCG-IV. Stimulus artifacts have been removed for clarity. *D,* averaged data ($n = 6$) demonstrate that in the juvenile 300 nM DCG-IV produced a significant reduction in feedback inhibition that was reversed by LY341495. DCG-IV (300 nM) produced significantly less inhibition in the adult ($n = 4$).

LY341495 did not increase feedback inhibition in the adult animal, a significant difference from the juvenile. Subsequent application of bicuculline and D-APV completely blocked all inhibition in this circuit in both adult and juvenile animals. These results indicate that by regulating excitation of interneurones, group II mGluRs modulate feedback inhibition in the dentate gyrus of juvenile animals and that this regulation is dramatically reduced in adulthood.

Discussion

Our results indicate that group II mGluR-mediated presynaptic depression of transmitter release at MF inputs to hilar border interneurones declines during development. In addition, synaptic activation of group II mGluRs by a train of MF input depresses feedback inhibition of dentate granule cells by suppressing transmission between granule cells and interneurones. Thus, group II mGluR-mediated suppression of excitatory drive onto hilar border interneurones is an effective and developmentally regulated mechanism for modulating feedback inhibition in the dentate circuit.

Since most, if not all, hilar border interneurones are GABAergic and project onto granule cells (Freund & Busáki, 1996), mGluR-mediated STD of MF synapses onto interneurones in the juvenile animal has the potential to be disinhibitory when granule cells fire at sufficiently high rates of discharge. Our results predict that depression of excitatory input to interneurones transiently reduces GABAergic control of granule cells, resulting in greater excitation of CA3 pyramidal cells and CA3 interneurones in juvenile, but not adult animals. Because individual hilar border interneurones make inhibitory synapses on large numbers of granule cells (Halasy & Somogyi, 1993; Han *et al.* 1993), dynamic regulation of interneurone excitability by group II mGluRs in juvenile animals can be expected to have disproportionately large consequences for network function.

Although dentate granule cells *in vivo* typically fire at frequencies less than 0.5 Hz (Jung & McNaughten, 1993), during hippocampal sharp waves they can burst fire at higher frequencies (> 10 Hz; Penttonen *et al.* 1997). Feedback inhibition in dentate circuitry of juvenile animals should be very sensitive to sharp wave activation, since MF inputs to hilar border interneurones undergo short-term

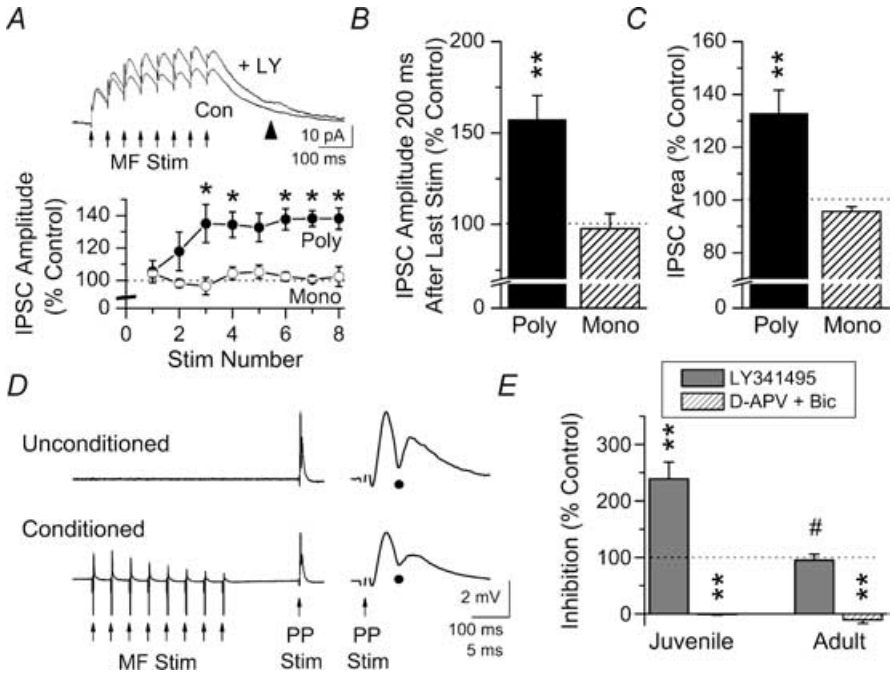

Figure 4. LY341495 enhances summation of polysynaptic IPSCs in dentate granule cells
A, sample traces showing the effect of LY341495 on summation of polysynaptic IPSCs (top). Averaged amplitude of each polysynaptic ($n = 5$) or monosynaptic IPSC ($n = 3$) during a 20 Hz stimulus train in LY341495 expressed as a percentage of the corresponding IPSC of the train in control (bottom). *B,* effect of LY341495 on polysynaptic or monosynaptic IPSC amplitude measured 200 ms after the last stimulus of the train (arrowhead in panel *A* top). IPSC amplitude was measured from the monoexponential fit of the IPSC decay (dark lines in panel *A* top). *C,* effect of LY341495 on the polysynaptic or monosynaptic IPSC area. *D,* in LY341495 the PP-evoked PS (●; top, expanded on right) was inhibited by a MF conditioning train (20 Hz, 8 pulses) delivered 200 ms earlier (bottom). The amplitude of the positive wave following the antidromic spike declines during the stimulus train, suggesting a progressive reduction in the spike AHP. *E,* averaged data show that in juvenile, but not adult animals LY341495 caused a significant increase in inhibition of the PP-evoked PS following the MF conditioning train ($n = 8$). Inhibition was blocked by addition of bicuculline and D-APV ($n = 3$). Dotted line represents the percent inhibition in control.

depression at frequencies similar to sharp wave input. High frequency granule cell discharges can also precede seizures in experimental models of chronic epilepsy (Bragin *et al.* 1999; Finnerty & Jefferys, 2000), suggesting that STD of MF inputs to interneurones may contribute to seizure induction in the juvenile hippocampus. Interestingly, group II mGluR-mediated STD of MF inputs to interneurones is selectively enhanced in the adult dentate during epileptogenesis (Doherty & Dingledine, 2001), adding further weight to the hypothesis that group II mGluR-mediated changes in interneurone excitation can contribute to the epileptic state.

References

Bragin A, Engel J Jr, Wilson CL, Fried I & Mathern GW (1999). Hippocampal and entorhinal cortex high-frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. *Epilepsia* **40**, 127–137.

Cobb SR, Buhl EH, Halasy K, Paulsen O & Somogyi P (1995). Synchronization of neuroneal activity in hippocampus by individual GABAergic interneurones. *Nature* **378**, 75–78.

Conn PJ (2003). Physiological roles and therapeutic potential of metabotropic glutamate receptors. *Ann N Y Acad Sci* **1003**, 12–21.

Conn PJ & Pin J-P (1997). Pharmacology and functions of metabotropic glutamate receptors. *Ann Rev Pharmacol Toxicol* **37**, 205–237.

Dobrunz LE & Stevens CF (1997). Heterogeneity of release probability, facilitation, and depletion at central synapses. *Neurone* **18**, 995–1008.

Doherty J & Dingledine R (1998). Differential regulation of excitatory synaptic inputs to hilar border interneurones in the dentate gyrus by metabotropic glutamate receptors. *J Neurophysiol* **79**, 2903–2910.

Doherty J & Dingledine R (2001). Reduced excitatory drive onto interneurones in the dentate gyrus after status epilepticus. *J Neurosci* **21**, 2048–2057.

Finnerty GT & Jefferys JGR (2000). 9–16 Hz oscillation precedes secondary generalization of seizures in the rat tetanus toxin model of epilepsy. *J Neurophysiol* **83**, 2217–2226.

Freund TF & Busáki G (1996). Interneurones of the hippocampus. *Hippocampus* **6**, 347–470.

Halasy K & Somogyi P (1993). Distribution of GABAergic synapses and their target in the dentate gyrus of rat: a quantitative immunoelectron microscopic analysis. *J Hirnforsch* **34**, 299–308.

Han Z-S, Buhl E, Lorinczi Z & Somogyi P (1993). A high degree of spatial selectivity in the axonal and dendritic domains of physiologically identified local-circuit neurones in the dentate gyrus of the rat hippocampus. *Eur J Neurosci* **5**, 395–410.

Jung MW & McNaughten BL (1993). Spatial selectivity of unit activity in the hippocampal granule cell layer. *Hippocampus* **3**, 165–182.

Kilbride J, Huang L-Q, Rowan MJ & Anwyl R (1998). Presynaptic inhibitory action of the group II metabotropic glutamate receptor agonists, LY354740 and DCG-IV. *Eur J Pharmacol* **356**, 149–157.

Kingston AE, Ornstein PL, Wright RA, Johnson BG, Mayne NG, Burnett JP, Belagaje R, Wu S & Schoepp DD (1998). LY341495 is a nanomolar potent and selective antagonist of group II metabotropic glutamate receptors. *Neuropharmacol* **37**, 1–12.

Miles R, Tóth K, Gulyás AI, Hajos N & Freund T (1996). Differences between somatic and dendritic inhibition in the hippocampus. *Neurone* **16**, 815–823.

Mott DD, Turner DA, Okazaki MM & Lewis DV (1997). Interneurones of the dentate-hilus border of the rat dentate gyrus: morphological and electrophysiological heterogeneity. *J Neurosci* **17**, 3990–4005.

Mott DD, Xie CW, Wilson WA, Swartzwelder HS & Lewis DV (1993). $GABA_B$ autoreceptors mediate frequency-dependent disinhibition and enhance signal transmission in the dentate gyrus. *J Neurophysiol* **69**, 674–691.

Penttonen M, Kamondi A, Sik A, Acsády L & Buzsáki G (1997). Feed-forward and feed-back activation of the dentate gyrus in vivo during dentate spikes and sharp wave bursts. *Hippocampus* **7**, 437–450.

Shimizu H, Crevelling CR & Daly JW (1969). A radioisotopic method for measuring the formation of adenosine 3′,5′-cyclic monophosphate in incubated slices in brain. *J Neurochem* **16**, 1609–1619.

Sik A, Ylinen A, Penttonen M & Buzsáki G (1994). Inhibitory CA1-CA3-hilar region feedback in the hippocampus. *Science* **265**, 1722–1724.

Acknowledgements

This work was supported by the Epilepsy Foundation (J.D., D.D.M), the Culpeper Foundation (J.D), NARSAD (D.D.M), and the NINDS (D.D.M., R.D., P.J.C., S.A).

Authors' present addresses

J. J. Doherty: AstraZeneca Pharmaceuticals, CNS Discovery, 1800 Concord Pike, Wilmington, DE 19803, USA.

S. Alagarsamy: Ferring Research Institute, Inc., Room 442, Building 23550, General Atomics Court, San Diego, CA 92121, USA.

P. J. Conn: Vanderbilt University, Department of Pharmacology, 23rd Avenue South Pierce, 452-B Preston Research Building, Nashville, TN 37232-6600, USA.