Developmental Decrease in Short-Term Facilitation at Schaffer Collateral Synapses in Hippocampus Is mGluR1 Sensitive

Haley E. Speed and Lynn E. Dobrunz

Department of Neurobiology, Civitan International Research Center, and Evelyn F. McKnight Brain Institute; University of Alabama, Birmingham, Alabama

Submitted 5 June 2007; accepted in final form 19 November 2007

Speed HE, Dobrunz LE. Developmental decrease in short-term facilitation at Schaffer collateral synapses in hippocampus is mGluR1 sensitive. J Neurophysiol 99: 799–813, 2008. First published November 21, 2007; doi:10.1152/jn.00625.2007. Developmental changes can occur in the dynamic properties of synapses, known as short-term plasticity. Using rat acute hippocampal slices at room temperature, we have previously shown a decrease in short-term facilitation at Schaffer collateral synapses from young adults compared with juveniles in response to temporally complex natural stimulus patterns such as synapses receive in vivo. Here we show that this developmental decrease in facilitation is also seen at 32°C and investigate the underlying mechanism. Addition of the mGluR1 antagonist LY367385 increases short-term facilitation in response to the natural stimulus pattern, showing that mGluR1 is activated by synaptically released glutamate. Although synaptic activation of mGluR1 occurs at both ages, the effect is larger in young adults. Furthermore, blocking mGluR1 eliminates most of the developmental decrease in short-term facilitation during the natural stimulus pattern. We investigated possible retrograde/downstream messengers involved after synaptic activation of mGluR1. Blocking cannabinoid receptors has no effect on the response during the natural stimulus pattern, indicating that the reduction in facilitation during synaptic activation of mGluR1 does not occur through release of endocannabinoids. We find that blocking GABA_B receptors increases facilitation during the natural stimulus pattern and occludes the effect of the mGluR1 antagonist, indicating a role for the modulation of GABA release from inhibitory interneurons by mGluR1 activation. These data suggest a model where synaptic activation of mGluR1 on inhibitory interneurons causes an increase in GABA release by inhibitory interneurons, which activates GABA_B receptors on Schaffer collateral synapses and inhibits short-term facilitation during the natural stimulus pattern.

INTRODUCTION

The strength and dynamics of synapses are both important for the proper activity-dependent remodeling of neuronal circuits that occurs during early postnatal development (reviewed in Goodman and Shatz 1993). In hippocampus, a part of the brain critical for learning and memory (Bliss and Collingridge 1999), excitatory synapses undergo extensive developmental changes as juveniles mature into young adults. For Schaffer collateral synapses from CA3 pyramidal cells onto CA1 pyramidal cells in rodents, this occurs between postnatal weeks 2 and 5. There is a large increase in the strength of synaptic transmission (Dumas and Foster 1995) caused in part by an increase in the density of Schaffer collateral synapses (Harris et al. 1992). Developmental changes can also occur in synaptic short-term plasticity, which governs the dynamic properties of synapses. This activity-dependent modulation of neurotransmitter release occurs on time scales of milliseconds to tens of seconds and causes the strength of synaptic transmission to depend on the recent history of use (reviewed in Zucker and Regehr 2002). At Schaffer collateral synapses, several studies have reported a decrease in a simple form of short-term plasticity, paired-pulse facilitation in slices from young adults compared with juveniles (Dekay et al. 2006; Dumas and Foster 1995, 1998b). In addition, our lab has shown a decrease in short-term depression in response to constant high-frequency trains in young adults versus juveniles (Dekay et al. 2006). Changes therefore occur in both the strength and dynamics of Schaffer collateral synapses during early postnatal development.

Although short-term plasticity is most commonly studied using simple stimuli such as pairs of pulses or constant frequency trains, synapses in vivo instead receive temporally complex inputs that are highly variable in their timing and contain a mixture of frequencies (Fenton and Muller 1998). Previous studies have shown that synaptic strength varies over a wide dynamic range in response to stimulus patterns taken from in vivo recordings of action potential timing from hippocampal place cells (Dekay et al. 2006; Dobrunz and Stevens 1999). These patterns are temporally complex, consisting of bursts of stimuli with short interstimulus intervals separated by long intervals with little or no activity (Fenton and Muller 1998) and have been referred to as natural stimulus patterns to reflect their physiological origin (Dobrunz and Stevens 1999).

Using these natural stimulus patterns, our lab has previously investigated developmental differences in short-term plasticity at Schaffer collateral synapses between juveniles and young adults (Dekay et al. 2006). We found that the pattern of responses of Schaffer collateral synapses varied over a wide dynamic range in response to these temporally complex stimuli but was very reproducible from trial to trial for synapses at both ages (juveniles and young adults). In addition, we found that the responses were highly correlated for different stimulation pathways within the same slice, for responses in different slices from the same animal and for slices from animals of similar age. Finally, we found a developmental decrease in the amount of short-term facilitation in response to the natural stimulus pattern in slices from young adult rats versus juveniles. This appeared to shift the balance from predominantly short-term facilitation in juveniles to short-term depression in...
young adults. The mechanisms for these developmental differences in short-term plasticity are not yet known. One possibility is a developmental difference in the activity of an endogenous neuromodulator.

Schaffer collateral synapses have receptors for several neuromodulators that can regulate presynaptic function and the effects of which in response to exogenous agonists vary with age during postnatal development (e.g., Dumas and Foster 1997, 1998a,b). This includes group I metabotropic glutamate receptors, which consist of the mGluR1 and mGluR5 subtypes. Bath application of a general group I mGluR agonist inhibits synaptic transmission at Schaffer collateral synapses (Gereau and Conn 1995; Manzoni and Bockaert 1995), an effect that is larger in young adults versus juveniles (Dumas and Foster 1997; Nosyreva and Huber 2005). This effect is due to mGluR1 and not mGluR5 (Gereau and Conn 1995). Together, these pharmacological studies suggest a developmental increase in the capacity of mGluR1s to regulate synaptic transmission at Schaffer collateral synapses. However, a role for endogenous synaptically released glutamate in activating mGluR1s and regulating short-term plasticity at Schaffer collateral synapses has yet to be demonstrated. Because metabotropic glutamate receptors are more likely to be activated by glutamate released during bursts of stimuli (Kew et al. 2001), the temporally complex natural stimulus pattern is a useful tool for testing whether synaptically released glutamate can activate mGluR1s and regulate short-term plasticity.

Here we investigate the mechanism for the developmental decrease in facilitation by testing for a role of mGluR1 activation in short-term plasticity in response to the natural stimulus pattern. We find that addition of the mGluR1 antagonist LY367385 increases the amount of short-term facilitation in response to the natural stimulus pattern. This shows that during the natural stimulus pattern, mGluR1s are being activated by synaptically released glutamate and that their normal effect is to reduce short-term facilitation. Although synaptic activation of mGluR1s occurs at both ages, the effect is larger in slices from young adults. Furthermore, we find that blocking this mechanism eliminates most of the developmental decrease in short-term facilitation in response to the natural stimulus in young adults versus juveniles. These results show that a developmental difference in the synaptic activation of mGluR1 is an important mechanism underlying the age-dependent differences in short-term plasticity between Schaffer collateral synapses in juveniles and young adults. Finally, we investigate downstream messengers that might mediate the mGluR1 effect. Although blocking cannabinoid receptors has no effect, we find that blocking GABA<sub>B</sub> receptors mimics and also occludes the effect of blocking mGluR1 receptors. These data suggest a role for the modulation of GABA release from inhibitory interneurons by mGluR1 activation in reducing short-term plasticity at Schaffer collateral synapses.

**METHODS**

**Hippocampal slices**

Transverse hippocampal slices were prepared from Long Evans rats as previously described (Dobrunz and Stevens 1997, 1999). Animal care and handling were carried out according to approved institutional guidelines (University of Alabama at Birmingham). Rats were postnatal days 13–18 (juveniles) or 28–42 (young adults). Briefly, 400-μm hippocampal slices were prepared using a Leica VT1000s vibrating microtome while immersed in ice-cold dissection solution composed of (in mM) 120 NaCl, 3.5 KCl, 0.7 CaCl<sub>2</sub>, 4.0 MgCl<sub>2</sub>, 1.25 NaH<sub>2</sub>PO<sub>4</sub>, 26 NaHCO<sub>3</sub>, and 10 glucose. The CA3 region was surgically removed at the time of dissection to prevent recurrent excitation. Slices were stored submerged in room temperature (~25°C) dissection solution (composition described above), which was bubbled with 95% O<sub>2</sub>-5% CO<sub>2</sub>. Slices were stored in the holding chamber for >1.5 h prior to recording.

**Extracellular field recordings**

Experiments were performed in a submersion recording chamber. Slices were perfused with extracellular solution composed of (in mM) 120 NaCl, 3.5 KCl, 2.5 CaCl<sub>2</sub>, 1.3 MgCl<sub>2</sub>, 1.25 NaH<sub>2</sub>PO<sub>4</sub>, 26 NaHCO<sub>3</sub>, and 10 glucose. The solution was bubbled with 95% O<sub>2</sub>-5% CO<sub>2</sub> and the pH was adjusted to 7.35 using NaHCO<sub>3</sub>. Picrotoxin (100 μM) was added to block fast inhibitory responses. The solution also contained 100 μM (±)-2-amino-5-phosphono-pentanoic acid (d,L-APV) to block N-methyl-D-aspartate (NMDA) receptors and prevent possible NMDA-receptor-dependent long-term plasticity. Recordings were done at 32.0–32.5°C (near physiological temperature) or 24.5–25.0°C (room temperature). Slices were warmed to 32°C over a period of 30 min by raising the temperature of the superfusion solution. Blocking NMDA receptors also blocks possible activity-dependent changes in axon firing threshold that can occur at the cooler recording temperatures (McNaughton et al. 1994).

Extracellular field potentials were elicited with 100-μs duration pulses via a nickel dichromate bipolar electrode placed in the stratum radiatum. Dendritic field excitatory postsynaptic potentials (fEPSPs) were recorded using glass micropipettes (2–4 MΩ) filled with extracellular solution (described in the preceding text). In each experiment, the stimulus amplitude and duration were held constant. Stimulus intensity was set at 45–50% of the threshold for observing populations spikes at the recording electrode.

The slope of the initial linear part of the fEPSP was used as a measure of the synaptic response. Stimulation was applied as either pairs of pulses (30- to 500-ms intervals, 20 repetitions per interval) at 0.1 Hz or as natural stimulus patterns as described in the following text.

**Natural stimulus patterns**

The methods for the natural stimulus pattern experiments are described in Dekay et al. (2006) and Dobrunz and Stevens (1999). The stimulus patterns referred to as natural stimulus patterns were derived from the timing of action potentials recorded in vivo from hippocampal place cells of awake, freely moving rats, which were generously provided by Dr. Robert Muller (see Fenton and Muller 1998 for details of the recording methods). The stimulus consisted of 128 points from the natural stimulus pattern separated by sections of 32 points at a slow constant frequency (0.1 Hz) for normalization. The timing of the pattern (excluding the constant frequency period) is illustrated in Fig. 4A. Example traces (fEPSPs vs. time) are shown in Figs. 2A and 4A. For each slice and experimental condition (e.g., control, drug), the same pattern was presented four to seven times, and the responses for each point in the pattern were averaged across the repetitions. The responses were then normalized to the average response size measured at 0.1 Hz to control for differences in the number of synapses stimulated and/or initial response size and thus provide a measure of short-term plasticity. The result is called the normalized fEPSP. Normalized fEPSPs are plotted versus stimulus number, rather than time, because the stimuli come in clusters separated by long intervals. Examples from individual slices are shown in Fig. 5A (mean ± SE, 5 repetitions of the pattern). Mean values for each point from individual slices are averaged to obtain group data, which are shown mean ± SE, with n numbers indicating numbers of
slices. Mean normalized fEPSP values are the average of the 128 point natural stimulus pattern and do not include the 32 point constant frequency stimulus.

Analysis

All data are presented as means ± SE. Except where noted, statistical comparisons were made using the Student’s t-test. In Fig. 1, two-way ANOVA followed by Tukey’s post hoc analysis was used to show that there are effects of both temperature and age on the paired pulse ratio. In Fig. 4B, each burst was analyzed by one-way ANOVA followed by Tukey’s post hoc analysis to demonstrate an effect of age on the amount of short-term facilitation and to determine the stimulus within the burst where the difference between juvenile and young adult responses first became statistically significant. For all statistical tests, differences are considered significant when \( P < 0.05 \).

Chemicals

APV, picrotoxin, LY367385, AM251, and CGP55845 were obtained from Tocris Cookson. SR141716 was obtained from the National Institute of Mental Health’s Chemical Synthesis and Drug Supply Program. All other chemicals were from Fisher Scientific or from Sigma.

RESULTS

All experiments use acute hippocampal slices from juvenile (P13—P18) compared with young adult (P28—42) rats. fEPSPs from Schaffer collateral synapses are recorded in response to extracellular stimulation with both stimulating and recording electrodes located in stratum radiatum of area CA1. Short-term plasticity is recorded in response to either paired-pulse stimulation at different intervals or the temporally complex natural stimulus pattern. The GABA\(_A\) receptor antagonist picrotoxin is included to block fast inhibitory synaptic transmission and NMDA receptors are blocked with APV to prevent long-term plasticity.

Developmental decrease in paired-pulse facilitation at Schaffer collateral synapses persists at 32°C

We have previously demonstrated a developmental decrease in short-term facilitation between young adults and juveniles at Schaffer collateral synapses recorded at room temperature (Dekay et al. 2006). Because short-term plasticity at CA3-CA1 synapses is temperature-dependent (Klyachko and Stevens 2006), we first tested whether the developmental decrease in facilitation is also seen at 32°C using the paired-pulse protocol as previously described (Dekay et al. 2006). Figure 1A shows that there are effects of both temperature and age on the paired pulse ratio (fEPSP slope 2/slope1) versus interstimulus interval (30–500 ms) from juveniles (Fig. 1A1) and young adults (A2) at 25°C (■) and 32°C (○). Paired-pulse facilitation is larger at 32°C compared with 25°C in slices from both ages ( \( P < 0.05 \) ), although the magnitude of the difference (averaged across the intervals) is greater in juveniles than young adults (32°C/25°C = 115.5 ± 1.8% in juveniles, \( n = 7 \); 108.9 ± 2.8%, in young adults, \( n = 6 \), \( P < 0.05 \)). Furthermore, the developmental decrease in paired-pulse facilitation that occurs at 25°C (Fig. 1B1, \( P < 0.05 \)) is also seen at 32°C (B2, \( P < 0.05 \)). In fact, the decrease in paired pulse ratio in young adults (averaged across the intervals) is slightly greater at 32°C (young adult/juvenile = 84.8 ± 2.1% at 32°C vs. 90.0 ± 2.9% at 25°C, \( P < 0.05 \)). These data show that although both juveniles and young adults have slightly greater paired-pulse facilitation at 32°C compared with 25°C, the developmental decrease in paired-pulse facilitation occurs at both temperatures.

![Fig. 1](https://example.com/fig1.png)

**FIG. 1.** Developmental decrease in paired pulse facilitation that is seen at 25°C also occurs at 32°C. The average paired-pulse ratio is larger at 32°C (○) than at 25°C (■) in slices from (A1) juveniles and (A2) young adults across a range of interpulse intervals (30–500 ms). The average paired-pulse ratio is larger in juveniles compared with young adults at (B1) 25°C and (B2) 32°C (juvenile: 25°C, \( n = 6 \) and 32°C, \( n = 7 \); young adult: 25°C, \( n = 6 \) and 32°C, \( n = 7 \)). *Insets*: example traces of paired-pulse facilitation at 25°C (black) and 32°C (red) from a juvenile (P15, A1) and young adult (P30, A2); example traces from juvenile (black) and young adult (red) at 25°C (B1) and 32°C (B2). Each trace is the average of 20 repetitions at the 50 ms interval. Scale bars: 15 ms, A1: 0.20 mV 25°C, 0.13 mV 32°C; A2: 0.16 mV 25°C and 0.16 mV 32°C; B1: 0.2 mV juvenile, 0.16 mV young adult; B2: 0.08 mV juvenile, 0.16 mV young adult.
Warmer temperature causes an increase in facilitation in response to the natural stimulus pattern in both juveniles and young adults

We next tested the effects of recording at 32 versus 25°C on the responses to a temporally complex natural stimulus pattern derived from in vivo recording of action potential firing of hippocampal place cells (Dekay et al. 2006; Dobrunz and Stevens 1999). This pattern contains bursts of stimuli with variable interstimulus intervals separated by long periods with little or no activity (see Fig. 4A). Figure 2A shows that short-term facilitation is greater at 32°C (red ○) versus 25°C (■) in both juveniles (A1) and young adults (A2). Both of these graphs show the normalized fEPSP slope for a 128 point natural stimulus pattern followed by a 32-point low-frequency period (constant frequency stimulation at 0.1 Hz for normalization). Note that the responses are plotted as normalized fEPSP versus stimulus number, not time, for clarity. Figure 2B shows the cumulative frequency curves generated from the histograms of the natural stimulus pattern responses at each temperature for juveniles (B1) and young adults (B2). The rightward shift in the curves at 32°C reflects enhanced short-term facilitation and reduced short-term depression at both ages. At each age, the normalized response size averaged over the entire natural stimulus pattern is larger at 32°C compared with 25°C (Fig. 2C, P < 0.05). The enhancement in short-term facilitation at 32 versus 25°C is larger in the slices from young adults (11.0 ± 1.7%) than from juveniles (5.6 ± 1.4%, P < 0.05). The fact that the mean fEPSP is lower in young adults than in juveniles (Fig. 2C) is described in more detail in the following figure, Fig. 3.

Developmental decrease in short-term facilitation in response to natural stimulus pattern at Schaffer collateral synapses persists at 32°C

Figure 3 shows the comparison of the responses to the natural stimulus pattern of Schaffer collateral synapses in slices from juveniles versus young adults recorded at both room temperature (25°C) and at 32°C. Figure 3A shows the average normalized fEPSPs for each stimulus number of the pattern and that the normalized responses from young adults (○) are smaller than juveniles (■) at both 25°C (Fig. 3A1) and 32°C (A2). At 25°C, although the responses from juveniles are nearly all facilitated (>1), there is a clear decrease in the amount of facilitation in the responses from young adults, and some responses show short-term depression (<1). At 25°C, the results confirm our previously published results that there is a
A developmental decrease in short-term facilitation in response to the natural stimulus pattern (Dekay et al. 2006). The developmental decrease in short-term facilitation in response to the natural stimulus pattern is also seen at 32°C (Fig. 3A2). Although nearly all of the responses in the pattern are facilitated (>1) and very few are depressed (<1) for both ages, the responses from the juveniles (■) are larger than those for the young adults (○) for most points in the pattern.

The effect is clearly represented by the differences in the cumulative frequency curves of young adults versus juveniles at both 25°C (Fig. 3B1) and 32°C (B2). The leftward shift of the curve for young adults shows an overall decrease in the amount of short-term facilitation and an increase in short-term depression. This results in a decrease in the response size averaged across the whole pattern in young adults versus juveniles at both 25°C (Fig. 3C1, P < 0.05) and at 32°C (C2, P < 0.05). The magnitude of the decrease is similar at the two temperatures (young adult/juvenile = 82.4% at 25°C and 85.6% at 32°C). Together these data show that the developmental decrease in short-term facilitation occurs at both room temperature and at 32°C. The remainder of the experiments for this study were done at 32°C.

**Developmental decrease in short-term facilitation is more pronounced during the latter part of bursts within the natural stimulus pattern**

The natural stimulus pattern consists of clusters of stimuli with relatively short interstimulus intervals separated by long periods with little or no activity, as shown in Fig. 4A1. The timing of the stimuli is variable within each cluster as illustrated by the example traces shown from a juvenile in Fig. 4A2 and young adult in A3. Next we did a closer inspection of the developmental effects on the responses within the clusters of high-frequency stimulation. Figure 4B shows data from juveniles versus young adults (replotted from Fig. 3A) during six different bursts within the pattern; the stimuli in these bursts are indicated by dashed boxes in Fig. 4A. For this analysis, we defined a burst as a cluster of four or more stimuli where the interval preceding the first stimulus is >3 s [14.4 ± 11.0 (SD) s; range = 4.0–33.7 s]. A burst is considered over when the next interval is >10 s (25.3 ± 6.2 s; range = 19.3–33.7 s). In each case, the normalized fEPSP begins very near 1 and then increases as the burst progresses. After the rest period, the normalized fEPSP is again close to 1. In all six bursts, there is little or no difference between the juvenile (■) and young adult (○) responses at the beginning of the pattern, but clear differences emerge in the middle of the burst that persist until the end.

The stimulus within each burst where the difference between juvenile and young adult responses first becomes statistically significant is marked by a vertical line in Figs. 4B, I–6. This range from the 6th to 12th stimulus in the burst (mean ± SD = 9.0 ± 2.5). The time within the burst that this transition occurs ranges from 2.2 to 6.2 s [3.8 ± 1.7 (SD) s]. This indicates that the mechanism responsible for the developmental difference in short-term plasticity requires a fairly long train of stimuli and/or several seconds to become detectible. The differences between the beginning and end of the bursts are quantified in Fig. 4C. Figure 4C1 shows the cumulative frequency curves from the responses at the beginning of the bursts.
apses has been shown to inhibit synaptic transmission through facilitation during natural stimulus pattern. Synaptic activation of mGluR1 receptors reduces short-term evoked neuromodulator. This suggests the possible involvement of an action potential in short-term facilitation between juveniles and young adults. 

Length of the burst stimulation required to elicit the difference seen at the beginning of each burst. Furthermore, the difference observed within the natural stimulus pattern with little increase in short-term facilitation is evident only in the latter part (C1, n = 6) during the latter phase of bursts than in the early phase. The cumulative frequency distribution shows a large shift toward less facilitated responses in young adults compared with juveniles in the latter phase of the bursts (C2) but not in the early phase of the bursts (CI, n = 6 juvenile; n = 6 young adult).

The developmental decrease in short-term facilitation is more pronounced during the latter part of bursts within the natural stimulus pattern at 32°C. (prior to point marked with a vertical line) pooled from all six burst are not different between juveniles and young adults, while the cumulative frequency curves from the end of the bursts (point from vertical line to the end of the burst, pooled for all 6 bursts) show a large leftward shift for young adults (Fig. 4C2). This analysis shows that the developmental decrease in short-term facilitation is evident only in the latter part of each burst within the natural stimulus pattern with little difference seen at the beginning of each burst. Furthermore, the length of the burst stimulation required to elicit the difference in short-term facilitation between juveniles and young adults suggests the possible involvement of an action potential evoked neuromodulator.

Synaptic activation of mGluR1 receptors reduces short-term facilitation during natural stimulus pattern

Activation of mGluR1 receptors at Schaffer collateral synapses has been shown to inhibit synaptic transmission through presynaptic depression of glutamate release in addition to other postsynaptic effects (Mannaioni et al. 2001). This has been shown pharmacologically, suggesting a possible role for mGluR1 receptors as autoreceptors to modulate short-term plasticity. However, a role for mGluR1 activation by synaptically released endogenous glutamate in regulating short-term plasticity had not previously been demonstrated.

We investigated whether the mGluR1 subtype of metabotropic glutamate receptor plays a role in regulating short-term plasticity by testing whether blocking mGluR1 receptors causes changes in short-term plasticity during the natural stimulus pattern at 32°C. We first performed a control natural stimulus pattern in the presence of the antagonist. We then washed in the antagonist and repeated the stimulus pattern in the absence of drug, then washed in the mGluR1-specific antagonist LY367385 (10 μM) and repeated the natural stimulus pattern in the presence of the antagonist. Figure 5A shows individual examples from juveniles (Fig. 5A1) and young adults (A2) comparing the responses with (C) and without (■) LY367385. In slices from both ages, the
mGluR1 antagonist caused an increase in the amount of short-term facilitation during the natural stimulus pattern. The effect is relatively small in the slice from the juvenile, and larger in the slice from the young adult. Figure 5B shows average group data for juveniles (B1) and young adults (B2). This also shows that blocking mGluR1 receptors causes an increase in facilitation at both ages with a larger effect in young adults. These data show that synaptically released glutamate normally activates mGluR1 receptors during the natural stimulus pattern, which results in a reduction of short-term facilitation. The antagonist had no effect on the response during low frequency stimulation, indicating that the mGluR1 receptors were not tonically active (data not shown). Figure 5C shows that there is a rightward shift of the cumulative frequency curves in LY367385 for both juveniles (C1) and young adults (C2). Figure 5D shows that LY367385 causes an increase in the average response size of the pattern that is significant in both juveniles (D1) and young adults (D2), although the effect is larger in young adults (14.1 ± 2.6 vs. 6.1 ± 2.0%, P < 0.05).

Our prediction was that the effect of the mGluR1 antagonist would be greatest during the latter part of the bursts with less of an effect during the early parts of the bursts. We examined this in slices from young adults, where the effect of blocking mGluR1 receptors was largest. Figure 6A shows data for control (■) versus LY367385 (red ○) from young adults for six bursts (as in Fig. 4), with the control data from juveniles (blue ▲) shown for comparison, and error bars omitted for clarity. As predicted, the increase in facilitation due to blocking mGluR1 receptors is greatest at the end of the bursts and raises the response of the young adults closer to the response size of the juveniles. This is quantified in Fig. 6B, which shows the average response size in LY367385 (as a percent of the control) for the beginning of the burst versus the end of the burst (divided as in Fig. 4). Although the increase in the response in LY367385 is significant in both cases (P < 0.05), it is much larger at the end...
of the bursts ($P < 0.05$). This is consistent with the idea that multiple high-frequency stimuli are needed to activate mGluR1 receptors and depress synaptic transmission and that the effect accumulates during the bursts. Blocking cannabinoid receptors does not alter the response to the natural stimulus pattern

Developmental decrease in short-term facilitation at Schaffer collateral synapses due in part to activation of mGluR1 receptors

Because the effect of mGluR1 activation is largest in young adults, we next tested whether mGluR1 activation contributes to the developmental decrease in short-term facilitation seen in response to the natural stimulus pattern. Figure 7A compares the responses of juveniles (●) and young adults (○) to the natural stimulus pattern when mGluR1 receptors are blocked by LY367385. Although the responses of the juveniles are still more facilitated than the young adults, the magnitude of the difference is reduced as seen by a decrease in the amount of the leftward shift of the cumulative frequency curve (compare Fig. 7B with Fig. 2 Fig. 3B). Figure 7C shows that there is still a decrease in young adults versus juveniles in the average response size across the whole pattern when both populations are exposed to the mGluR1 antagonist LY367385, although it is reduced from a 14.4% decrease (in Fig. 3C2) to a 5.8% decrease with mGluR1 receptors blocked (Fig. 7C). This shows that blocking mGluR1 receptors reduces the developmental decrease in short-term facilitation in response to the natural stimulus pattern and therefore that synaptic activation of mGluR1 receptors is one mechanism that contributes to the developmental decrease in short-term facilitation.

Blocking cannabinoid receptors does not alter the response to the natural stimulus pattern

We next investigated possible mechanisms by which synaptic activation of mGluR1 causes a reduction in short-term facilitation at Schaffer collateral synapses. Because agonist studies have shown that the effect of mGluR1 activation occurs presynaptically at Schaffer collateral synapses (Faas et al. 2002; Gereau and Conn 1995; Mannaioni et al. 2001), yet immunohistochemical studies and electron microscopy show mGluR1 located postsynaptically and not presynaptically (Lujan et al. 1997; Shigemoto et al. 1997), we investigated possible retrograde or downstream messengers. For these experiments, we used slices from young adults, where the effect of synaptic mGluR1 activation was the largest, and recorded at 32°C.

One obvious candidate for a retrograde signal is an endocannabinoid because activation of postsynaptic group I mGluRs with exogenous agonist causes release of endocannabinoids (Ohno-Shosaku et al. 2002; Varma et al. 2001) that activate presynaptic cannabinoid receptors and inhibit gluta-
mGluR1s DECREASE SHORT-TERM FACILITATION AT SC SYNAPSES

SR141716 (1 nmol) reduces short-term facilitation in response to the natural stimulus pattern (Fig. 8, A). We therefore tested for a possible role for endocannabinoids as a retrograde signal during stimulation with the natural stimulus pattern by determining whether blocking cannabinoid receptors alters short-term plasticity. As in Fig. 5, we performed a control natural stimulus pattern, washed in the antagonist, and repeated the natural stimulus pattern in the presence of the drug. We found that blocking cannabinoid receptors with the specific CB1 receptor antagonist AM251 (1 μM) (Gatley et al. 1996; Youssef et al. 2007) had no effect on short-term plasticity during stimulation with the natural stimulus pattern (Fig. 8, A–C, n = 6). We confirmed this result by testing the effect of the cannabinoid antagonist SR141716 (1 μM) (Hoffman et al. 2003; Rinaldi-Carmona et al. 1994), which also had no effect (n = 6, data not shown). These results suggest that endocannabinoids do not serve as retrograde messengers underlying the effect of mGluR1 activation during stimulation with the natural stimulus pattern.

GABA_B receptors mediate the effects of mGluR1 activation on short-term plasticity

Immunohistochemical studies have shown that mGluR1 receptors are also located on inhibitory interneurons in hippocampus (Baude et al. 1993; Ferraguti et al. 2004; Lujan et al. 1996). Activation of mGluR1 receptors can increase the excitability of interneurons (Gee and Lacaille 2004; McBain et al. 1994) and enhance the release of the inhibitory neurotransmitter GABA (Huang et al. 2004). Because our experiments showing the effect of mGluR1 activation on short-term plasticity of Schaffer collateral synapses were done with ionotropic GABA_A receptors blocked, an effect of GABA would need to be mediated through the activation of G-protein-coupled GABA_B receptors. GABA_B receptors are located presynaptically at Schaffer collateral synapses onto pyramidal cells (Lopez-Bendito et al. 2004), and studies with bath applied agonists have shown that their activation inhibits glutamate release (Otmakhova and Lisman 2004). We next investigated a possible role for GABA_B receptors in short-term plasticity alterations due to synaptic activation of mGluR1 at Schaffer collateral synapses.

We first investigated the effect of blocking GABA_B receptors with the antagonist CGP55845 (10 μM) on short-term plasticity during the natural stimulus pattern. We applied a control natural stimulus pattern, washed in the GABA_B receptor antagonist, and then applied a natural stimulus pattern again in the presence of the antagonist. Figure 9A shows group results (n = 7) comparing the results with CGP55845 (○) and without (■). We find that blocking GABA_B receptors causes an increase in short-term facilitation during the natural stimulus pattern in slices from young adults at 32°C. This causes a rightward shift of the cumulative frequency curve (Fig. 9B, n = 7) and results in an increase in the average response amplitude during the whole pattern (Fig. 9C, n = 7, P < 0.05). These data show that GABA_B receptors are activated during stimulation with the natural stimulus pattern and normally function to decrease short-term facilitation of Schaffer collateral synapses...
onto pyramidal cells. We repeated the experiments in the absence of picrotoxin and found that the GABA_B antagonist CGP55845 increases short-term facilitation of Schaffer collateral synapses when GABA_A-mediated inhibition is intact (104.6 ± 2.1%, n = 6, P < 0.05, data not shown). Similarly, blocking mGluR1 receptors with LY367385 increases short-term facilitation in the absence of picrotoxin (107.0 ± 3.6%, n = 6, P < 0.05, data not shown), indicating that disinhibition of the slice is not required for these effects. Together these results show that activation of mGluR1 receptors by endogenously released glutamate and activation of GABA_B receptors by endogenously released GABA both occur during stimulation of Schaffer collateral synapses with the natural stimulus pattern.

This is consistent with the idea that GABA_B receptors are downstream of the effect of mGluR1 activation. However, activation of presynaptic GABA_B receptors at Schaffer collateral synapses onto CA1 pyramidal cells could also be modulating short-term plasticity during the natural stimulus pattern by a mechanism that is independent of the activation of mGluR1. We tested whether blocking GABA_B receptors prevents the increase in short-term facilitation normally seen when mGluR1 receptors are blocked. We applied a natural stimulus pattern in the presence of CGP55845, washed in LY367385, and repeated the natural stimulus pattern with CGP55845 plus LY367385. We find that there is no effect of blocking mGluR1 receptors on short-term plasticity if GABA_B receptors are already blocked (Fig. 9, D and E). Because blocking GABA_B receptors prevents the enhancement of short-term facilitation previously seen when blocking mGluR1 receptors, this suggests that the GABA_B receptors are downstream of the mGluR1 receptors that are activated during the natural stimulus pattern.

**DISCUSSION**

Developmental decrease in facilitation occurs at both room temperature and 32°C

Our previous study showing a developmental decrease in short-term facilitation (Dekay et al. 2006) was conducted at room temperature to help maintain the health of the slices during the prolonged recordings and enable comparison with other results from the literature. Some aspects of synaptic transmission are temperature dependent, including some forms of short-term plasticity (Klyachko and Stevens 2006; Kushmerick et al. 2004). The temperature of the recording may also affect the balance between different forms of short-term plasticity (Klyachko and Stevens 2006). However, it is not known whether there are differences between juveniles and young adults in the sensitivity to recording temperature. We therefore first revisited the question of developmental changes in short-term plasticity using recordings at 32°C.

We find that the developmental decrease in short-term facilitation at Schaffer collateral synapses in hippocampal slices from young adult rats versus juveniles that we previously observed at room temperature (Dekay et al. 2006) also occurs when recordings are done at 32°C. This is seen as both a developmental decrease in paired-pulse facilitation and as a developmental decrease in short-term facilitation in response to temporally complex stimuli derived from in vivo recordings. Short-term facilitation is slightly greater at 32 versus 25°C, which is in agreement with other reports of larger short-term facilitation at higher temperature (e.g., Klyachko and Stevens 2006; Sun and Dobrunz 2006). Because the effect occurs at both ages, recording at 32°C does not alter the basic finding of a developmental difference in short-term plasticity between juveniles and young adults. This is consistent with other results in the literature that show similar findings obtained between recordings done at room temperature and those done nearer to physiological temperature (e.g., Dietz and Murthy 2005; Sun and Dobrunz 2006). When comparing two different recording groups, such as juveniles and young adults, differences ob-
served at room temperature in synaptic processes such as short-term plasticity will also be found at warmer temperatures, unless the two groups are differentially sensitive to temperature.

**Temporally complex spike trains cause synaptic activation of mGluR1 that modifies short-term plasticity**

It has been known for many years that the pharmacological activation of mGluR1 receptors through bath applied agonists causes a decrease in synaptic transmission at Schaffer collateral synapses. The mechanism is presynaptic, caused by a decrease in the probability of glutamate release (Gereau and Conn 1995; Mannaieni et al. 2001), as a result of a reduction in presynaptic calcium influx (Faas et al. 2002). These experiments have uncovered an essential regulatory feature of Schaffer collateral synapses, which is the capability of mGluR1 receptors to act as autoreceptors in response to endogenous glutamate. However, the physiological role of these receptors was unclear. In particular, it was not known whether they could be activated during normal synaptic transmission or only during pathological conditions that lead to accumulation of high levels of extracellular glutamate. Ours are the first experiments showing that synaptically released glutamate can activate mGluR1 receptors and alter short-term facilitation at Schaffer collateral synapses during temporally complex trains, suggesting that it could happen in vivo during normal synaptic transmission and possibly play a role in information processing.

The effect of mGluR1 activation on short-term plasticity is seen during temporally complex spike trains derived from in vivo recordings but not in response to simple stimulus paradigms such as paired-pulse stimuli that are commonly used to study short-term plasticity. This illustrates the importance of using this type of stimulation to study synapses because it can reveal synaptic mechanisms that would otherwise go undetected. However, it is meant to be a way to investigate the effects of temporal complexity and irregular firing patterns on synaptic function rather than an exact duplication of in vivo stimulation because there are potentially an infinite number of different patterns that synapses might receive in vivo. Recordings of spiking patterns in vivo have shown large variability in the firing patterns between cells and even within the same cell during different repetitions of a behavioral task (e.g., Fenton and Muller 1998). What is consistently found is that the firing patterns are highly variable in their timing and that their spiking patterns do not resemble constant frequency stimulation. We have previously shown differences in short-term plasticity (Dekay et al. 2006), and another study found differences in the effects of presynaptic inhibition (Ohliger-Frerking et al. 2003) in response to temporally complex stimulus patterns versus constant frequency trains. Although no slice experiment can directly reproduce the stimulation that synapses receive in the intact animal, the use of temporally complex stimulus patterns taken from in vivo recordings is an important tool that has enabled investigation of the effects of irregular firing patterns on synaptic function.

In our experiments, a spiking pattern that was recorded from an individual hippocampal neuron in vivo is used to stimulate a population of Schaffer collateral axons in the slice. Future experiments will be needed to determine if synaptic activation of mGluR1s can occur during stimulation of single Schaffer collateral axons. However, because we are recording in slices with GABA_A receptors blocked, the stimulus intensity we use is low compared with typical extracellular stimulation done with inhibition intact, and therefore a relatively small number of afferents are being stimulated. Because groups of CA3 neurons in vivo fire synchronously (Buzsaki et al. 1983; Csicsvari et al. 2000), the synchronous stimulation of multiple Schaffer collateral axons with the same temporal pattern is likely to occur in vivo as well.

Metabotropic glutamate receptors could either be tonically activated by ambient levels of glutamate or transiently activated by synaptically released glutamate. Tonic activation of group II mGluRs has been shown at several different excitatory synapses in the brain, including excitatory synapses in neocortex (Bandrowski et al. 2003; Chen and Roper 2004) and the subthalamic nucleus (Wang et al. 2005), and excitatory synapses onto a subgroup of hippocampal inhibitory interneurons in stratum oriens/alveus (Losonczy et al. 2003). Tonic activation of mGluRs can cause a decrease in the initial release probability and an increase in short-term facilitation (Chen and Roper 2004). In contrast, we saw no effect of the mGluR1 antagonist on baseline response size during low-frequency stimulation in either young adults or juveniles, indicating that mGluR1s are not tonically active at Schaffer collateral synapses. Instead, our results show that synaptically released glutamate activates mGluR1 receptors and decreases glutamate release within bursts of high-frequency stimulation, resulting in decreased short-term facilitation. Activation of mGluRs by synaptically released glutamate during bursts therefore has the opposite effect on short-term facilitation than tonic activation by ambient glutamate. Because short-term facilitation is usually inversely related to the initial release probability of synapses (Dobrunz 2002; Dobrunz and Stevens 1997), presynaptic mechanisms usually result in changes in both synaptic efficacy and short-term plasticity. The decrease in short-term facilitation by synaptically released glutamate activating mGluR1 receptors during bursts of stimulation therefore provides a way of modulating short-term plasticity without changing the initial efficacy of synapses.

The effect of mGluR1 activation is largest during the later part of the bursts, suggesting that it takes multiple high-frequency stimuli and/or a certain amount of time to accumulate. This could reflect either the need for glutamate to accumulate and diffuse to presynaptic sites and activate the mGluR1 receptors, and/or the buildup of a second messenger in response to mGluR1 activation. The need for high-frequency burst stimulation to activate the mGluR1 receptors at Schaffer collateral synapses is comparable to what has been seen at perforant path synapses to dentate gyrus and CA1, where high-frequency burst stimulation causes synaptic activation of group II mGluRs that depress glutamate release (Kew et al. 2001). Similarly, high-frequency trains cause activation of group II mGluRs that depress transmission at thalamocortical synapses (Mateo and Porter 2007) and corticogeniculate synapses (Alexander and Godwin 2005). In contrast, synaptic activation of group II mGluRs causes a depression of glutamate release after only a single stimulus at mossy fiber synapses onto hilar border interneurons in hippocampus (Doherty et al. 2004). Further experiments will be needed to fully explore the range of frequencies and length of bursts needed to activate the...
mGluR1 receptors involved in regulating short-term plasticity at Schaffer collateral synapses.

Developmental decrease in short-term facilitation is due in part to mGluR1

Previous studies have shown that the expression of group I metabotropic glutamate receptors is developmentally regulated (reviewed in Ferraguti and Shigemoto 2006; Lujan et al. 2005). In hippocampus, levels of mGluR1 are low at birth and increase during postnatal development (Lopez-Bendito et al. 2002; Shigemoto et al. 1992). Pharmacological experiments have shown that the acute depression of synaptic transmission at Schaffer collateral synapses in response to bath application of a general group I mGluR agonist is larger in young adults versus juveniles (Dumas and Foster 1997; Nosyreva and Huber 2005). Because this effect is due to mGluR1 rather than mGluR5 (Gereau and Conn 1995), this suggests a developmental increase in mGluR1 function. Consistent with these results, we find a greater effect of mGluR1 activation by synaptically released glutamate in young adults versus juveniles in response to the temporally complex natural stimulus pattern as seen by the addition of the antagonist LY367385. Future experiments will be needed to determine whether the developmental increase in mGluR1 effects is caused by an increase in the density of mGluR1 receptors and/or a change in mGluR1 function. However, our results suggest that the developmental increase in mGluR1 activity enables greater modulation of short-term facilitation in young adults versus juveniles.

Developmental regulation of metabotropic glutamate receptors has been shown to contribute to changes in synaptic function at other synapses in the CNS. The tonic activation of group II mGluRs at synapses onto layer IV/V pyramidal cells in neocortex occurs in young adults but not in juveniles (Chen and Roper 2004). This results in a developmental decrease in the initial release probability and an increase in short-term facilitation in young adults versus juveniles (Chen and Roper 2004), which is the opposite of the developmental decrease in facilitation that we observe at Schaffer collateral synapses as a result of developmental changes in mGluR1. Metabotropic glutamate receptor function can also decrease during development. For example, group II modulation of excitatory synapses onto interneurons in dentate gyrus occurs in juveniles but not young adults (Doherty et al. 2004). Possible developmental changes in mGluR function still remain to be investigated at many synapses in the CNS as most studies are conducted using animals of only one developmental age.

Finally, our results show that blocking mGluR1 receptors with the subtype specific antagonist LY367385 significantly reduces the developmental decrease in short-term facilitation in response to the natural stimulus pattern. This indicates that developmental differences in the synaptic activation of mGluR1 receptors and their effects on short-term plasticity are one major mechanism contributing to the developmental decrease in short-term facilitation with the natural stimulus pattern. However, the difference between young adults and juveniles is not completely eliminated; a small developmental decrease in short-term facilitation persists even in the presence of LY367385. Although this could result from incomplete block of mGluR1 receptors during the bursts, it is more likely to reflect the existence of one or more additional mechanisms that also contribute to the developmental decrease in short-term facilitation. Possible mechanisms include activation of other mGluR subtypes or the release of other neuromodulators that alter presynaptic function and short-term plasticity. Because differences in short-term plasticity can also result from differences in the initial release probability of synapses (Dobrunz and Stevens 1997; Sun et al. 2005), there may also be a developmental increase in release probability that contributes to the reduced short-term facilitation in young adults. This could be caused by increases in the readily releasable vesicle size, the release probability per vesicle, or both (Dobrunz 2002). Future experiments will be needed to address these possibilities to determine the basis for the developmental difference in short-term facilitation that remains when mGluR1 receptors are blocked.

Location of mGluR1 receptors that reduce short-term facilitation at Schaffer collateral synapses

Electrophysiological studies have shown that the acute effect of activating mGluR1 with agonists occurs presynaptically at Schaffer collateral synapses onto CA1 pyramidal cells (Faas et al. 2002; Mannai et al. 2001). Calcium imaging studies have also demonstrated the presynaptic effect of mGluR1 activation, showing that it causes a reduction in calcium influx into Schaffer collateral terminals (Faas et al. 2002). However, mGluR1 receptors in hippocampus appear to be located postsynaptically, rather than presynaptically (reviewed in Ferraguti and Shigemoto 2006), and studies using immunohistochemistry and electron microscopy have not found evidence of presynaptic mGluR1 receptors located in Schaffer collateral axon terminals (Ferraguti et al. 1998; Shigemoto et al. 1997). The mGluR1 receptors may be located in the postsynaptic CA1 neurons, which express mRNA for mGluR1 (Berthele et al. 1998; Shigemoto et al. 1992). There are multiple splice variants of mGluR1 receptors, including mGluR1α, mGluR1β, and mGluR1d. The results of immunolocalization studies on the location of mGluR1 can vary depending on the particular antibody used and the splice variants it recognizes (Kosinski et al. 1998). Immunoreactivity for mGluR1β has been detected in CA3 pyramidal cells but not CA1 pyramidal cells (Ferraguti et al. 1998; Kosinski et al. 1998; Lujan et al. 1996), and mGluR1α is strongly expressed in inhibitory interneurons (Baude et al. 1993; Ferraguti et al. 2004; Hampson et al. 1994). It is also possible that some mGluR1αs are located presynaptically at Schaffer collateral synapses that have not yet been detected by immunohistochemistry. The location of the mGluR1 receptors that underlie the observed presynaptic effects at Schaffer collateral synapses onto CA1 pyramidal cells is still not clear.

If the mGluR1 receptors that reduce short-term facilitation are located on postsynaptic CA1 neurons, this implies that there must be a retrograde messenger to cause the presynaptic effects. One mechanism of action of group I mGluRs in hippocampus is through the production of endocannabinoids (Varma et al. 2001). Cannabinoid agonists inhibit synaptic transmission at Schaffer collateral synapses by reducing glutamate release (Misner and Sullivan 1999), and endocannabinoids released in response to postsynaptic activation of group I mGluRs can act as retrograde messengers to presynaptically inhibit transmission at Schaffer collateral synapses (Rouach
with baclofen (Luscher et al. 1997), we do not think they are facilitation. Synaptic activation of presynaptic GABAB receptors are located on Schaffer collateral axon terminals (Lopez-Bendito et al. 2004). Our results indicate that these GABAB receptors are activated by synaptic stimulation during the temporally complex natural stimulus pattern, resulting in a decrease in glutamate release and lower short-term facilitation. Synaptic activation of presynaptic GABAB receptors at Schaffer collateral synapses has previously been shown in response to short trains of high-frequency stimuli, which causes heterosynaptic depression of a second stimulus pathway (Isaacson et al. 1993). GABAB receptors are also located postsynaptically on CA1 pyramidal cells (Lopez-Bendito et al. 2004; Thompson and Gahwiler 1992), where they activate G-protein-coupled inwardly rectifying K⁺ currents (GIRKs) (Luscher et al. 1997). Because GIRKs do not play a role in the inhibition of glutamate release by GABAB receptor activation with baclofen (Luscher et al. 1997), we do not think they are involved in observed GABAB receptor effect on short-term facilitation.

We also find that blocking GABAB receptors does cause an increase in short-term facilitation during the natural stimulus pattern. Activation of GABAB receptors by application of the agonist baclofen has long been known to depress synaptic transmission at Schaffer collateral synapses onto pyramidal cells (Ault and Nadler 1982; Lanthorn and Cotman 1981; Wu and Saggu 1997). Presynaptic GABAB receptors decrease glutamate release by reducing calcium influx (Wu and Saggu 1995), and electron microscopy has demonstrated that GABAergic receptors are located on Schaffer collateral axon terminals (Lopez-Bendito et al. 2004). We also find that blocking GABAB receptors completely prevents the increase in short-term facilitation by the mGluR1 receptor antagonist. This indicates that GABA plays a role in the mGluR1 effect and that the GABAB receptors are downstream of the mGluR1 receptors, suggesting that the mGluR1 receptors involved are located on inhibitory interneurons. Immunohistochemical studies have found mGluR1 to be highly enriched on the soma and dendrites of somatostatin-containing inhibitory interneurons in hippocampus (Baude et al. 1993; Ferraguti et al. 2004; Hampson et al. 1994) as well as on other interneuron subtypes (Ferraguti et al. 2004). Activation of group I mGluRs increases the excitability of GABAergic interneurons, both in hippocampus (Mannaioni et al. 2001; Mori and Gerber 2002; Poncer et al. 1995; Yanovsky et al. 1997) and in other brain regions (Chu and Hablitz 1998; Zheng and Johnson 2003). This can cause an increase in the release of GABA (Chu and Hablitz 1998; Mannaioni et al. 2001; Mori and Gerber 2002), thus increasing inhibition of pyramidal cells. For example, in the CA3 region of hippocampus, a disynaptic inhibitory synaptic response in CA3 pyramidal cells caused by extracellular stimulation in stratum pyramidale is mediated by group I mGluRs on CA3 interneurons (Mori and Gerber 2002). In addition, activation of mGluR1 on a subset of interneurons in the s. oriens enhances the disynaptic inhibition of CA1 pyramidal cells (Huang et al. 2004). Our results suggest that stimulation of Schaffer collateral axons with the temporally complex natural stimulus pattern leads to activation of mGluR1s on interneurons, leading to increased GABA release, increased activation of GABAergic receptors, and a decrease in short-term facilitation at Schaffer collateral synapses onto pyramidal cells. Our results are unique in that we see the effects of mGluR1 activation of interneurons and enhanced GABA release acting through GABAergic receptors that inhibit glutamate release rather than through enhancement of disynaptic inhibitory synaptic responses via GABAergic receptors. The effect of presynaptic GABAergic receptors by activation with the GABAergic agonist baclofen has shown to be developmentally regulated at Schaffer collateral synapses with larger effects in young adults compared with juveniles (Dumas and Foster 1998a). A developmental increase in GABAB receptor expression and/or function may therefore contribute to or even cause the developmental increase in young adults in the effect of mGluR1 activation on short-term plasticity of Schaffer collateral synapses. Although future experiments will be needed to determine the respective contributions of these two receptors to the observed developmental decrease in short-term facilitation, our results reveal a novel mechanism for modulating short-term plasticity at Schaffer collateral synapses that depends on the activation of both mGluR1 and GABAB receptors by endogenously released neurotransmitter.

Conclusions

In summary, our results demonstrate that synthetically released glutamate can activate mGluR1 receptors during stimulation with temporally complex patterns, resulting in a decrease in short-term facilitation at Schaffer collateral synapses onto CA1 pyramidal cells. The effect is prevented by blocking GABAergic receptors, suggesting that the mGluR1 receptors involved are located on interneurons and cause enhanced GABA release and activation of presynaptic GABAergic receptors that reduce glutamate release from the Schaffer collateral axon terminals. This effect is small in juveniles and larger in young adults and contributes to the observed developmental decrease in short-term facilitation. A developmental increase in the activation of mGluR1 receptors and/or GABAergic receptors is therefore a mechanism to developmentally regulate the short-term dynamics of Schaffer collateral synapses onto CA1 pyramidal cells during high-frequency bursts of stimulation. This may be important for the activity-dependent remodeling of synaptic circuits that occurs as animals first begin to explore their environment.

Acknowledgments

We thank Dr. Smadar Lapidot for assistance in editing, Dr. Lori McMahon and Dr. Aundrea Bartley for helpful comments on this manuscript, and Dr. Sreelatha Meleth for help with statistical questions.

Grants

This work was supported by National Institutes of Health Grants P01 HD-38760 and R01 MH-65328 to L. E. Dobrunz and NIH Neuroscience Blueprint Core Grant NS-57098 to the University of Alabama at Birmingham.


Fenton AA, Muller RU. Place cell discharge is extremely variable during individual passes of the rat through the firing field. *Proc Natl Acad Sci USA* 95: 3182–3187, 1998.


Lujan R, Nusser Z, Roberts JD, Shigemoto R, Somogyi P. Perisynaptic localization of metabotropic glutamate receptor mGluR1 and mGluR5 on dendrites and dendritic spines in the rat hippocampus. *Eur J Neuroscience* 8: 1488–1500, 1996.


