

# GABA<sub>B</sub> Presynaptic Inhibition Has an In Vivo Time Constant Sufficiently Rapid to Allow Modulation at Theta Frequency

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**Molyneaux, Bradley J. and Michael E. Hasselmo.** GABA<sub>B</sub> presynaptic inhibition has an in vivo time constant sufficiently rapid to allow modulation at theta frequency. *J Neurophysiol* 87: 1196–1205, 2002; 10.1152/jn.00077.2001. Cyclical activity of GABAergic interneurons during theta rhythm could mediate phasic changes in strength of glutamatergic synaptic transmission in the hippocampal formation if presynaptic inhibition from activation of GABA<sub>B</sub> receptors is sufficiently rapid to change within a theta cycle. The experiments described here analyzed the time course of GABA<sub>B</sub> modulation using a heterosynaptic depression paradigm in anesthetized rats at physiological temperatures. Heterosynaptic depression of the slope of evoked potentials decayed with a time constant that would allow significant changes in transmission across different phases of the theta cycle. This heterosynaptic depression was significantly reduced by local infusion of the GABA<sub>B</sub> receptor antagonist CGP55845A.

## INTRODUCTION

Theta rhythm oscillations appear in the hippocampal electroencephalogram (EEG) during active exploration (Buzsaki et al. 1983; Chrobak and Buzsaki 1994; Fox et al. 1986; Green and Arduini 1954) and under urethane anesthesia (Fox et al. 1986). These oscillations are accompanied by cyclical changes in the slope of evoked excitatory synaptic potentials (Rao et al. 1998; Wyble et al. 1997, 2000) and population spike amplitude (Buzsaki et al. 1981; Rudell and Fox 1984; Rudell et al. 1980). These changes could result from rhythmic inhibition from the medial septum (Stewart and Fox 1990; Toth et al. 1997) causing phasic changes in interneuron activity during theta (Fox et al. 1986; Skaggs et al. 1996).

Phasic interneuron activity could cause cyclical changes in the magnitude of synaptic transmission. Data from slice preparations demonstrate that activation of presynaptic GABA<sub>B</sub> receptors inhibits glutamatergic transmission in stratum radiatum at synapses between pyramidal cells within the hippocampus (Ault and Nadler 1982; Colbert and Levy 1992; Vogt and Regehr 2001). In contrast, GABA<sub>B</sub> agonists do not inhibit transmission at perforant path synapses in s. lacunosum-moleculare, which bring afferent input from entorhinal cortex (Ault and Nadler 1982; Colbert and Levy 1992). The selective presynaptic inhibition of internal connections could allow new sensory input arriving via afferent fibers to dominate. This would provide effective dynamics for encoding of new information due to synaptic modification of synapses in s. radiatum,

without interference from previous memories due to synaptic transmission at previously modified synapses (Hasselmo et al. 2002; Sohal and Hasselmo 1998a,b; Wallenstein and Hasselmo 1997). Subsequently, rapid decay of this presynaptic inhibition could allow a dominant influence of intrinsic connections to mediate retrieval of previous information. Oscillations between encoding and retrieval dynamics within each cycle of the theta rhythm would require a time course of GABA<sub>B</sub> presynaptic inhibition sufficiently rapid to change within each theta cycle.

One method of measuring the time course of GABA<sub>B</sub> presynaptic inhibition of glutamatergic transmission is to analyze heterosynaptic depression (Isaacson et al. 1993). The putative mechanism for heterosynaptic depression is summarized in Fig. 1A. In this experimental phenomenon, strong “conditioning” stimulation of one synaptic input to a region causes spiking of local inhibitory interneurons which release GABA. The GABA diffuses to presynaptic receptors on glutamatergic terminals and suppresses excitatory synaptic potentials elicited by subsequent “test” stimulation through a different stimulating electrode (Dittman and Regehr 1997; Isaacson et al. 1993; Vogt and Nicoll 1999). The heterosynaptic depression elicited in these conditions is blocked by GABA<sub>B</sub> receptor antagonists, ruling out a role of other receptors. The heterosynaptic depression is accompanied by an increase in paired-pulse facilitation. The increase in paired-pulse facilitation is taken as evidence for presynaptic inhibition (Dittman and Regehr 1997; Valentino and Dingledine 1981; Zucker 1989) because postsynaptic inhibition should affect both potentials similarly, whereas a decrease in release of transmitter induced by the initial pulse should increase the available store for the second pulse.

Previous work has analyzed the time course of this effect in slice preparations with different delays between conditioning and test stimulation, showing a peak at about 300 ms and a return to baseline around 1.4 s in slice preparations of hippocampal region CA1 (Isaacson et al. 1993). A similar peak is seen in cerebellar slices (Dittman and Regehr 1997). Depression of inhibitory synaptic potentials by activation of presynaptic GABA<sub>B</sub> autoreceptors shows a similar time course in hippocampal slices (Otis et al. 1993). These time courses were obtained at nonphysiological temperatures (24 and 32°C in Dittman and Regehr 1997, 30–32°C in Isaacson et al. 1993), but the  $Q_{10}$  derived for this effect (Dittman and Regehr 1997)

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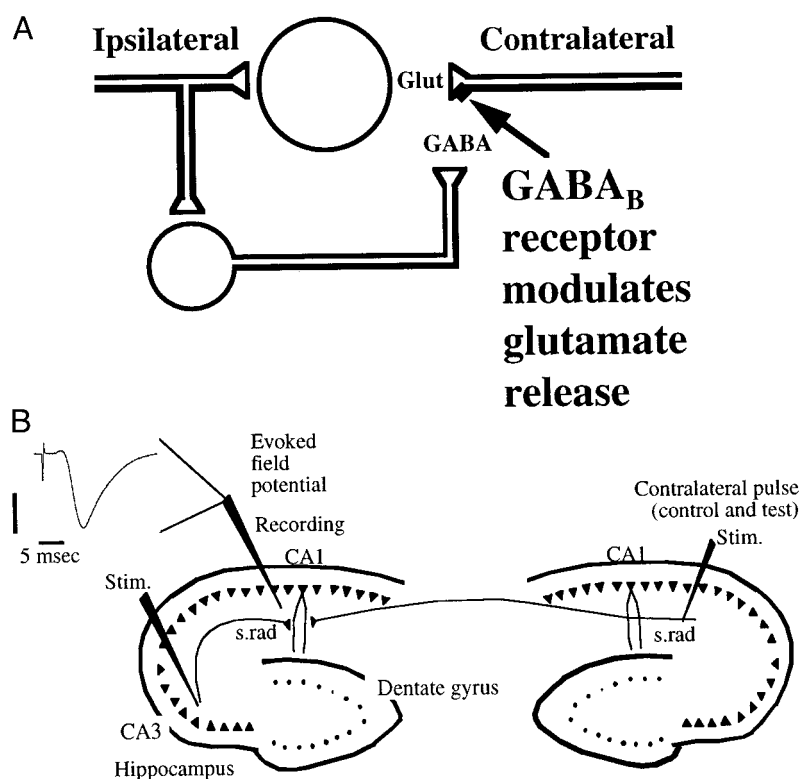


FIG. 1. *A*: schematic circuit illustrating the theoretical mechanism of heterosynaptic depression in physiological studies of hippocampal region CA1. The circle is a schematic representation of a region CA1 pyramidal cell receiving synaptic input from fibers activated with either ipsilateral stimulation (*left*) or contralateral stimulation (*right*). Ipsilateral stimulation causes activation of local inhibitory interneurons (represented schematically by small circle). These local interneurons release GABA, which activates presynaptic GABA<sub>B</sub> receptors on the terminals of fibers activated by contralateral stimulation. The activation of presynaptic GABA<sub>B</sub> receptors inhibits the release of glutamate from the terminals of fibers activated by contralateral stimulation, thereby decreasing the rising slope of these evoked potentials. (The heterosynaptic depression is independent of the excitatory synaptic potentials induced by the ipsilateral stimulation.) *B*: design of experiment. A recording electrode is positioned in s. radiatum of region CA1 on one side of the brain. An ipsilateral stimulating electrode is positioned in region CA3 of the same side, and a contralateral stimulating electrode is positioned in region CA3 of the opposite side. Evoked potentials elicited with contralateral stimulation are recorded, allowing comparison of the initial slope of evoked potentials before and after an ipsilateral stimulus pulse.

suggests that the time course at physiological temperatures might be much more rapid. Suppression of synaptic transmission has also been tested with rapid pulsed perfusion of baclofen (Pfrieger et al. 1994) or photolysis of caged compounds (Dittman and Regehr 1997). However, these experiments were also performed at nonphysiological temperatures.

To obtain a measurement of the time course of presynaptic GABA<sub>B</sub> receptor effects in normal physiological conditions, the time course of heterosynaptic depression was tested *in vivo* in anesthetized rats at physiological temperatures. This allowed measurement of the faster time course with natural receptor and second-messenger kinetics and functional GABA reuptake mechanisms.

## METHODS

To test heterosynaptic paired-pulse depression *in vivo*, two separate pathways into s. radiatum of hippocampal region CA1 were stimulated during extracellular recording of evoked synaptic potentials in this region, allowing recording of the excitatory synaptic transmission from these pathways as negative-going field potentials. The location of stimulation and recording electrodes is summarized in Fig. 1*B*. Release of GABA was elicited by a single pulse or a pair of pulses through a stimulating electrode in region CA3 ipsilateral to the recording electrode. Subsequently, two stimuli were presented through the contralateral stimulating electrode at intervals ranging between 30 and 1,500 ms after the last ipsilateral pulse. The magnitude of the initial negative slope of these stimuli was compared with baseline evoked potentials obtained with contralateral stimulation 10 s preceding the ipsilateral stimulation. Pairs of stimuli were used at the contralateral stimulation site to test for changes in the magnitude of paired-pulse facilitation. The relative timing of contralateral and ipsilateral stimulation pulses is summarized in Fig. 2.

## Surgery

Male Sprague-Dawley rats (325–500 g) obtained from Charles River (Wilmington, MA) were anesthetized with an intraperitoneal injection of urethan (1.5 g/kg), and anesthesia was maintained with additional injections of urethan as necessary. Body temperature was monitored with a rectal thermometer and maintained at 37°C (Lillie et al. 1996) with a heating pad. Rats were placed in a David Kopf stereotaxic frame, and holes were drilled into the skull using a David Kopf stereotaxic drill. The recording electrode and stimulation electrodes were guided stereotaxically through previously drilled holes in the skull according to coordinates from Paxinos and Watson (1986). The recording electrode was placed in the s. radiatum of region CA1

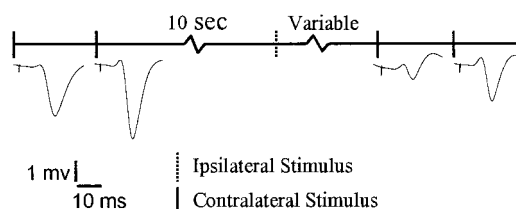


FIG. 2. Timing of synaptic stimulation during experiment. Each trial of the experiment consisted of the following stimulation. First, a pair of pulses (—) are delivered through the contralateral stimulation electrode. These are used to establish a baseline magnitude of evoked potential slope (examples of baseline evoked potentials are shown). This is followed by a 10-s delay to ensure the baseline does not play a role in heterosynaptic depression. Second, a single stimulus pulse (---) is delivered through the ipsilateral stimulation electrode to cause putative local release of GABA. This is followed by a variable delay of 30–1,500 ms. Third, a pair of pulses (—) are delivered through the contralateral stimulation electrode. These are used to measure the change in rising slope of evoked synaptic potentials caused by the previous ipsilateral stimulation. The evoked potentials shown directly beneath the timeline show examples of the evoked potentials elicited with each stimulus pulse. The potentials evoked by contralateral stimulation show strong heterosynaptic depression of rising slope in these potentials occurring at 40 ms after ipsilateral stimulation. The use of a pulse pair allows analysis of the change in magnitude of paired-pulse facilitation.

(−3.1 mm from Bregma, 2.0 mm lateral, 2.5–3.0 mm deep). Stimulating electrodes were placed bilaterally in region CA3 (−3.8 mm from Bregma, 3.7 mm lateral, 3.0 mm deep). Note that positioning of stimulating electrodes required analysis of the evoked potentials elicited at the recording site with an emphasis on positioning electrodes so that an ipsilateral pulse followed by a contralateral pulse did not produce any paired-pulse facilitation, whereas two pulses to one pathway produced paired-pulse facilitation (which appears to be primarily an intracellular, homosynaptic phenomenon).

Electrodes were custom-made stainless steel wires coated with Formvar of 0.004-in-diam cut square (stimulating electrodes consisted of 2 wires twisted together and recording electrodes consisted of a single wire). Recording electrodes were connected to Grass P15 preamplifiers that fed into Neuralynx differential amplifiers connected to a Data Translation A/D board for data storage and visualization in a 100-MHz Pentium computer. All data acquisition was performed using Experimenter's Workbench Software by DataWave. Stimulation was controlled by a Grass S88 stimulator in conjunction with Grass PSIU6 photoelectric stimulus isolation units.

### Drug infusion

Administration of GABAergic antagonists was performed by local infusion through a 25-gauge steel cannula (Small Parts) connected to a 10  $\mu$ l Hamilton syringe with fused silica tubing (Harvard Apparatus). The beveled cannula was fixed 1 mm from the recording electrode. Pharmacological agents were infused in 3  $\mu$ l of artificial cerebrospinal fluid (ACSF) maintaining a flow rate of 0.2  $\mu$ l/min. for 15 min with a microinfusion syringe pump (WPI). All drugs were dissolved in ACSF [which contained (in mM) 120 NaCl, 3.3 KCl, 25 NaHCO<sub>3</sub>, 1.33 NaH<sub>2</sub>PO<sub>4</sub>, 0.9 MgSO<sub>4</sub>, 1.3 CaCl<sub>2</sub>, and 10 dextrose]. CGP 55845A was infused at a concentration of 5 mM and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) at 1 mM. CGP 55845A (Davies et al. 1993) was a gift of Novartis AG (Basel). CNQX and all other chemicals were purchased from Sigma.

### Data analysis

All data analysis was performed with MATLAB version 5.2 (Mathworks) as in previous studies (Linster et al. 1999; Wyble et al. 2000). For analysis, synaptic potentials were averaged across the five potentials obtained at a particular time interval between ipsilateral and contralateral stimulation. The maximum magnitude of the initial negative slope of the averaged potential was then determined using a sliding window of 0.42-ms duration (30 data points). This slope was then normalized to a percentage value relative to the average slope of the baseline potential recorded 10 s before the ipsilateral pulse in each trial. Normalized slopes were then plotted according to the interval between ipsilateral and contralateral stimulation and could be combined with data from other animals (with an error bar representing the standard error resulting from variance across animals). The time course of this depression was estimated by curve fitting of a dual exponential curve to this time course. Homosynaptic facilitation was measured by comparing response to the second pulse of the ipsilateral paired-pulse stimulation with the corresponding first pulse at that interval (i.e., the 2nd pulse of a pair at 10 and 50 ms was compared with the 1st pulse of a pair at 50 and 90 ms), producing a plot of the time course of change in paired-pulse facilitation. Paired-pulse stimuli on the same pathway were presented with a 40-ms interval between each pulse in the pair. In contrast, the interval between ipsilateral and contralateral stimulation in testing heterosynaptic depression was varied between 30 and 1,500 ms.

To ensure there was not a systematic change in the time course of depression, the delays between the conditioning and test stimulus were tested using interdigitated blocks of intervals (e.g., 10, 40, 70,

120 ... followed by 20, 50, 80, 140 ... followed by 30, 60, 100, 160 ...). Comparison of interdigitated curves provided a measure of any long-term drift in measurement of synaptic potentials, such as would be produced by long-term depression or potentiation. A slow increase in the magnitude of the negative slope of evoked potentials over time was observed in some of the preparations. This was minimized by waiting 1 h after the final placement of the electrodes and was controlled for by always calculating the percent depression using a control potential evoked 10 s before the test potential. The increase in negative slope over time was not due to long-term potentiation but rather was most likely a result of recovery from the trauma of electrode placement and surgery (Rick and Milgram 1999). Changes in evoked potentials can be measured most effectively when these potentials are not saturated. To avoid saturation, initial measurement of the evoked potential was performed at a number of different stimulus magnitudes to determine the asymptotic maximum of the evoked potential amplitude. After determination of this maximum amplitude, the stimulation was reduced until the evoked potential amplitude was approximately 50% of the maximum amplitude, ensuring that the evoked potentials were recorded in the more central linear range of the input-output curve. At the start of the experiment, these evoked potentials had an initial amplitude of 0.8–2.8 mV. The use of interdigitated stimulation protocols would ensure that any nonlinearities of response properties should cause inconsistencies in the time course of heterosynaptic depression that were not detected.

There were differences in the time course of heterosynaptic depression and the change in paired-pulse facilitation depending on the initial magnitude of paired-pulse facilitation. Therefore in the analysis, the experimental data were divided on the basis of a single objective criterion based on the initial magnitude of paired-pulse facilitation in the evoked potentials elicited by contralateral stimulation. If the contralateral paired-pulse facilitation was greater than 180% of control, the rats were grouped into the strong initial paired pulse facilitation category. If this facilitation was less than 150% of control, the rats were grouped into the weak initial facilitation category. These widely separate facilitation levels were chosen to reflect the strong clustering of data at values below 150% of control [there were 4 experiments in this category, with a mean facilitation of  $145 \pm 6\%$  of control and (mean  $\pm$  SD)] and clustering of values around 200% of control (there were 7 experiments in this category with a mean of  $204 \pm 22\%$ ). Three experiments did not satisfy these criteria. Figures illustrate differences in the time course for these two different groups as well as a differential effect on paired-pulse facilitation in the two groups.

Curve fitting on the time course of heterosynaptic depression was utilized to estimate the time constants of these curves. The curves showing average time course were fitted with equations representing either the baseline level minus a single exponential decay, or the baseline level minus a dual exponential time course. These time constant parameters were obtained using the curve fitting function in DeltaGraph 3.0.

### Histology

At the end of the experiments, recording and stimulation sites were marked by passage of a positive current of 5 mA for 2.5 s; this produced a lesion and deposited iron from the electrode. After recording, rats were deeply anesthetized and perfused transcardially with physiological saline followed by 250 ml of 10% formalin, with 10 ml glacial acetic acid and 10 g of potassium ferrocyanide (to achieve a Prussian Blue reaction with iron deposits). After removal, brains were stored in 10% formalin/20% sucrose for 1–2 wk before sectioning. Recording and stimulation sites were later localized on the basis of both lesions and blue electrode marks after staining with Neutral Red.



## RESULTS

*Heterosynaptic depression*

Stimulation of the ipsilateral hippocampus caused heterosynaptic depression of potentials elicited by stimulation of the contralateral hippocampus. An example of this heterosynaptic depression is illustrated in Fig. 2. This figure shows the baseline potentials induced by contralateral stimulation 10 s before the ipsilateral stimulation pulse. Repeating this same pair of stimulus pulses after ipsilateral stimulation induced synaptic potentials with much smaller initial negative slopes, as seen in Fig. 2. As described in the INTRODUCTION and Fig. 1, this heterosynaptic depression is theoretically due to the release of GABA as a result of ipsilateral stimulation activating GABA<sub>B</sub> receptors on synapses mediating contralateral evoked synaptic potentials.

The term heterosynaptic depression specifically refers to presynaptic inhibition caused at one set of synapses through activation of a separate set of inputs to a region. To test whether the decrease in synaptic potentials observed here resulted from heterosynaptic depression, experiments analyzed whether depression only occurred with crossed ipsilateral-contralateral stimulation but not with ipsilateral-ipsilateral stimulation or contralateral-contralateral stimulation. In all the experiments described here, before heterosynaptic depression was measured, pairs of stimuli on the same pathway were used to test whether only paired-pulse facilitation appeared on each pathway (a homosynaptic effect). Paired-pulse facilitation was measured by comparing the negative slope of the second synaptic potential to the negative slope of the first synaptic potential induced 40 ms previously. Experiments were only performed with electrode locations in which contralateral-contralateral pairs consistently induced paired-pulse facilitation (as shown in Fig. 2) and ipsilateral-contralateral pairs did not. In addition, experiments were only performed if ipsilateral-ipsilateral pairs also induced homosynaptic paired-pulse facilitation. This ruled out the possibility that depression arose from synaptic vesicle depletion—a homosynaptic mechanism that could cause depression at a number of synapses, particularly in the neocortex. The depression was only observed with ipsilateral-contralateral stimulation—that is, if two different pathways were stimulated. If there was any overlap in the synapses activated by ipsilateral and contralateral stimulation, it would not contribute to heterosynaptic depression because these overlapping synapses would undergo facilitation.

*Time course of heterosynaptic depression*

Once heterosynaptic depression was obtained with ipsilateral-contralateral stimulation, the time course of this heterosynaptic depression was measured by varying the interval between the ipsilateral conditioning pulse and the contralateral test pulse between 30 and 1,500 ms. An example of the time course of heterosynaptic depression in a single experiment is shown in Fig. 3A. The magnitude of the initial negative slope of potentials elicited by contralateral stimulation is plotted for intervals ranging from 30 to 1,000 ms, demonstrating a rapid early heterosynaptic depression that starts out strong and decays back to baseline (100%) in about 250 ms. The traces in Fig. 3B show averaged evoked synaptic potentials at different time delays in this example animal, clearly illustrating the

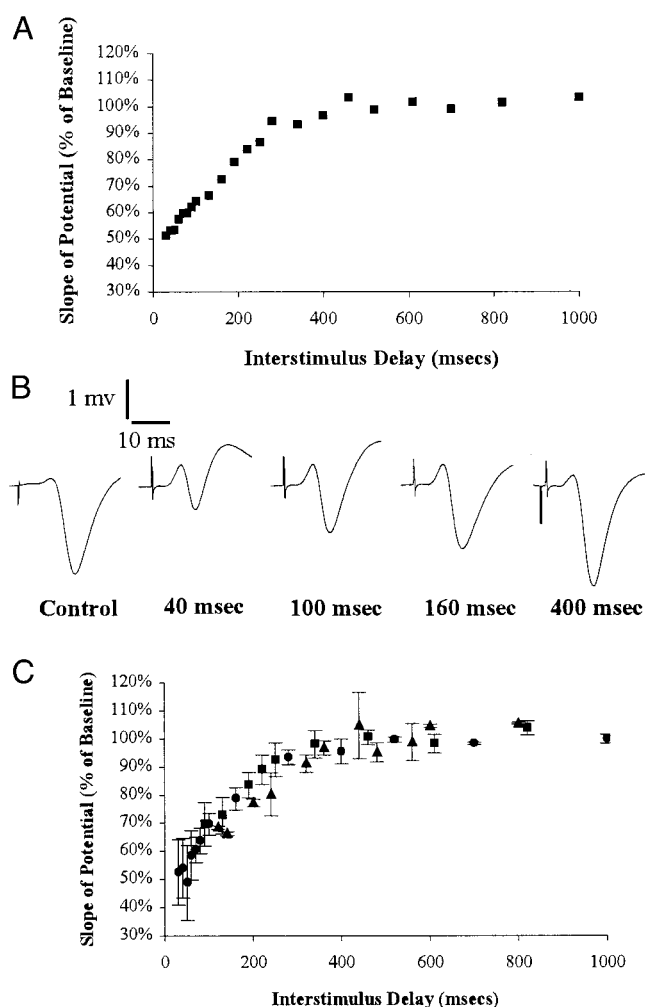


FIG. 3. *A*: example of the time course of heterosynaptic depression appearing in rats showing weak initial paired-pulse facilitation. The initial slope of potentials elicited by contralateral stimulation is plotted for intervals ranging from 30 to 1,000 ms, demonstrating that heterosynaptic depression decays over about 250 ms in rats starting with weak initial facilitation in response to contralateral paired pulses. *B*: these traces show the averaged potentials elicited by the 1st pulse of the contralateral pulse pairs for a number of different time points, including the baseline stimulation 10 s before the ipsilateral pulse (control) and several different time delays after the ipsilateral pulse. *C*: average time course of heterosynaptic depression in rats showing weak initial paired-pulse facilitation. For each experiment, the initial slope of averaged test potentials at different intervals was calculated and then normalized relative to the slope of the 1st baseline potential (baseline slope = 100%). The mean for each rat was then combined with other available data at that time point from other rats, giving an overall mean and a SE (plotted as error bars). The number of recordings at each time point are represented by different symbols (■ = 2 rats, ▲ = 2 different rats, ● = 4 rats). This illustrates a consistent time course of heterosynaptic depression in rats that started with a magnitude of paired-pulse facilitation less than 150% of control.

strength of heterosynaptic depression in this preparation. The positive component at the start of the potential could reflect a passive source induced by a more distant excitatory sink in the molecular layer of the dentate gyrus. We feel this positive component has been unmasked by the reduction in the local potential rather than the passive source causing the entire change in the local potential. This rat showed weak initial paired pulse facilitation (less than 150% of control), which increased significantly during heterosynaptic depression (see Fig. 5).

Figure 3C shows average time course of heterosynaptic

depression across several experiments. For each experiment, the mean initial negative slope of test potentials at different intervals was calculated and then normalized relative to the initial negative slope of the first baseline potential (baseline slope = 100%). The mean for each rat was then combined with other available data at that time point from other rats with weak initial paired pulse facilitation (less than 150% of control), giving an overall mean and SE (plotted as error bars). The number of recordings at each time point are represented by different symbols. Data points were obtained at different time delays in different rats, but they all fall on the same decay curve in this figure. Using curve fitting with a single exponential, this data had a decay time constant of 141.5. If modeled with a dual exponential (which would more accurately represent the properties of diffusion of GABA released in response to the ipsilateral pulse), the best estimate was for a rising time constant of 13.5 ms and a decay constant of 140.1 ms. The weak initial paired-pulse facilitation in all these rats increased significantly during the period of heterosynaptic depression (see Fig. 5).

As described in METHODS, different properties appeared in rats in which the initial paired-pulse facilitation in response to contralateral stimulation was larger. An example of the faster time course of heterosynaptic depression in rats with strong initial facilitation (more than 180% of control) is shown in Fig. 4A. Figure 4B shows averaged evoked potentials for different time delays. Figure 4C shows the average time course of heterosynaptic depression in all rats showing strong initial paired-pulse facilitation (more than 180% of control). This illustrates a consistently faster time course of heterosynaptic depression in experiments that started with a stronger magnitude of paired-pulse facilitation. In these experiments, the heterosynaptic depression was somewhat stronger on average and decayed back to baseline more rapidly, reaching values at 100% of baseline in less than 180 ms. The rapid time course seen in the example in Fig. 4A appears consistently across seven different experiments with strong initial facilitation. If the curve was modeled with a single exponential decay, the time constant is estimated as 72.3 ms. If the curve was modeled as a dual exponential, then the best estimate would have a rising time constant of 16.1 ms and a decay time constant of 59.3.

Anatomical localization of the recording sites for these two different groups of rats showed that recordings with weak facilitation appeared to be consistently more distal in s. radium, whereas at least some of the recordings with strong facilitation appeared to be more proximal to s. pyramidale. However, the size of the lesions marking electrode location prevented an accurate quantitative analysis of these differences. It is very likely that these differences are due to electrode placement in specific experiments rather than differences in the physiology of individual rats.

#### *Interaction of heterosynaptic depression and paired-pulse facilitation*

The changes in paired-pulse facilitation during the period of heterosynaptic depression were also examined. As noted in the preceding text and in Fig. 2, in all experiments, presentation of homosynaptic pulse pairs to each pathway was used to test whether paired-pulse facilitation was present before testing for

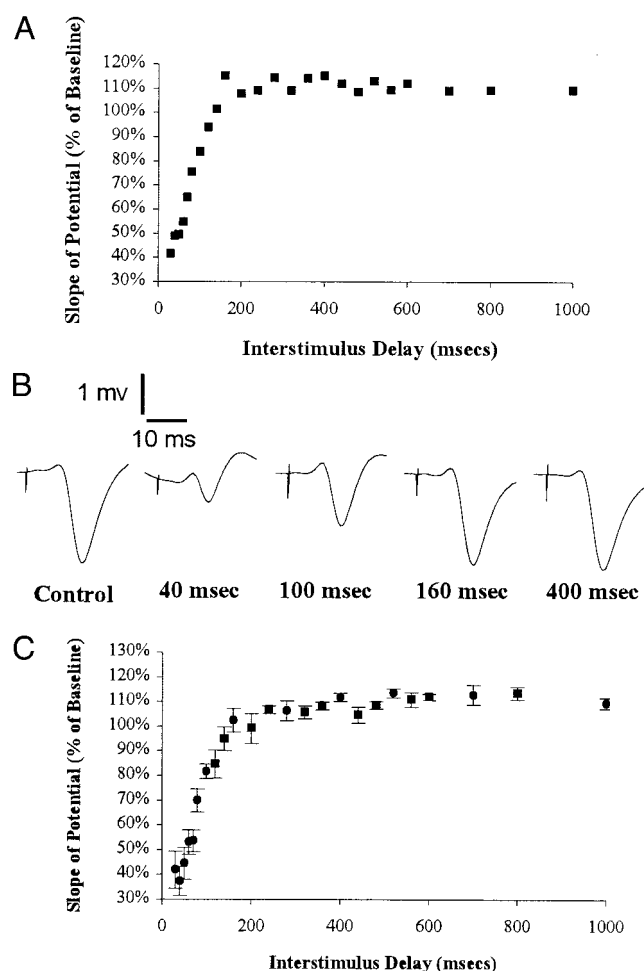


FIG. 4. A: example of the time course of heterosynaptic depression in rats showing strong initial paired-pulse facilitation. The initial slope of potentials elicited by contralateral stimulation is plotted for intervals ranging from 30 to 1,000 ms, demonstrating a rapid early heterosynaptic paired-pulse depression that has returned to baseline within about 180 ms. B: these traces show the averaged potentials elicited by the 1st pulse of the contralateral pulse pairs for a number of different time points, including the baseline stimulation 10 s before the ipsilateral pulse (control) and several different time delays after the ipsilateral pulse. Pulses show a strong decrease in initial slope and overall magnitude during heterosynaptic depression. C: average time course of heterosynaptic depression across several experiments. The number of recordings at each time point are represented by different symbols ( $\blacksquare$  = 6 rats,  $\bullet$  = 7 rats). These data illustrate a consistent time course across all rats with strong initial paired pulse facilitation to contralateral stimulation (facilitation more than 180% of control).

heterosynaptic depression. The additional analysis described here was utilized to determine if there was a change in magnitude of this previously measured contralateral paired-pulse facilitation during heterosynaptic depression. The magnitude of paired-pulse facilitation is measured by comparing the second pulse of the contralateral paired-pulse stimulation with the corresponding first pulse at that interval. For example, the second pulse of a pair consisting of one pulse at 30- and a second pulse at 70-ms delays was compared with the first pulse of a pair at presented at 70 and 110 ms. In the figures shown here, the magnitude of paired-pulse facilitation at different time delays after ipsilateral stimulation ( $\square$ ) is plotted relative to the paired-pulse facilitation observed in the baseline pulses 10 s before ipsilateral stimulation ( $\circ$ ).

Figure 5A shows an example of the change in paired-pulse facilitation during and after heterosynaptic depression in an experiment starting with weak paired-pulse facilitation (around 140% of control in this example). The experiment shows a large increase in paired-pulse facilitation during the period of heterosynaptic depression ( $\square$ ) as compared with the facilitation obtained during the baseline period preceding each test interval by 10 s ( $\circ$ ). Figure 5B shows the change in paired-pulse facilitation across the full set of experiments in which facilitation started out weak. There was a consistent increase in paired-pulse facilitation across this set of experiments. The best fit of a dual exponential to this equation was obtained with delay to onset of 27.2 ms, and equal rising and falling time constants of 68.7 ms. Previous experiments assume that pre-synaptic inhibition should be accompanied by an increase in paired-pulse facilitation (Dittman and Regehr 1997; Valentino and Dingledine 1981; Zucker 1989). If this is true, the time course of increased facilitation seen in these experiments might give the most accurate estimate of presynaptic inhibition.

Figure 6A shows the change in paired-pulse facilitation during and after heterosynaptic depression in a rat starting with strong paired-pulse facilitation. This rat showed a decrease in

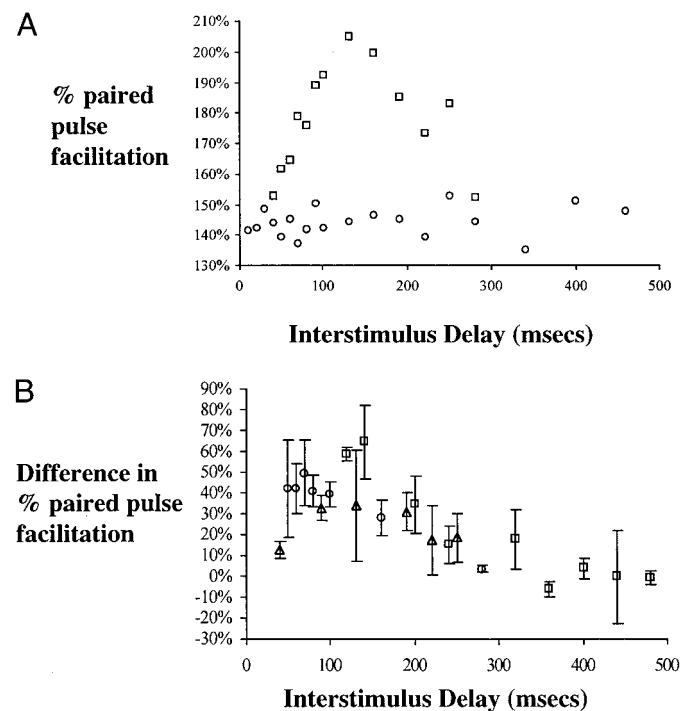


FIG. 5. A: example of the change in paired-pulse facilitation during and after heterosynaptic depression in a rat starting with weak paired pulse facilitation (about 140% of control in this example). These rats showed a clear increase in magnitude of paired-pulse facilitation during heterosynaptic depression.  $\square$ , the paired-pulse facilitation at different intervals after ipsilateral stimulation;  $\circ$ , the baseline control measurements given 10 s before each of the paired pulses plotted with  $\square$ . (Note that baseline measurements involved paired pulses that are plotted according to the time interval between the ipsilateral pulse and the later contralateral paired pulse.) Baseline measurements are also shown for long interval paired pulses where facilitation measurements were not obtained. B: average change in paired-pulse facilitation during and after heterosynaptic depression in preparations starting with weak paired-pulse facilitation (less than 150% of control). The rats starting with weak paired-pulse facilitation show a consistent increase in paired-pulse facilitation during the period of heterosynaptic depression from 0 to 250 ms (note the difference in time scale from Figs. 3 and 4). Symbols represent different numbers of data points at different intervals ( $\square$  = 2 rats,  $\triangle$  = 2 different rats,  $\circ$  = 4 rats).

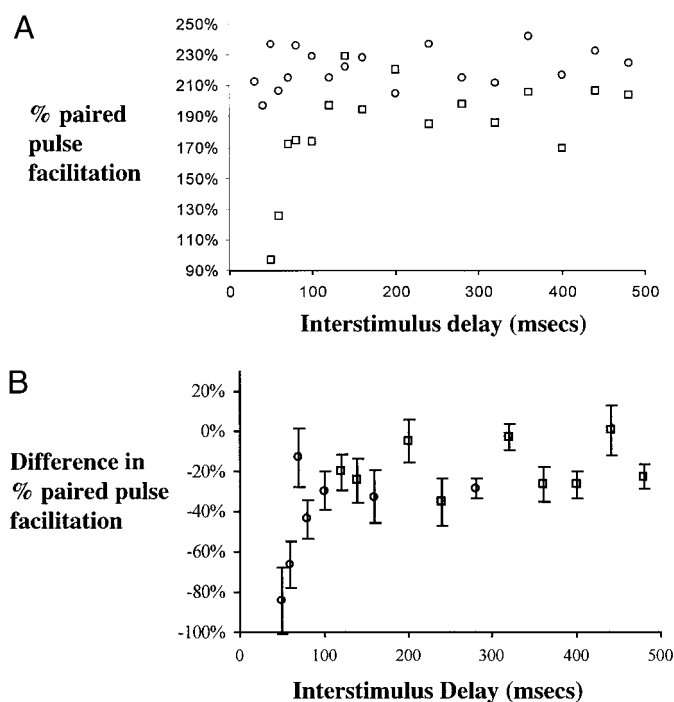


FIG. 6. A: example of the change in paired-pulse facilitation during and after heterosynaptic depression in preparations starting with strong paired-pulse facilitation.  $\square$ , average paired-pulse facilitation in this experiment at different intervals after ipsilateral stimulation;  $\circ$ , the average paired-pulse facilitation obtained with baseline stimulation 10 s before each of the  $\square$  plotted here. Note that these all show very strong initial baseline facilitation (around 220% of control). This rat showed a decrease in paired-pulse facilitation during heterosynaptic depression. B: average change in paired-pulse facilitation during and after heterosynaptic depression in preparations starting with strong paired-pulse facilitation.  $\square$ , data points averaged over 6 rats;  $\circ$ , points averaged over 7 rats. The change in facilitation is consistent across all rats with strong initial facilitation.

paired-pulse facilitation during heterosynaptic depression with a time course of change similar to the time course observed for heterosynaptic depression. However, note that even though the magnitude was decreased, contralateral stimulation pairs still exhibited paired-pulse facilitation, again suggesting that the heterosynaptic depression is not due to homosynaptic effects. Figure 6B shows the average change in magnitude of paired-pulse facilitation across all the experiments starting with strong paired-pulse facilitation. For these experiments, the facilitation was consistently reduced from the initial high baseline during heterosynaptic depression with a similar time course across experiments. This may suggest a postsynaptic contribution to heterosynaptic depression in these experiments.

### Pharmacology

To determine whether the observed heterosynaptic paired-pulse depression was due to activation of presynaptic GABA<sub>B</sub> receptors, we utilized local infusion of pharmacological agents near the field potential recording site. To test this technique, we performed local infusion of the glutamatergic AMPA receptor antagonist CNQX in a single experiment, expecting to see a decrease in the magnitude of the excitatory field potentials. This infusion of CNQX caused the field potentials to decrease in size, as shown in Fig. 7. A complete blockade of potentials was not expected, as infusion was done at relatively low

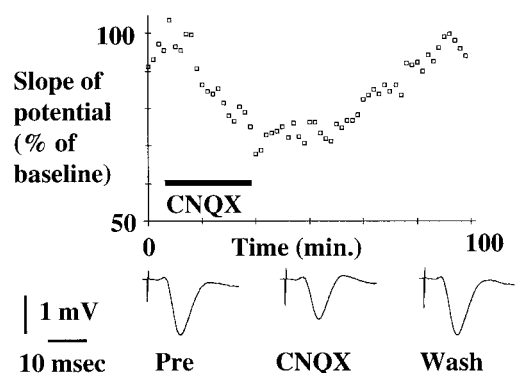


FIG. 7. Evaluation of the effectiveness of local infusion by testing effects of infusion of the AMPA receptor blocker 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) on field potentials recorded in s. radiatum of region CA1 during stimulation of the contralateral hippocampus. *Top*: slope of synaptic potentials plotted against time before, during, and after local infusion of CNQX through the cannula near recording site. *Bottom*: averages of field potentials recorded before infusion (pre), during infusion (CNQX), and after infusion (wash).

concentrations to prevent nonspecific effects. After a 75-min wash period, the potentials had returned to their preinfusion magnitude.

Next, the effect of the GABA<sub>B</sub> antagonist CGP55845A (Davies et al. 1993) on heterosynaptic depression was tested. In these experiments, the time course of heterosynaptic depression was first recorded with a range of different delay intervals between ipsilateral and contralateral pulses. Then to observe the effect of pharmacological infusion, the level of depression was monitored with consistent alternating use of contralateral pulse pairs starting at only two intervals (40 or 80 ms) after the ipsilateral pulse. The magnitude of heterosynaptic depression at these time intervals remained consistent across a 35-min baseline period, after which infusion of CGP55845A was initiated. The infusion of CGP 55845A strongly reduced the

depression in four of four animals showing strong initial facilitation and also strongly reduced the depression in the one animal tested with weak initial facilitation. Thus the pharmacological effect was consistent in every animal tested. Approximately 10 min after the CGP 55845A infusion was initiated, the level of depression was greatly reduced. These data suggest that a significant portion of the heterosynaptic depression resulted from activation of GABA<sub>B</sub> receptors.

Figure 8A shows the effect of the GABA<sub>B</sub> receptor antagonist on heterosynaptic depression in the one case of weak initial facilitation in which pharmacological infusion was tested. The initial negative slope of potentials is plotted relative to the baseline. Before infusion, the heterosynaptic depression at 40 ms maintained a consistent level of about 35% reduction from baseline. After about 10 min of antagonist infusion, the level of heterosynaptic depression was greatly reduced, returning the initial negative slope of potentials to a magnitude close to the baseline magnitude (observed 10 s before presentation of the ipsilateral pulse). In this experiment, the increase in facilitation caused by heterosynaptic depression was reduced when the heterosynaptic depression was reduced by the antagonist. The initial negative slope of the baseline potentials did increase during infusion of antagonists, possibly due to loss of tonic endogenous activation of GABA<sub>B</sub> receptors, but the decrease in magnitude of depression was greater than would result from the increase in baseline alone. Figure 8B shows the effect of the GABA<sub>B</sub> receptor antagonist on the magnitude of heterosynaptic depression at the 40-ms interval in the four experiments starting with strong facilitation. Before drug infusion, the average depression at 40 ms remained steady at a mean of about 60% below baseline. Drug infusion consistently reduced the magnitude of depression to an average magnitude of about 30%.

Infusion of the GABA<sub>B</sub> receptor antagonist CGP55845A had effects on paired-pulse facilitation consistent with the

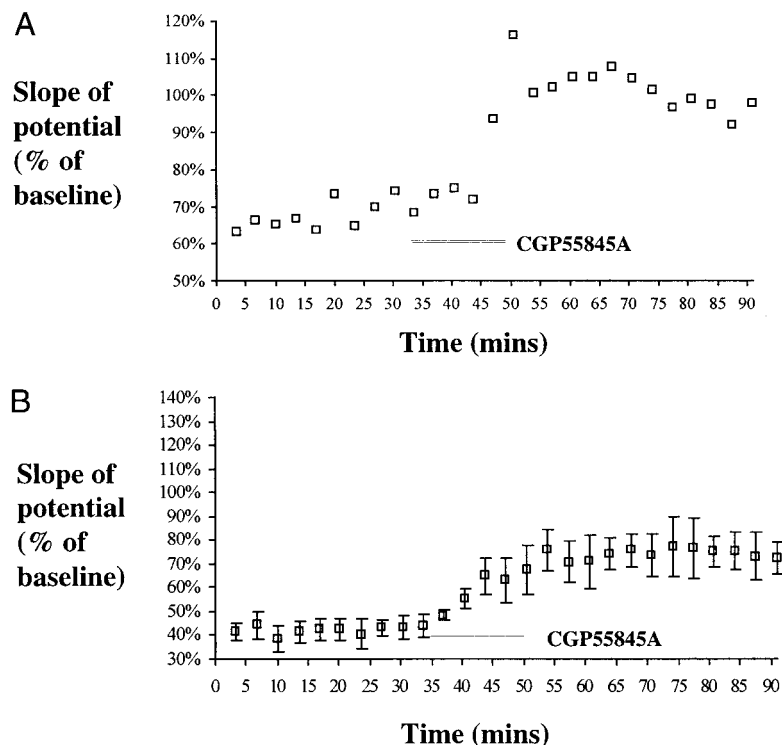


FIG. 8. *A*: the effect of local infusion of the GABA<sub>B</sub> receptor antagonist CGP 55845A on the magnitude of heterosynaptic depression for contralateral evoked potentials following ipsilateral stimulation by 40 ms in the experiment starting with weak facilitation in which drug infusion was performed. *B*: the effect of local infusion of the GABA<sub>B</sub> receptor antagonist CGP55845A on the magnitude of heterosynaptic depression at 40 ms in the experiments starting with strong facilitation in which pharmacological infusion was performed ( $n = 4$ ).



notion that this antagonist reduces the magnitude of heterosynaptic depression. As described in the preceding text, presynaptic inhibition during heterosynaptic depression (after ipsilateral stimulation) should reduce the size of the first negative potential in each pair of potentials, leaving a larger store of unreleased transmitter and allowing greater paired-pulse facilitation (Dittman and Regehr 1997; Valentino and Dingledine 1981; Zucker 1989). Blockade of this presynaptic inhibition by the antagonist should increase the size of the first potential in each pair after ipsilateral stimulation, resulting in a reduction in the amount of paired-pulse facilitation.

As shown in Fig. 9, *A* and *B*, the GABA<sub>B</sub> receptor antagonist caused a reduction in the amount of facilitation of test pulses (after ipsilateral stimulation) relative to the facilitation of baseline potentials (before ipsilateral stimulation). The increase in the amount of facilitation of baseline pulse pairs (before ipsilateral stimulation) could result from blockade of the GABA<sub>B</sub>-mediated presynaptic inhibition of inhibitory synaptic transmission induced by the first pulse in each pair. As shown in Fig. 9*B*, average data from four cases starting with strong facilitation shows that there was a significant absolute reduction in the facilitation of test potentials. The reduction in facilitation shown in this figure is consistent with the idea that the GABA<sub>B</sub> receptor antagonist blocks presynaptic inhibition, allowing more transmitter release in response to the first pulse,

leaving less transmitter available for the second pulse, and thereby resulting in less paired-pulse facilitation.

## DISCUSSION

These *in vivo* data demonstrate that heterosynaptic depression in region CA1 of anesthetized rats has a time course which is more rapid than was previously inferred from *in vitro* data. This heterosynaptic depression was significantly blocked by local infusion of the GABA<sub>B</sub> receptor antagonist CGP 55845A, suggesting that presynaptic inhibition by GABA<sub>B</sub> receptors contributes to a significant component of this heterosynaptic depression, as proposed for heterosynaptic depression in brain slice preparations of hippocampal region CA1 (Isaacson et al. 1993) and cerebellum (Dittman and Regehr 1997).

The time course of heterosynaptic depression observed here appears sufficiently rapid to underlie significant changes in strength of synaptic transmission within each cycle of the theta rhythm. This evidence supports the possibility that presynaptic inhibition by GABA<sub>B</sub> receptors could contribute to the observed changes in magnitude of evoked synaptic potentials at different phases of the theta cycle (Rao et al. 1998; Wyble et al. 2000). In addition, these effects could contribute to the change in magnitude of evoked population spikes at different phases of the theta cycle (Buzsaki et al. 1981; Rudell and Fox 1984; Rudell et al. 1980).

### Relation to heterosynaptic depression in slice preparations

The time course of heterosynaptic depression observed was significantly more rapid than the time course observed in slice experiments. In those experiments, the time course of decay of heterosynaptic depression was around 1 s, whereas here the depression decayed to baseline in less than 300 ms.

These differences could arise from different factors including the use of nonphysiological temperatures in most slice experiments and the change in amount of GABA reuptake and in intracellular metabolic processes in slice preparations. In slice experiments (Dittman and Regehr 1996), the  $Q_{10}$  of 3.3 reported for changes in the time course of heterosynaptic depression at different temperatures is consistent with a much faster time course at the temperatures maintained in these experiments (37°C), although the exact values extrapolated for physiological temperatures are still somewhat slower than those observed here. They reported a decay time constant of 680 ms at 32°, which for a  $Q_{10}$  of 3.3 would result in a decay time constant of 412 ms at 37°. Blockade of GABA reuptake has been demonstrated to enhance heterosynaptic depression in the slice preparation (Isaacson et al. 1993; Mitchell and Silver 2000). Stronger reuptake *in vivo* could significantly speed the decay of extracellular activation of GABA<sub>B</sub> receptors, just as it influences the speed of decay of GABA<sub>A</sub> currents (Mody et al. 1994; Rossi and Hamann 1998) and glutamatergic currents (Asztely et al. 1997).

### Relation to functional changes during theta

These results suggest that phasic changes in the magnitude of excitatory postsynaptic potentials (EPSPs) and populations spikes during theta could at least partly result from changes in activation of presynaptic GABA<sub>B</sub> receptors. Computational modeling suggests that such phasic changes in strength of

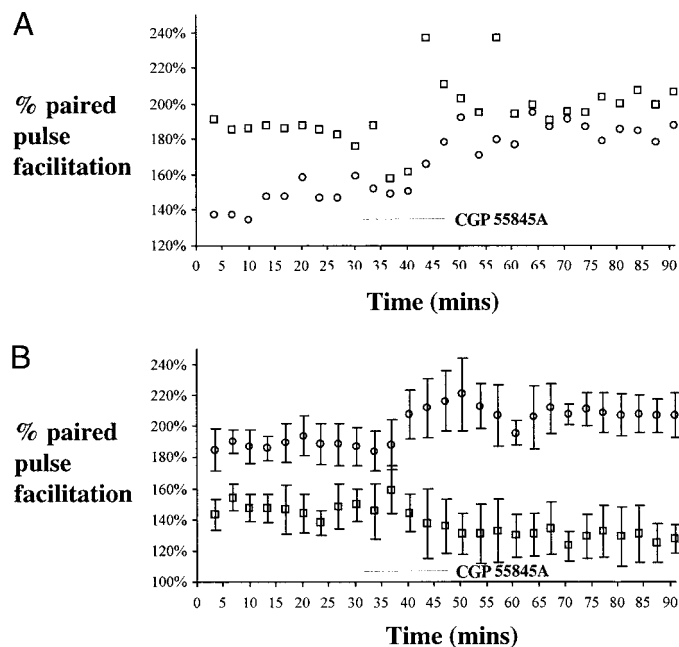


FIG. 9. Effect of infusion of the GABA<sub>B</sub> antagonist CGP 55845A on the magnitude of paired-pulse facilitation. *A*: effect of GABA<sub>B</sub> antagonist in the experiment starting with weak facilitation. ○, after antagonist infusion there is an increase in facilitation of the baseline pulse pair (stimulated before ipsilateral stimulation). □, facilitation of the test pulse pair (after ipsilateral stimulation) shows transient changes followed by stabilization at the same level as baseline. This reduction in the relative amount of facilitation is consistent with the reduction in heterosynaptic depression caused by the antagonist. *B*: effect of antagonist in 4 experiments starting with strong facilitation. ○, an increase in average facilitation in baseline pulse pairs (before ipsilateral stimulation) consistent with *A*. □, the magnitude of facilitation of the test pulse pair (after ipsilateral stimulation) was significantly reduced after antagonist. Again, this suggests that the blockade of presynaptic inhibition by CGP55845A allows more transmission for the 1st pulse and thereby decreases the amount of facilitation possible with the 2nd pulse.



synaptic transmission could allow separate phases of encoding and retrieval in the hippocampal formation (Hasselmo et al. 1996, 2001; Wallenstein and Hasselmo 1997). Models of hippocampal function demonstrate that effective encoding of new information requires weakening of synaptic transmission at connections mediating retrieval—including the Schaffer collaterals studied here (Hasselmo et al. 1996, 2001). Weak transmission prevents the retrieval of previously encoded information from being re-encoded and interfering with new learning. The GABAergic presynaptic inhibition of transmission at the Schaffer collaterals described here could provide a mechanism for phasically weakening retrieval activity. During a separate retrieval phase, the rapid decay of this presynaptic inhibition could allow stronger transmission at the Schaffer collaterals, allowing retrieval activity to activate region CA1 neurons and cause retrieval output from the hippocampus (Hasselmo et al. 2001).

Modeling (Hasselmo et al. 2001) can account for behavioral data showing that lesions of the medial septum or the fornix, which block theta rhythm generation in the hippocampus, cause strong impairments in spatial reversal tasks (M'Harzi et al. 1987; Whishaw and Tomie 1997) and delayed alternation tasks (Numan and Quaranta 1990; Numan et al. 1995). In these tasks, animals must distinguish the retrieval of previously encoded information from the encoding of new sensory information. Computational modeling demonstrates how phasic changes in the strength of intrinsic transmission could enhance this distinction by reducing the influence of retrieval activity during the encoding of new information (Hasselmo et al. 1996, 2001; Sohal and Hasselmo 1998a,b; Wallenstein and Hasselmo 1997). Loss of this phasic modulation due to lesions allows retrieval of previous memories for reward location to occur during new encoding, even if the reward has been moved to a different location. This prevents the extinction of initial learned associations and greatly slows the learning of a reversal (Hasselmo et al. 2001), consistent with behavioral data. Modeling also shows that phasic changes allow effective retrieval of weak associations in a network with other associations of similar or greater strength (Sohal and Hasselmo 1998a,b). This modeling provides a circuit level mechanism for previously proposed functions of theta, including selection of novel and significant stimuli for encoding in the face of irrelevant stimuli (Oddie and Bland 1998; Vinogradova 1995).

The separation of encoding and retrieval phases requires that synaptic modification should be strongest at the time of weakest synaptic transmission. This requirement is supported by evidence for the best induction of LTP at the peak of the local theta when transmission is weakest (Hasselmo et al. 2001; Holscher et al. 1997; Huerta and Lisman 1993; Pavlides et al. 1988). In fact, the activation of GABA<sub>B</sub> receptors appears to simultaneously decrease synaptic transmission and enhance LTP (Mott and Lewis 1991, 1994).

Modeling also demonstrates that phasic changes in magnitude of synaptic transmission during theta could contribute to the theta phase precession effect (O'Keefe and Recce 1993; Skaggs et al. 1996). During theta phase precession, the spiking of place cells appears later in a theta cycle when a rat first enters the place field and then moves to earlier phases. This effect can be obtained in the model if GABA<sub>B</sub> presynaptic inhibition is strong at early phases, ensuring that place cells are only activated by entorhinal cortical input bearing information

about external cues (Wallenstein and Hasselmo 1997). As the presynaptic inhibition becomes weaker at late phases of theta, this allows previously modified excitatory synapses to cause associative activation of place cells further along in a familiar pathway, causing late phase firing to be strong as a rat first enters the place field (Wallenstein and Hasselmo 1997).

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