Brief Communication

$GABA_B$ Receptor-Mediated Presynaptic Inhibition Has History-Dependent Effects on Synaptic Transmission during Physiologically Relevant Spike Trains

Patricia Ohliger-Frerking,[1] Sherman P. Wiebe,[2] Ursula Stäubli,[3] and Matthew Frerking[1]

[1]Neurological Sciences Institute, Oregon Health & Science University, Beaverton, Oregon 97006, [2]Plexon Inc., Dallas, Texas 75206, and [3]Cortex Pharmaceuticals, Irvine, California 92618

Presynaptic inhibition is a form of neuromodulation that interacts with activity-dependent short-term plasticity so that the magnitude, and sometimes even the polarity, of that activity-dependent short-term plasticity is changed. However, the functional consequences of this interaction during physiologically relevant spike trains are poorly understood. We examined the effects of presynaptic inhibition on excitatory synaptic transmission during physiologically relevant spike trains, using the $GABA_B$ receptor ($GABA_BR$) agonist baclofen to engage presynaptic inhibition and field EPSPs (fEPSPs) in hippocampal slices to monitor synaptic output. We examined the effects of baclofen on the relationship between an fEPSP during the spike train and the timing of spikes preceding that fEPSP, a relationship that we refer to as the history dependence of synaptic transmission. Baclofen alters this history dependence by causing no inhibition during short interspike intervals (ISIs) in the spike train but a maximal inhibition during long ISIs. This effect strengthens the dependence of the fEPSP on the first ISI preceding it. One consequence of this effect is that the apparent affinity of baclofen is strongly reduced during physiologically relevant spike trains when compared with conventional stimulus paradigms, and a second consequence is that the overall inhibition experienced by a synapse will vary considerably during repeated trials of a behavioral task. We conclude that $GABA_BR$-mediated presynaptic inhibition is more accurately described as a high-pass filter than as a simple inhibition, and that this filtering must be taken into account to accurately assess the effects of presynaptic inhibition under physiologically relevant conditions.

Key words: **baclofen; spike timing; hippocampus; Schaffer collateral; neuromodulator; synaptic transmission**

Introduction

A major form of neuromodulation is the presynaptic inhibition of transmitter release, which in the hippocampus is engaged by presynaptic $GABA_B$ receptors ($GABA_BRs$), as well as receptors for other neuromodulators (for review, see Wu and Saggau, 1997). It is universally observed that presynaptic inhibition interacts with activity-dependent short-term synaptic plasticity (for review, see Miller, 1998), an effect frequently observed as an enhancement in paired-pulse facilitation (PPF). Activity-dependent effects of presynaptic inhibitors have also been observed during brief spike trains, in which these inhibitors enhance the size of steady-state responses relative to the first EPSP in the train (Varela et al., 1997; Kreitzer and Regehr, 2000). In absolute terms, presynaptic inhibitors have an inhibitory effect only on the first few spikes during brief, high-frequency spike trains, with no effect on steady-state responses (Tsodyks and Markram, 1997; Selig et al., 1999) or even a facilitation of steady-state responses (Brenowitz et al., 1998). Similar results have also been observed during irregular spike trains (Varela et al., 1997; Kreitzer and Regehr, 2000).

Presynaptic inhibition interacts with activity-dependent short-term plasticity, but the consequences of this interaction remain obscure, in part because the stimulus paradigms used in most experiments bear little resemblance to activity patterns *in vivo*. Most neurons do not reach a steady state; instead, they fire sporadically, with gaps between spikes that range in duration over several orders of magnitude. Studies that have examined synaptic transmission during random irregular spike trains indicate that activity-dependent short-term plasticity is a major determinant of EPSP size during these trains (Abbott et al., 1997; Tsodyks and Markram, 1997; Varela et al., 1997; Dittman et al., 2000) (for review, see Zador and Dobrunz, 1997), and similar results have been obtained using physiologically relevant spike trains derived from *in vivo* spike patterns (Dobrunz and Stevens, 1999). Activity-dependent short-term plasticity is a mechanism by which the size of an EPSP encodes information about the recent history of afferent activity, so activity-dependent short-term plasticity imparts a history dependence to synaptic transmission. Because presynaptic inhibition interacts with at least some forms of activity-dependent short-term plasticity, it is necessary to determine whether presynaptic inhibition affects this history dependence during physiologically relevant spike trains to gain insight into the actions of these neuromodulators *in vivo*.

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Correspondence should be addressed to Dr. Matthew Frerking, Neurological Sciences Institute, Oregon Health & Science University, Beaverton, OR 97006. E-mail: frerking@ohsu.edu.

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We examined whether the $GABA_BR$ agonist baclofen induces changes in the history dependence of synaptic transmission at Schaffer collateral synapses in the hippocampus. Using spike trains from *in vivo* recordings of CA3 pyramidal cells from rats during performance of a maze (Wiebe and Stäubli, 1999), we found that baclofen alters the history dependence of the synapse. This effect reduces the apparent affinity of baclofen during physiologically relevant spike trains and will cause baclofen to vary widely in its overall inhibition during repeated trials of a behavioral task. These results suggest that presynaptic inhibition leads to complex effects during physiologically relevant spike trains, which can be predicted only by taking effects on the history dependence of synaptic transmission into account.

Materials and Methods

General approaches. Two constraints impede progress in synaptic physiology during complex spike trains. The first is that, in whole-cell recording, probabilistic release introduces substantial noise in synaptic responses, which must be removed by averaging together many repetitions of the train. This makes even simple experiments impractical unless the train is very short, which provides a limited description of the history dependence during synaptic transmission. This problem can be circumvented by using field recordings that sample from a large population of synapses simultaneously. A single application of a physiologically relevant spike train generates highly reliable field responses (Dobrunz and Stevens, 1999), and studies using field recordings (Abbott et al., 1997; Varela et al., 1997; Pananceau et al., 1998) in response to both constant-frequency and complex trains have provided results that are indistinguishable from those obtained using heavily averaged whole-cell recordings (Tsodyks and Markram, 1997; Varela et al., 1997; Selig et al., 1999). We therefore used field recording to measure responses during physiologically relevant spike trains.

The second constraint is that few analytical methods have been developed to examine the responses generated during physiologically relevant spike trains. However, a simple assay for changes in synaptic properties during these trains was recently developed by Dobrunz and Stevens (1999). They applied the same train to the same synapses twice and then plotted each field EPSP (fEPSP) slope during the first application of the train against the corresponding fEPSP slope generated by the same spike during the second application of the train. They then calculated the correlation coefficient (r) for the plot. The squared value of r is the fraction of variance in the responses to the first train that covaries with the responses to the second train. If the history dependence is similar during both applications of the train, the r^2 value is high; if the history dependence changes between the trains, the r^2 value is low. Dobrunz and Stevens (1999) used this assay to determine that the history dependence of synaptic transmission during a physiologically relevant spike train is stable during repeated trials of the same train and across different sets of synapses in the same slice. We used this assay to determine whether history dependence is affected by baclofen (see below).

Slice preparation and recording techniques. Hippocampal slices (300–500 μm thick) were prepared from 2- to 8-week-old Sprague Dawley rats (Frerking et al., 2001). Slices were transferred to a recording chamber at 32–36°C and perfused with a solution consisting of the following: 119 mM NaCl, 26.2 mM $NaHCO_3$, 11 mM glucose, 2.5 mM KCl, 4 mM $CaCl_2$, 4 mM $MgSO_4$, 1 mM NaH_2PO_4, and 100 μM APV to prevent the induction of long-term plasticity during the spike train and 100 μM picrotoxin to block $GABA_A$ receptors (bubbled with 95% O_2–5% CO_2). A cut was made between area CA1 and area CA3 to ensure that transmission was monosynaptic.

Stimulation and recording techniques were similar to those used by Frerking et al. (2001). fEPSPs were evoked by physiologically relevant spike trains that were derived from *in vivo* recordings of CA3 pyramidal cells from Wiebe and Stäubli (1999). These spike trains are temporally complex and are poorly described by homogeneous Poisson statistics, because there are more long interspike intervals (ISIs) than expected for a Poisson process (data not shown). All ISIs of <20 msec were set to 20 msec to prevent overlap of sequential fEPSPs, which would preclude accurate initial slope measurements. Fiber excitability, assessed by monitoring the fiber volley, was constant during the train ($n = 6$; data not shown). Recording stability was assessed by 3–5 min of responses to constant 0.1 Hz stimulation between presentations of the trains.

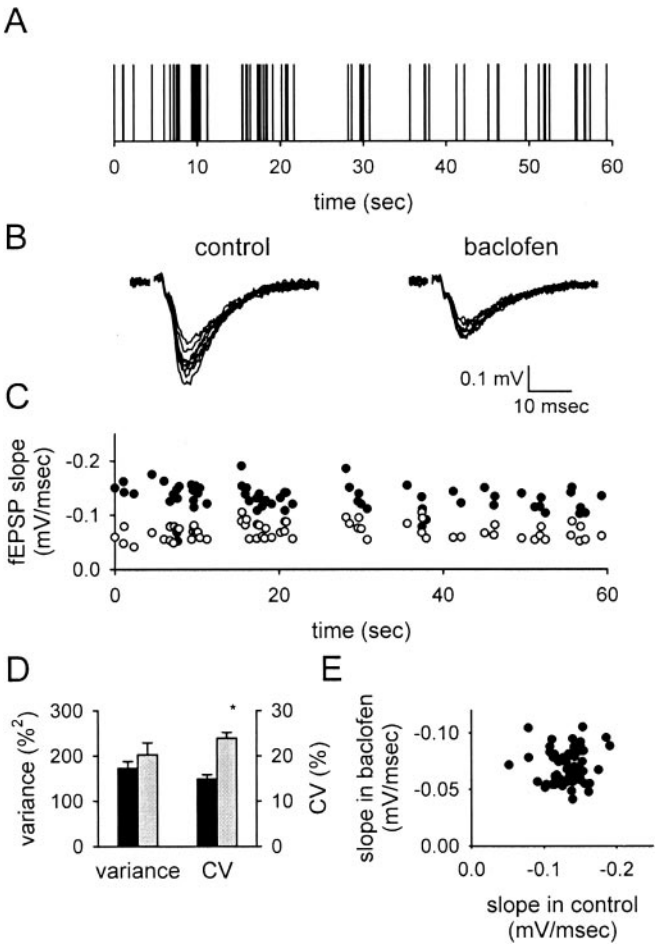

Figure 1. *A*, A physiologically relevant spike train is shown from a CA3 pyramidal cell of an awake rat during performance of a maze. The average firing frequency was 1 Hz. *B*, Selected fEPSPs generated in response to the spike train shown in *A* are shown in control conditions, and the corresponding fEPSPs from a second application of the same train in 2 μM baclofen are also shown. *C*, The fEPSP slopes during the train are shown as a function of time in control conditions (filled circles) and in baclofen (open circles). *D*, The variance in fEPSP slope was not significantly different in response to the train in control conditions (black bars) or in baclofen (gray bars), but the CVs of the fEPSP slopes in baclofen were larger than in control conditions. *E*, The fEPSP slopes during the train in baclofen were poorly correlated with the corresponding fEPSP slopes during the train in control conditions.

fEPSP slopes were calculated using 1–2 msec after the fiber volley. In a few cases, the fEPSPs preceded by activity at ISIs of 20–30 msec generated a population spike during the fEPSP that contaminated the slope measurement. This contamination was easily identified by visual examination, and contaminated fEPSPs were excluded from analysis. All data are presented as mean ± SEM, and all error bars in figures display SEMs. Significance was assessed at $p < 0.05$.

Results

A physiologically relevant spike train from an *in vivo* recording of a CA3 pyramidal cell, shown in Figure 1*A*, was used to drive a stimulating electrode in stratum radiatum of area CA1 of the hippocampus, and fEPSPs in response to the train were recorded. Baclofen was then bath applied to achieve a stable level of inhibition, assessed by responses to 0.1 Hz stimulation, and the train

was applied again. Different fEPSPs during the train were highly variable in size, as shown by selected responses in Figure 1*B*, in both control conditions (left-hand traces) and baclofen (right-hand traces). When the individual fEPSP slopes during the train were plotted as a function of time, it was clear that the variability in fEPSP slope could not be explained as baseline instability during the train (Fig. 1*C*), because considerable variability in fEPSP slope was evident even during relatively small epochs during the train. This was true in both control conditions (filled circles) and baclofen (open circles).

Under these conditions, the vast majority of this variance results from the history dependence of synaptic transmission (Dobrunz and Stevens, 1999). To quantitatively describe this variability, we compared the variance, as well as the coefficient of variation (CV) (SD/mean), for the fEPSP slopes during the trains in control conditions and in baclofen. The variance was not significantly affected by baclofen, but the CV was increased in six experiments in which these parameters were quantified (Fig. 1*D*). The observation that the variance of fEPSP slopes during the train is not altered by baclofen does not necessarily indicate that the history dependence is unchanged; this would be the case only if the same fEPSP slopes covaried in the two conditions. To evaluate whether this is the case, we performed a correlation assay (see Materials and Methods), in which we plotted the fEPSP slope for each spike during the spike train in control conditions against the corresponding fEPSP slope for the corresponding spike during the same spike train in baclofen. If the history dependence of synaptic transmission is unchanged by baclofen, the responses should covary, and the r^2 value of the correlation should be high. Contrary to this expectation, the correlation between individual responses in control conditions and in baclofen was very poor ($r^2 = 0.09 \pm 0.04$; $n = 6$) (Figs. 1*E*, 2*D*), indicating that the history dependence of synaptic transmission is changed by baclofen.

Because this application of the correlation assay is novel, we performed several control experiments to ensure that it is valid. First, we examined whether there is a high correlation between responses to the same train delivered twice under the same conditions to ensure that history dependence is stable. This was the case ($r^2 = 0.86 \pm 0.03$; $n = 8$) (Fig. 2*A*,*D*), as reported previously (Dobrunz and Stevens, 1999). Next, we reasoned that the correlation between responses to two trials of the same train might be degraded if the responses during the second trial are smaller than those during the first as a result of the higher relative contribution of noise to the measured slope during the second trial. To address this error, we compared responses to two trials of the spike train, applied at different stimulus strengths. The r^2 values for two trials at high- and low-stimulus strengths ($r^2 = 0.76 \pm 0.03$; $n = 5$) (Fig. 2*B*,*D*) were slightly lower than those obtained by comparing two trials at the same high-stimulus strength, but this effect was not significant. Finally, we reasoned that the history dependence of synaptic transmission might not be stable in the presence of baclofen. The fEPSPs for two trials that were both in baclofen were not significantly different from those of two trials that were both in control conditions ($r^2 = 0.80 \pm 0.02$; $n = 5$) (Fig. 2*C*,*D*).

The correlation assay indicates that baclofen changes the history dependence of synaptic transmission, without characterizing the history dependence in either baclofen or control conditions. We therefore examined the relationship between the fEPSP slopes during the spike train, and the ISI between the spike generating each fEPSP and the spike preceding it, which we will refer to as the first ISI (Fig. 3*A*,*B*, circles). In control conditions (Fig. 3*A*), this function was complex, as reported previously (Dobrunz and Stevens, 1999; Dittman et al., 2000). In baclofen, (Fig. 3*B*), short first ISIs generated larger responses than long first ISIs. To estimate the degree to which the total history dependence can be explained by this first ISI, we smoothed this data (Fig. 3*A*,*B*, lines) and subtracted the smoothed function from the data to generate residual fEPSP slopes. The difference between the variance of the unmodified slopes and the variance of the residual slopes estimates the variance accounted for by this ISI during the train. The fraction of the total variance that was attributable to the first ISI was significantly higher in baclofen than in control conditions ($n = 6$) (Fig. 3*C*). The fraction of the total variance that was attributable to noise (measured as history-independent variance in fEPSP slope; obtained during steady-state stimulation at a constant frequency of 1 Hz) was not significantly different in the two conditions, so this increased importance of the first ISI for history-dependent synaptic transmission in baclofen implies a decreased importance of other spikes further back in the history of the spike train. The baclofen-induced increase in the fraction of variance in fEPSP slope that was attributable to the first ISI was caused by a general improvement in the fit of the smoothed function over all ISIs in the presence of baclofen rather than a selective improvement in fitting the smoothed function to the data over a subset of ISIs (data not shown).

To further examine how baclofen changes the history dependence, we normalized each fEPSP slope during the spike train in baclofen to the corresponding fEPSP slope during the spike train in control conditions. The resulting ratios, when plotted as a function of the first ISI, showed that baclofen had no effect on fEPSPs preceded by a short ISI but a large effect on fEPSPs pre-

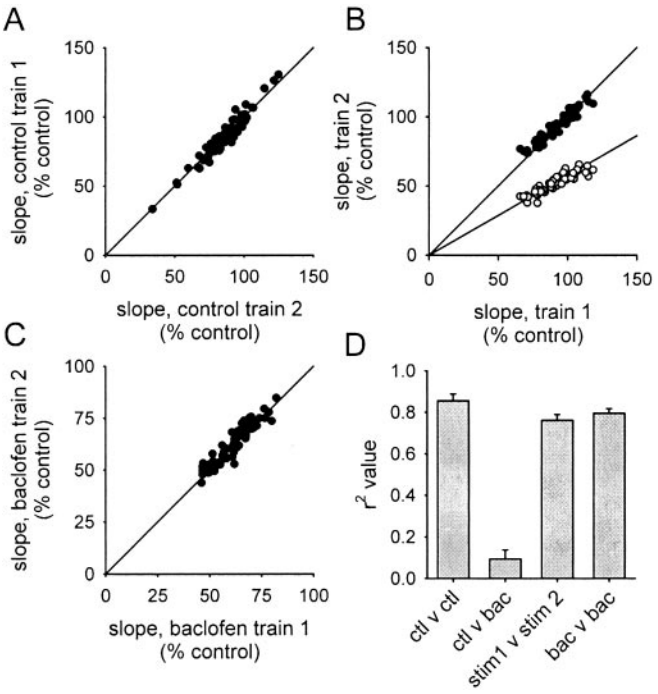

Figure 2. *A*, The corresponding fEPSP slopes during two applications of the same physiologically relevant spike train in control conditions were well correlated. *B*, The corresponding fEPSP slopes during two applications of the same train delivered at two different stimulus strengths (open circles) were well correlated, as were the fEPSP slopes during two applications of the train delivered at the same stimulus strength (filled circles). *C*, The corresponding fEPSP slopes during two applications of the same train, both in baclofen, were also well correlated. *D*, A summary of the r^2 values from experiments in Figures 1*E* and 2*A–C*. ctl, Control; bac, baclofen; stim, stimulus strength.

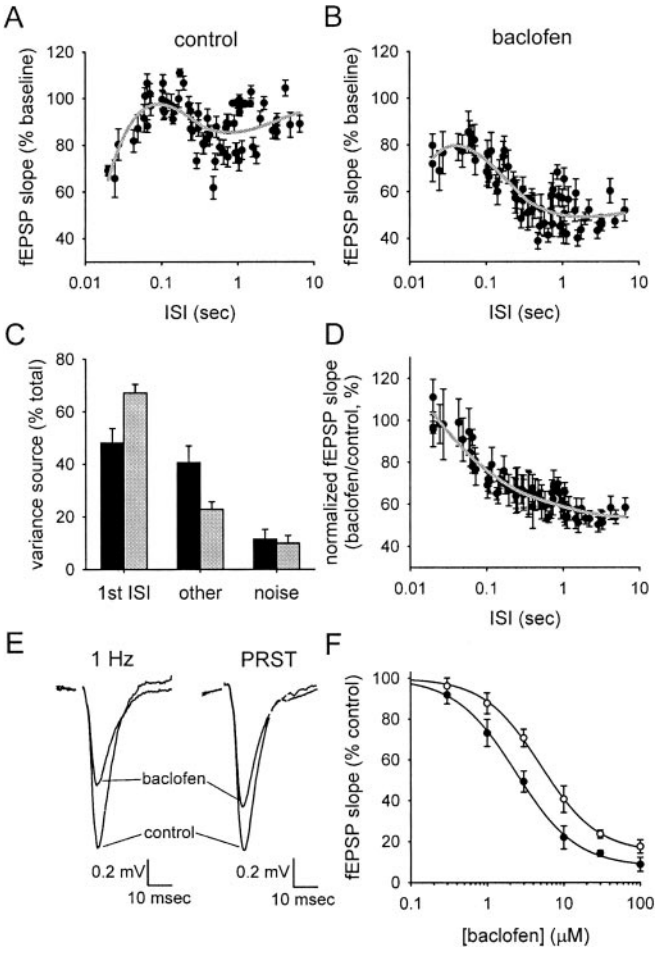

Figure 3. *A*, The fEPSP slope is plotted against the first ISI (see Results). Data shown in *A–D* are averaged from six experiments using 3 μM baclofen. A smoothed function (gray line) illustrates the analysis described in Results, and this function clearly accounts for some, but not all, of the variance in fEPSP slope. *B*, A similar analysis to that in *A* is shown but in the presence of baclofen. *C*, A summary of the sources of variance in fEPSP slope during the physiologically relevant spike train, in control conditions (black bars) and in baclofen (gray bars). *D*, The fEPSP slopes during the train in baclofen were normalized to the corresponding slopes in control conditions, and the normalized slope was plotted against the first ISI. Smoothing the normalized data provided a monotonic function (gray line) that accounted for most of the variance in the normalized data. *E*, Averaged fEPSPs are shown during 1 Hz constant-frequency stimulation (1 Hz) and during a physiologically relevant spike train (PRST), in control conditions and in 3 μM baclofen. Five to 20 sweeps were used for 1 Hz stimulation, and all of the spikes during the train were used for the physiologically relevant spike train. *F*, Dose–response curves are shown for the overall inhibitory effect of baclofen on fEPSPs during constant-frequency stimulation (filled circles) and on fEPSPs during the physiologically relevant spike train (open circles). For each dose, $n = 4–6$.

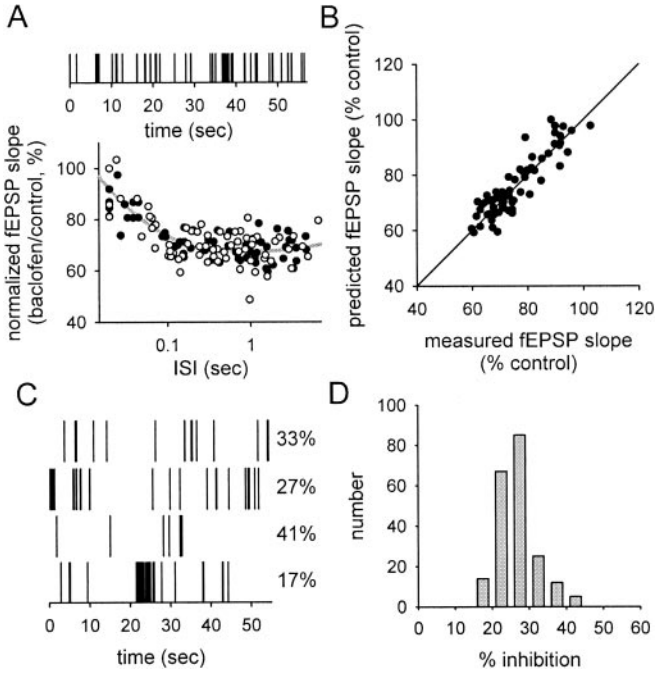

Figure 4. *A*, Top, A second physiologically relevant spike train, unrelated to the original one shown in Figure 1*A*, is shown. Bottom, The analysis shown in Figure 3*D* was performed for both the original spike train (open circles) and the new spike train (filled circles), both done in the same experiment. The responses to both trains fall on the smoothed function generated by the original train (gray line). *B*, The smoothed function from the original train was used to predict fEPSP slopes in response to the new train in 3 μM baclofen, given the fEPSP slopes during the new train in control conditions. These predicted responses are well correlated with the recorded responses. *C*, Raster plots from a CA3 pyramidal cell recorded *in vivo* are shown, during repeated behavioral trials of a maze. To the right of the data are the levels of overall inhibition predicted by the function in Figure 3*D*. *D*, A summary of the analysis in *C* is shown for 208 trials of the maze.

ceded by a long ISI (Fig. 3*D*, symbols). Smoothing this data provided a function that accounted for >90% of the variability in the averaged data (Fig. 3*D*, line), indicating that baclofen changes the history dependence of synaptic transmission primarily through effects on the synaptic responses to the first ISI.

It is not clear from this analysis whether the changes in history dependence induced by baclofen are large enough to have much functional impact on the actions of baclofen during physiologically relevant spike trains. We therefore compared the average inhibitory effect of baclofen on synaptic transmission during the physiologically relevant spike train and during steady-state responses to a constant-frequency train at the same average frequency (1 Hz stimulation). Baclofen was less effective at inhibiting transmission during the physiologically relevant spike train than it was at inhibiting transmission during constant-frequency trains, as shown by displaying averaged fEPSPs (Fig. 3*E*). Over a range of doses, this effect reduced the apparent affinity of the inhibition induced by baclofen during physiologically relevant spike trains (Fig. 3*F*). The overall inhibitory effectiveness of $GABA_B$R-mediated presynaptic inhibition during physiologically relevant spike trains is therefore overestimated by using constant-frequency stimulus trains, because these paradigms do not take into account the effects of baclofen on the history dependence of synaptic transmission.

Our results so far have examined the effects of baclofen on a representative physiologically relevant spike train, but we wondered whether conclusions drawn from these experiments could be extrapolated to other spike trains. We therefore examined fEPSPs generated by a second, unrelated physiologically relevant spike train (Fig. 4*A*, top) in the presence and absence of baclofen. A comparison of results from the original train in Figure 1*A* with those from the new train in the same experiment revealed that baclofen had similar effects on the history dependence of synaptic transmission for both trains (Fig. 4*A*, bottom). To quantify this effect, we measured the fEPSPs during the new train in control conditions. We then used this data, along with the relationship between the normalized fEPSP slope and the first ISI derived from data using the original train, to predict the values for the fEPSPs during the new train in baclofen. These predicted values are strongly correlated with the measured values ($r^2 = 0.73 \pm 0.05$; $n = 5$) (Fig. 4*B*), confirming that the changes in history dependence measured using one physiologically relevant spike

train can be extrapolated to other physiologically relevant spike trains.

The robust nature of this change in history dependence allowed us to consider the reliability of presynaptic inhibition during a behavioral task. *In vivo* recordings of CA3 pyramidal cells during repeated performances of a maze show considerable variability in the pattern of spiking from one trial to the next, even in the same cell (data from Wiebe and Stäubli, 1999), and it is not known whether baclofen would be similarly effective on each behavioral trial. We used the smoothed function in Figure 3*D*, and physiologically relevant spike trains from cells that were recorded during repeated trials in the maze, to determine how much the overall inhibition caused by baclofen on a given cell would vary from one trial to the next. Representative raster plots of spike trains from one cell during different trials are shown in Figure 4*C*, along with the expected average level of inhibition caused by 3 μM baclofen. There is considerable trial-to-trial variability in the overall inhibitory effectiveness of baclofen; when all trials from that cell were considered, the overall inhibition caused by baclofen during each trial ranged from 17 to 44% (Fig. 4*D*). To quantify this variability, we measured the trial-to-trial CV for the overall inhibition caused by baclofen; this CV was 21 $\pm$ 4% in an analysis of seven CA3 cells. This result indicates that, because of history-dependent effects on synaptic transmission, $GABA_BRs$ will vary substantially in their effectiveness at inhibiting synaptic transmission during different spike trains that occur during different trials of a behavioral task.

Discussion

We found that $GABA_BR$ activation alters the history dependence that relates synaptic output to spike timing during physiologically relevant spike trains. Our results are consistent with studies in which baclofen changes paired-pulse plasticity (Manabe et al., 1993; Gil et al., 1997). However, it is difficult to directly compare these previous findings with our present results, because we did not observe a facilitation at short ISIs that would match the PPF observed at these synapses during paired-pulse protocols. It is therefore unlikely that identical forms of activity-dependent short-term plasticity are engaged during paired-pulse stimulation and the physiologically relevant spike trains examined here, and it is unclear whether baclofen similarly affects those different forms of plasticity. To our knowledge, only two previous studies have considered the effects of $GABA_BRs$ during complex spike trains. In these studies, baclofen had nonuniform effects on synaptic responses during the trains, similar to that observed by lowering the calcium concentration (Varela et al., 1997; Kreitzer and Regehr, 2000), which were modeled as changes in multiple forms of activity-dependent short-term plasticity (Varela et al., 1997). Our results extend these observations by providing a model-independent description of the baclofen-induced changes in history dependence and by identifying functional consequences of these changes.

The observation that baclofen alters history dependence makes it difficult to predict the functional role of $GABA_BRs$ using data from low-frequency stimulus paradigms or brief spike trains. Using steady-state responses, different studies have found that baclofen can have an inhibitory effect, no effect at all, or even an excitatory effect, depending on the frequency of the stimulus train. We found that the overall effect of baclofen during physiologically relevant spike trains is inhibitory, although this overall effect is substantially less than would be predicted on the basis of low-frequency stimulation, and the actions of baclofen would be more appropriately described as a high-pass filter than as an inhibition.

We used extracellular recordings to measure the synaptic responses during physiologically relevant spike trains with minimal noise, which has allowed us to perform experiments that would be impractical using whole-cell recording. However, this configuration has two limitations that deserve consideration. First, we were unable to examine ISIs of $<$20 msec, because overlap of fEPSPs at these ISIs would introduce large errors in our measurements of fEPSP slope. Given that baclofen has little effect on ISIs at 20 msec, this limitation is unlikely to change our major conclusions and, if anything, is likely to cause underestimation of the true shift in the effectiveness of baclofen during physiologically relevant spike trains. Second, the field response is heavily averaged across many synapses. Our data are therefore a description of the average effects of baclofen, with the caveat that individual synapses may deviate from this average.

Our study has used baclofen to engage presynaptic inhibition. In this system, baclofen activates both presynaptic $GABA_BRs$, which inhibit transmitter release, and postsynaptic $GABA_BRs$, which engage G-protein-coupled inwardly rectifying K^+ (GIRK) currents. In principle, postsynaptic $GABA_BRs$ could contribute to the effects described here; however, it is difficult to imagine how tonic activation of the known postsynaptic effects of baclofen could lead to the observed history-dependent effects. Moreover, the $GABA_BR$-mediated inhibition of the fEPSP is known to be unaffected by genetic removal of the postsynaptic GIRK currents (Lüscher et al., 1997), and, to our knowledge, no direct effect of $GABA_BRs$ on AMPA receptors has been reported. For these reasons, the history-dependent effects seen here are almost certainly attributable to the activation of presynaptic $GABA_BRs$.

To understand the functions of these receptors *in vivo*, the conditions under which endogenous GABA activates these receptors must also be identified. These presynaptic $GABA_BRs$ are not activated during rhythmic activity in the hippocampus (Scanziani, 2000), and $GABA_BR$ antagonists had no effect during the spike trains used here (our unpublished observation). However, tetanic stimuli can activate these receptors (Isaacson et al., 1993). Once the endogenous conditions that activate these receptors have been clarified, that information could be combined with data from this study to develop a more realistic model for the endogenous $GABA_BR$-mediated presynaptic inhibition at this synapse.

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