Net Interaction Between Different Forms of Short-Term Synaptic Plasticity and Slow-IPSPs in the Hippocampus and Auditory Cortex

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Buonomano, Dean V. and Michael M. Merzenich. Net interaction between different forms of short-term synaptic plasticity and slow-IPSPs in the hippocampus and auditory cortex. *J. Neurophysiol.* 80: 1765–1774, 1998. Paired-pulse plasticity is typically used to study the mechanisms underlying synaptic transmission and modulation. An important question relates to whether, under physiological conditions in which various opposing synaptic properties are acting in parallel, the net effect is facilitatory or depressive, that is, whether cells further or closer to threshold. For example, does the net sum of paired-pulse facilitation (PPF) of excitatory postsynaptic potentials (EPSPs), paired-pulse depression (PPD) of inhibitory postsynaptic potentials (IPSPs), and the hyperpolarizing slow IPSP result in depression or facilitation? Here we examine how different time-dependent properties act in parallel and examine the contribution of γ-aminobutyric acid-B ($GABA_B$) receptors that mediate two opposing processes, the slow IPSP and PPD of the fast IPSP. Using intracellular recordings from rat CA3 hippocampal neurons and L-II/III auditory cortex neurons, we examined the postsynaptic responses to paired-pulse stimulation (with intervals between 50 and 400 ms) of the Schaffer collaterals and white matter, respectively. Changes in the amplitude, time-to-peak (TTP), and slope of each EPSP were analyzed before and after application of the $GABA_B$ antagonist CGP-55845. In both CA3 and L-II/III neurons the peak amplitude of the second EPSP was generally depressed (further from threshold) compared with the first at the longer intervals; however, these EPSPs were generally broader and exhibited a longer TTP that could result in facilitation by enhancing temporal summation. At the short intervals CA3 neurons exhibited facilitation of the peak EPSP amplitude in the absence and presence of CGP-55845. In contrast, on average L-II/III cells did not exhibit facilitation at any interval, in the absence or presence of CGP-55845. CGP-55845 generally ''erased'' short-term plasticity, equalizing the peak amplitude and TTP of the first and second EPSPs at longer intervals in the hippocampus and auditory cortex. These results show that it is necessary to consider all time-dependent properties to determine whether facilitation or depression will dominate under intact pharmacological conditions. Furthermore our results suggest that $GABA_B$-dependent properties may be the major contributor to short-term plasticity on the time scale of a few hundred milliseconds and are consistent with the hypothesis that the balance of different time-dependent processes can modulate the state of networks in a complex manner and could contribute to the generation of temporally sensitive neural responses.

INTRODUCTION

Long-term changes in synaptic strength, such as those seen during associative long-term potentiation, are generally accepted to be involved in learning and memory. However synaptic efficacy varies not only on a long time scale but also on a shorter time scale; these changes are referred to as short-term plasticity. Although the magnitudes of short-term and long-term changes are approximately the same, the functional role of short-term changes in synaptic strength is not well understood. We previously suggested that a functional role of short-term forms of plasticity and time-dependent properties in general is to enable temporal information processing in the range of tens to hundreds of milliseconds (Buonomano and Merzenich 1995; Buonomano et al. 1997). Specifically, by changing the state of neural networks in a time-dependent manner, short-term forms of plasticity and slow synaptic events may permit neurons to respond selectively to temporal features of stimuli such as duration, order, and interval.

Three time-dependent properties that are particularly robust and likely to significantly affect the temporal response characteristics of both hippocampal and neocortical neurons on the time scale of tens to hundreds of milliseconds are *1*) paired-pulse plasticity (PPP) of monosynaptic of excitatory postsynaptic potentials (EPSPs), *2*) paired-pulse depression (PPD) of the fast inhibitory postsynaptic potential (IPSP), and *3*) slow IPSPs. PPP of the fast EPSP refers to the homosynaptic changes in excitatory synapses that can take the form of facilitation (paired pulse facilitation, PPF) (Manabe et al. 1993; Ramoa and Sur 1996; Stratford et al. 1996; Zalutsky and Nicoll 1990) or depression (PPD) (Abbott et al. 1997; Markram and Tsodyks 1997; Thomson and Deuchars 1994). PPD of the $GABA_A$-mediated fast IPSP results in a decreased amplitude of the second of a pair of IPSPs and is mediated through presynaptic γ-aminobutyric acid-B ($GABA_B$) receptors (Davies et al. 1991; Deisz and Prince 1989; Fukuda et al. 1993; Lambert and Wilson 1993; Nathan and Lambert 1991). Finally, the slow IPSP is mediated through postsynaptic metabotropic $GABA_B$ receptors and can produce a large hyperpolarization of the postsynaptic neuron that peaks between 100 and 200 ms (Hablitz and Thalmann 1987; Newberry and Nicoll 1984).

Here we examine how excitatory and inhibitory synapses in hippocampal and neocortical circuits and short-term forms of plasticity act in parallel and whether the net effect of these different components is facilitatory or depressive, that is, is the cell closer or further from threshold. We also examine in detail the importance of $GABA_B$-dependent mechanisms in generating these time-dependent changes.

METHODS

Both hippocampal and auditory cortex slice experiments were performed on 400- to 500-μm thick slices from 21- to 40-day-

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old Spraque-Dawley rats. Slices were submerged in a oxygenated medium comprised of (in mM) 119 NaCl, 2.5 KCl, 1.3 $MgSO_4$, 1.0 NaH_2PO_4, 26.2 $NaCO_3$, 2.5 $CaCl_2$, and 10 glucose. After an equilibrium period of $\geq$1 h, slices were transferred to a recording chamber perfused at a rate of 2 ml/min and maintained at a temperature of 30–31°C.

Hippocampal experiments

For hippocampal slices the hippocampus was dissected out, and transverse hippocampal slices were cut with a vibratome. Intracellular recordings were made from CA3 pyramidal cells. For stimulation, a single bipolar electrode was placed in the hilus of the dentate gyrus.

Auditory cortex experiments

For auditory cortex slices the brain was removed and cut into two hemispheres. One hemisphere was placed with the medial surface on an agar block, and transverse slices were then cut starting from the posterior end. In the rat the auditory cortex occupies an area of ~15–20 mm^2 of the dorsolateral surface of the temporal lobe (Cox et al. 1992; Paxinos and Watson 1986; Roger and Arnault 1989; Sally and Kelly 1988; Swanson 1992; Winer and Larue 1987). Auditory cortex was located within two or three slices before and after the crossing of the corpus collossum. The medial geniculate nucleus is visible and contained within the same plane and can be used as a marker of the correct anterior–posterior level. Within each slice, the auditory cortex was located 2 ± 1 mm above (dorsal) the rhinal fissure, which is easily visualized in individual slices. In vivo experiments in the lab also confirmed that this area corresponds to the primary auditory cortex. Intracellular recording were made from L-II/III pyramidal neurons (200–400 μm from the surface). Stimulating electrodes were placed in the L-VI/white matter border.

Recording and stimulation

Intracellular recordings were made with sharp electrodes with an impedance of 40–100 MΩ when filled with 3 M KAc. For hippocampal cells, penetrations were considered acceptable if the resting potential was below −60 mV, the input resistance was $\geq$30 MΩ, and there were overshooting action potentials. The same criteria were used for neocortical neurons except that the resting potential criterion was −70 mV. In the cortical recordings cells were depolarized with a pulse of 0.1–0.2 nA during paired-pulse stimulation to permit visualization and measurement of the slow IPSP. Stainless steel bipolar electrodes were used for stimulation. Current intensity was adjusted to an intensity at which the slow IPSP was clearly visible but not saturated (generally between 30 and 200 μA with a pulse duration of 0.1 ms).

Drugs

For experiments 1–2 μM of the potent $GABA_B$ antagonist CGP-55845 was added to the bath from a stock solution of 1 mM in distilled water. CGP-55845 was kindly provided by Dr. Olpe and Dr. Fröestl from Ciba-Geigy.

Data analysis

Five different interpulse intervals (IPIs) were used for paired-pulse stimulation. The different IPIs were continuously presented in ascending order (50–100–200–300–400–50–100), with an intertrial interval of 15–20 s. Three parameters of the postsynaptic response to each pulse were measured (Fig. 1): peak EPSP amplitude, time-to-peak (TTP), and slope. An average of three traces at each IPI was used for parameter extraction and data analysis.

Statistics

To determine whether there was a significant difference between the different IPIs for a given measure, a one-way analysis of variance (ANOVA) with repeated measures was used. Because for some cells there were missing values at a given IPI where a spike may have occurred, only the cells without missing values were analyzed; thus the degrees of freedom used in the statistics reflect the number of cells with complete IPI functions. To determine whether CGP-55845 produced significant changes, a two-way ANOVA with repeated measures on one factor (IPI) was performed. *F* tests for simple effects were used to determine at which IPI the control and CGP-55845 groups were different (Brunning and Kintz 1987). Two-tailed statistics were used for all tests except the simple *F* tests for which prehoc hypotheses were established.

RESULTS

The primary goal of this study is to analyze how different synapses and short-term forms of plasticity interact and whether the net effect is of facilitation or depression, i.e., to increase or decrease the probability of firing to a given temporal input pattern. For this analysis and to obtain indirect measures of the different components contributing to postsynaptic responses, we measured paired-pulse changes in the peak amplitude, TTP, and slope of EPSPs. EPSP amplitudes were measured from resting membrane potential rather than from membrane potential at EPSP onset (Fig. 1). This measure provides absolute information as to whether, in relation to the first EPSP, the second EPSP was closer to or farther from threshold. Throughout this paper PPP of the EPSP amplitude is defined as the absolute difference in EPSP amplitude between the second and first EPSP, e.g., $EPSP_{300} - EPSP_0$ (ΔEPSP). Subtraction rather than the ratio was used because EPSP amplitude can take on

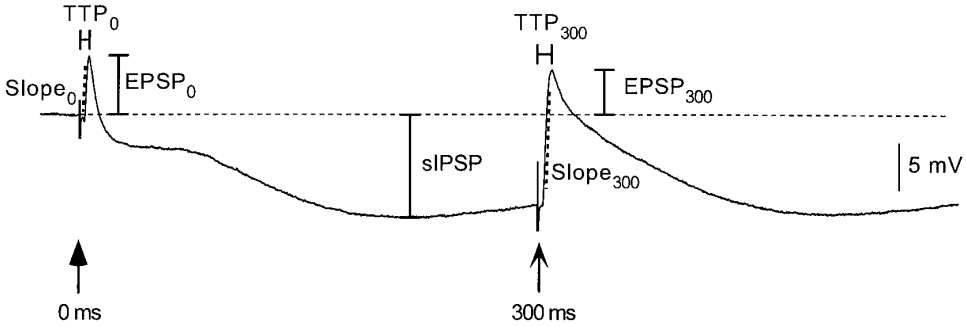

FIG. 1. Parameters used for the analysis of postsynaptic responses. excitatory postsynatpc potential (EPSP) amplitude for both the 1st and 2nd EPSP were measured from resting membrane potential. This measure provides information as to whether the net effect of different synaptic components was facilitatory or depressive. Time-to-peak (TTP) was defined as the time from stimulus artifact to the peak EPSP amplitude. Slope was measured as the maximum slope of the rising phase of the EPSP.

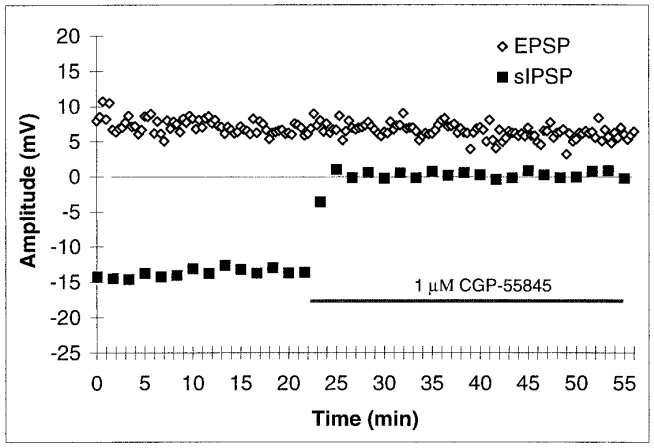

FIG. 2. The γ-aminobutyric acid-B ($GABA_B$)-receptor antagonist CGP-55845 abolishes the slow IPSP but does not significantly affect the amplitude of the 1st EPSP. After a baseline period in which both the amplitude of the 1st EPSP and the slow IPSP were stable, 1 μm CGP-55845 was applied to the bath. Because the maximal amplitude of the slow IPSP varies according to the interpulse interval (IPI, because of interaction with the 2nd pulse), the maximal amplitude at one IPI (50 ms) was plotted.

negative values (e.g., when the peak is below resting membrane potential because of hyperpolarization). Paired-pulse effects on TTP were also analyzed as the difference (ΔTTP), and paired-pulse effects on slope were analyzed as the ratio of the second EPSP over the first.

Analyzing changes in EPSP amplitude, slope, and TTP makes it possible to obtain indirect measures of the monosynaptic strengths of both the fast EPSP and the fast IPSP. The EPSP slope is determined primarily by an interaction between the strength of the monosynaptic EPSP and membrane potential at EPSP onset (i.e., driving force). Thus the slope of the second EPSP does not provide a pure measure of the strength of the monosynaptic EPSP because the cell may be hyperpolarized at the onset of the second EPSP. However, in the presence of a $GABA_B$ antagonist, the EPSP slope at the longer IPIs is primarily determined by EPSP strength. A second measure that provides information about the different components of the postsynaptic potential is the TTP. In the absence of inhibitory input, TTP was used as a measure of presynaptic facilitation (Gingrich et al. 1988; Hochner et al. 1986). With intact fast IPSPs the TTP of the EPSP is primarily determined by strength and onset time of the fast IPSP, which cuts off the EPSP. It is known that, in hippocampal and neocortical slices, as stimulation intensity increases, the TTP (and sometimes the amplitude) of the EPSP actually decreases (e.g., Hirsch and Gilbert 1991; Sutor and Hablitz 1989). This is due to an increase recruitment of inhibitory inputs. With sharp electrode recordings the TTP is generally <5 ms. The presence of bicuculline or picrotoxin, however, produces a dramatic increase in TTP (e.g., McCormick 1989; McCormick et al. 1993). In essence, the stronger the fast IPSP in relation to the fast EPSP the shorter the TTP. In this study increases in the TTP reflect a decrease in the fast IPSP and thus reflect a form of facilitation that results in a broadening of the EPSP width. TTP was used to quantify PPD of the fast IPSP rather than a measure of the EPSP width or area because the EPSP width and area are dramatically affected by changes in the driving force, particularly because the reversal potential of the fast IPSP is close to the resting membrane potential.

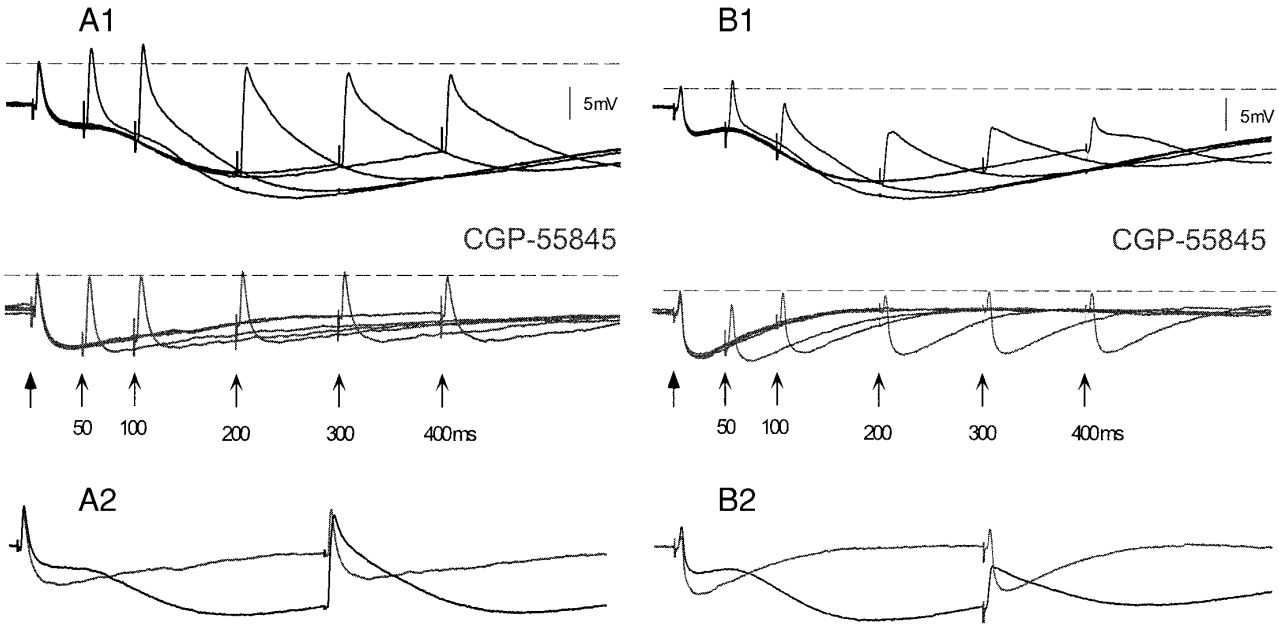

FIG. 3. Postsynaptic responses to paired-pulse stimulation of 2 CA3 neurons (*A.1* and *B.1*) before (*top panels* in black) and after application of CGP-55845 (*bottom panels* in red). Averages of 3 sweeps at each of the 5 IPI are overlaid. In comparison to the 1st EPSP, the 2nd EPSP at different IPIs differed in both peak amplitude TTP and width. In both cells CGP-55845 tended to remove the influence of the 1st pulse on the postsynaptic responses to the 2nd pulse, that is, there was relatively little difference between the 1st and 2nd EPSPs at the longer IPIs. CGP-55845 blocked the slow IPSP and blocked the paired-pulse changes in the width and TTP of the 2nd EPSP. *A.2* and *B.2*: overlaid traces for the 300-ms IPI before and after application of CGP-55845. Note that in *A.2*, although the peak of the second EPSP is approximately the same in the presence and absence of CGP-55845, that the width and TTP are dramatically different. This indicates that the change in width was not due to changes in the driving force produced by the slow IPSP.

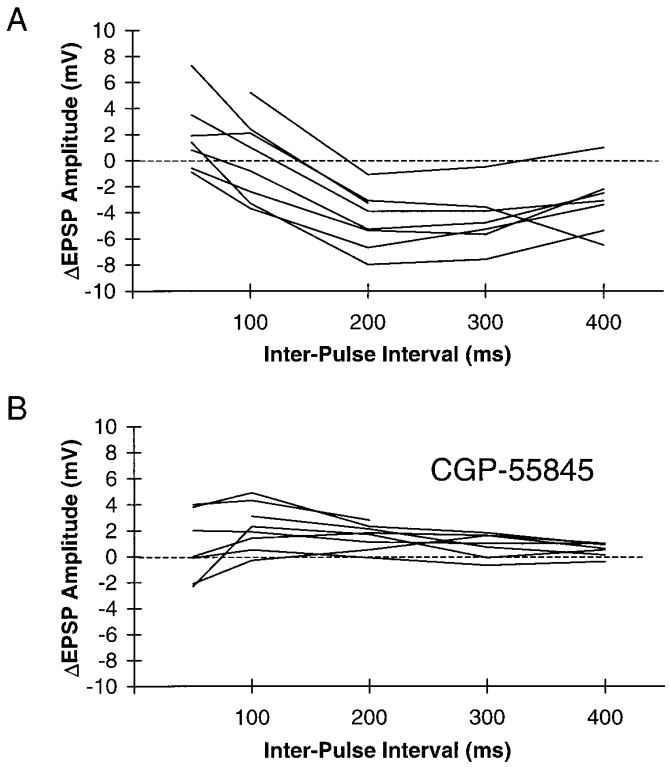

FIG. 4. Paired-pulse plasticity of the peak EPSP amplitude, expressed as ΔEPSP, as a function of IPI for each CA3 neurons. *A*: each trace represents ΔEPSP values at each of the 5 IPIs used for a given cell (n = 8). *B*: data from the same cells in the presence of CGP-55845. Some traces have <5 points because peak amplitude could not be measured in some instances.

Hippocampus

The $GABA_B$-antagonist CGP-55845 was highly effective in abolishing the slow IPSP, with little effect on the amplitude of the fast EPSP. Figure 2 shows a hippocampal experiment in which both the maximal amplitude of the slow IPSP and the amplitude of the first EPSP (obtained from all IPIs) were shown to be stable over a 20-min baseline period. Bath application of CGP-55845 abolished the slow IPSP without changing the magnitude of the fast EPSP. We were not able to wash out CGP-55845.

Postsynaptic potentials of two hippocampal CA3 pyramidal cells produced by paired-pulse stimulation are shown in Fig. 3. Short-term plasticity and time-dependent events are expressed in the differences between the first EPSP and the EPSP produced by the second pulse at different IPIs. Both cells exhibited differences in peak amplitude, an apparent broadening of the EPSP, and marked slow IPSPs. The addition of the $GABA_B$ antagonist CGP-55845 abolished the slow IPSP as well as the increase in the width of the second EPSP. The overlaid trace in Fig. 3*A* illustrates that the width of the second EPSP was much narrower in the presence of CGP-55945. The difference in EPSP width (and TTP) produced by CGP-55845 was due to changes in the strength of the fast IPSP rather than to changes in the driving force; because the peak amplitudes or the EPSP at 300 ms are similar at the onset of the fast IPSP, the driving force for the fast IPSP should be similar. Furthermore the decrease in the width and TTP of the second EPSP produced by CGP-55845 is not likely to be due to a decrease in the strength of the EPSP because $GABA_B$ antagonists do not seem to alter excitatory responses to single pulses (Davies and Collingridge 1996; Davies et al. 1991). In approximately one-half of the hippocampal cells there was an increase in the fast IPSP produced by the first pulse in the presence of CGP-55845, suggesting that there might be a ''baseline'' $GABA_B$-dependent presynaptic inhibition of the fast IPSP. However, the increase in the first IPSP did not affect the measure of the second PSP at the 50-ms IPI because on average there was no significant difference between EPSP amplitude and TTP at 50 ms.

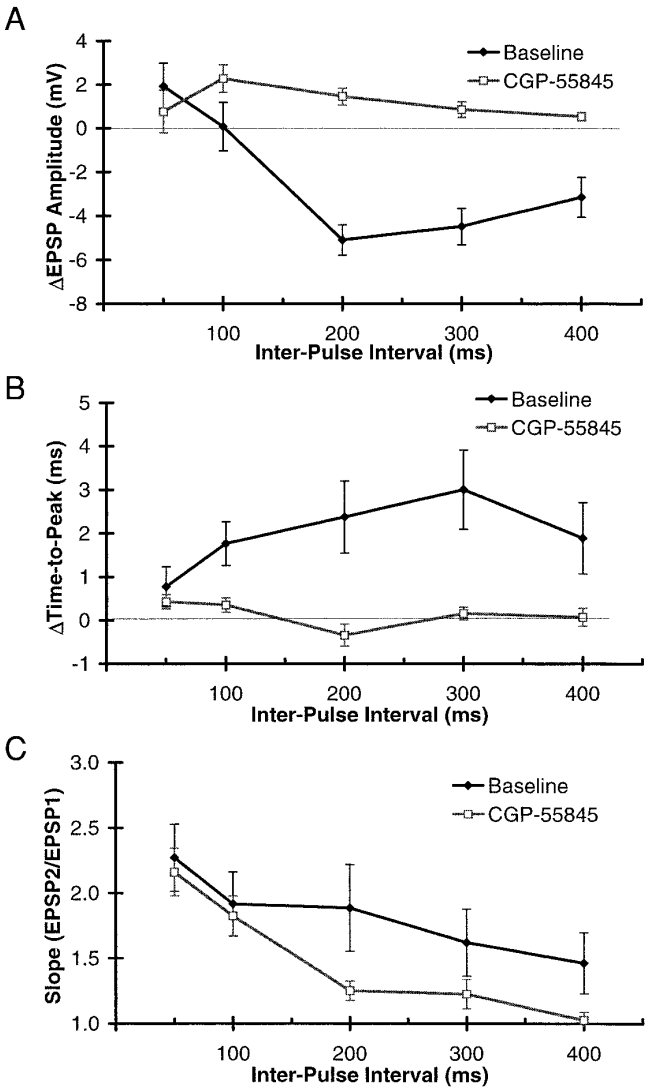

FIG. 5. Average effects of CGP-55845 on IPI functions for EPSP amplitude, TTP, and slope for hippocampal neurons. *A*: ΔEPSP amplitude. In the control condition (black) facilitation of 2 mV was generally seen for the IPI of 50 ms, and depression was seen for the interval of >100 ms. CGP-55845 flattened the IPI function and abolished any depression of peak EPSP amplitude. *B*: ΔTTPs were positive at all IPI, reflecting the increased TTP and broadening of the 2nd EPSP in relation to the 1st. CGP-55845 blocked the increases in TTP and again flattened the IPI function. *C*: EPSP slope was facilitated at all intervals but more so at the 50-ms IPI. CGP-55845 did not flatten the IPI function but did abolish most of the facilitation at the longer IPIs, which was largely due to increases in driving force produced by the slow IPSP.

The temporal profile of the facilitation/depression of the peak EPSP amplitude for all cells is shown in Fig. 4. At the 50- and 100-ms IPI either facilitation or depression was observed, whereas at the longer intervals depression was generally observed (Fig. 4*A*). Blocking all $GABA_B$-dependent processes generally flattened the IPI function, with some facilitation remaining at all intervals. Figure 5*A* shows the average results of EPSP amplitude. A two-way ANOVA in which IPI was a dependent factor and the presence or absence of CGP-55845 was an independent factor revealed a significant interaction ($F_{4,40} = 15.42$, $P < 10^{-4}$). The significant interaction indicates that CGP-55845 affected ΔEPSP but not at all IPIs. *F* tests for simple effects revealed that CGP-55845 increased the ΔEPSPs at all IPIs except at 50 ms. One-way ANOVAs revealed that, although there were significant differences between ΔEPSPs at different intervals for the control condition ($F_{4,20} = 21.6$, $P < 10^{-4}$), there were no significant differences in the IPI function in the presence of CGP-55845 ($F_{4,20} = 1.6$, $P > 0.2$).

Figure 5*B* displays the average data for the TTP analysis. The TTP of the second EPSP was longer than that of the first for all intervals (i.e., ΔTTP > 0 ms), approaching 3 ms for the 300-ms IPI. The two-way ANOVA revealed a significant interaction between IPI and the presence/absence of CGP-55845 ($F_{4,40} = 7.52$, $P < 0.001$). Post hoc analysis revealed that CGP-55845 significantly reduced ΔTTP at the 200 and 300 ms IPI. A one-way ANOVA revealed a significant dependence of the ΔTTPs on IPI in the control condition ($F_{4,20} = 4.87$, $P < 0.01$). In the presence of CGP-55845, there was little difference between the TTP of the first EPSP and of the second EPSP (ΔTTP ≅ 0 ms for all IPIs). However there was still a significant dependence on the IPI ($F_{4,20} = 7.4$, $P < 0.001$). In absolute terms in the presence of CGP-55845 the TTP difference between different intervals was <1 ms. Figure 5*C* displays the relationship between relative slope and IPI. For all intervals a facilitation of the slope measure was observed. The two-way ANOVA revealed no significant interaction between IPI and CGP-55845 ($F_{4,40} = 0.16$). Furthermore, there was no main effect of CGP-55845 ($F_{1,10} = 0.24$). The main effect of IPI was significant ($F_{4,40} = 17.5$, $P < 10^{-4}$), indicating that both in the absence and presence of CGP-55845 the slope ratio changed significantly with the IPI. The facilitation observed for the slope measure was in part due to the increased driving force produced by both the $GABA_A$- and $GABA_B$-dependent hyperpolarization. This effect was made clear by comparing the 200-ms IPI of the control and the CGP-55845 responses. Blocking the slow IPSP abolished hyperpolarization at 200 ms, which also dramatically decreased the degree of slope facilitation at that time point. However, the facilitation in the slope measure also reflects the monosynaptic PPF of the EPSP that was previously observed at these synapses (e.g., Xiang et al. 1994; Zalutsky and Nicoll 1990).

It is important to note that none of the changes in the paired-pulse analysis between the control and CGP-55845 conditions were due to changes in the response to the first pulse. CGP-55845 did not significantly alter the EPSP amplitude (control 4.71 ± 0.9 mV, CGP-55845 4.72 ± 1.06 mV), TTP (6.61 ± 0.5 ms, 6.64 ± 0.57 ms), or slope (1.67 ± 0.28 ms/mV, 1.69 ± 0.31 ms/mV) of the first EPSP. Thus

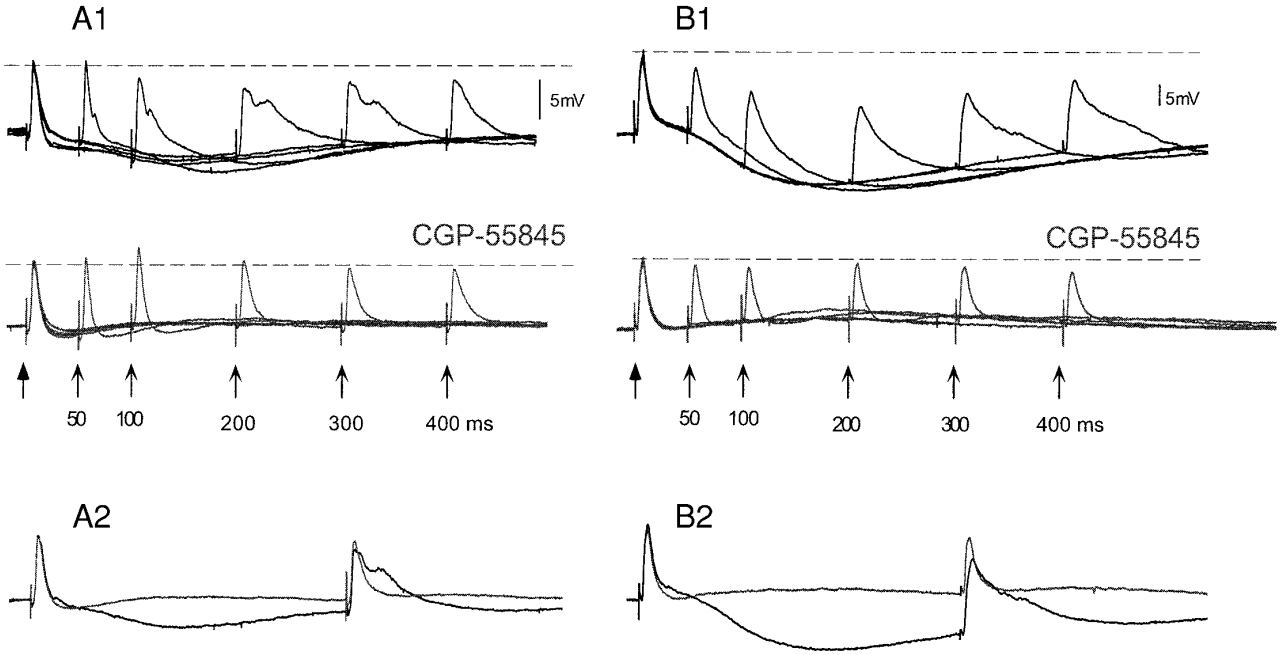

FIG. 6. Postsynaptic responses to paired pulse stimulation of 2 auditory cortex neurons (*A.1* and *B.1*) before (*top panels* with black traces) and after application of CGP-55845 (*bottom panels* with red traces). Averages of 3 sweeps at each of the 5 IPIs are overlaid. In both cells the 1st and 2nd EPSPs differed in peak amplitude, TTP, and width. CGP-55845 tended to remove the influence of the 1st pulse on the postsynaptic responses to the 2nd pulse. CGP-55845 blocked the slow IPSP and blocked the paired-pulse changes in the width and TTP of the 2nd EPSP. *A.2* and *B.2*: overlaid traces for the 300-ms IPI before and after application of CGP-55845. Note that in *A.2*, although the peak of the 2nd EPSP is approximately the same in the presence and absence of CGP-55845, that the width and TTP are dramatically different. This indicates that the change in width is not due to changes in the driving force produced by the slow IPSP.

$GABA_B$ properties operate primarily in a time-dependent fashion. Because it was not possible to wash out the CGP-55845, the stability of the first EPSP provided a means to control for nonspecific changes in cell or slice conditions. Changes in the first fast IPSP produced by CGP-55845 also did not seem to produce significant changes in the parameters measured here; changes in the first fast IPSP would be expected to primarily alter measurements at the 50-ms IPI, which was generally not significantly different between the control and CGP-55845 condition.

Auditory cortex

Figure 6 shows the response of two LII/III pyramidal cells to paired-pulse stimulation with the same five intervals used above. The magnitude of the slow IPSP was generally smaller then that observed in CA3 cells. As for CA3 neurons there were clear differences in the peak amplitude and width of the postsynaptic response of the first and second EPSP. The $GABA_B$ antagonist CGP-55845 was effective in blocking both the slow IPSP and the broadening of the second EPSP. Note that in the cell shown in Fig. 6*A* that, in addition to the EPSP broadening, late polysynaptic components were seen for the second EPSP at IPIs of 100–300 ms. Interestingly, CGP-55845 also seemed to block the polysynaptic inputs. It is possible that this is due to the facilitatory effect of presynaptic $GABA_B$ receptors; as a result of PPD of the fast IPSP other excitatory neurons may have reached threshold during the second pulse in the absence of CGP-5845 but not in its presence.

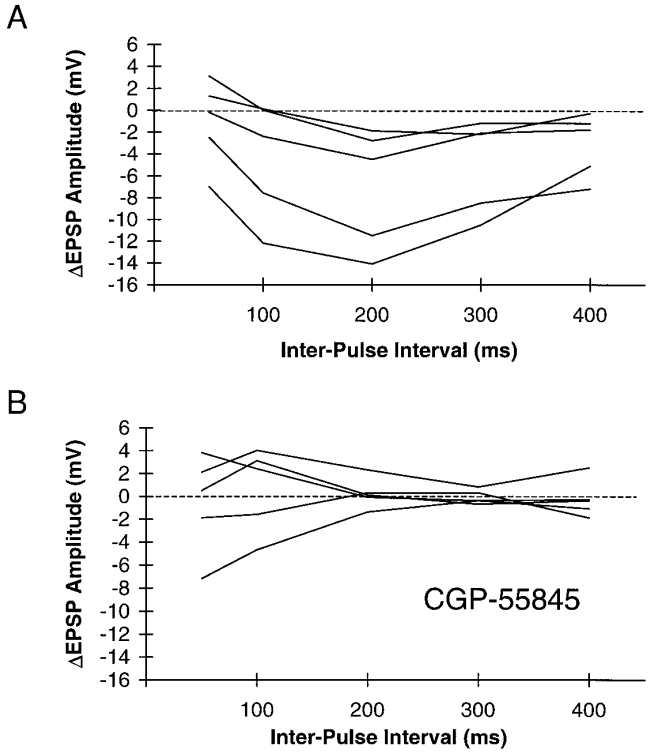

FIG. 7. Paired-pulse plasticity of the peak EPSP amplitude, expressed as ΔEPSP, as a function of IPI for each neocortical neuron. *A*: each trace represents ΔEPSP values at each of the 5 IPIs used for a given cell (n = 8). *B*: data from the same cells in the presence of CGP-55845. Some traces have <5 points because peak amplitude could not be measured in some instances.

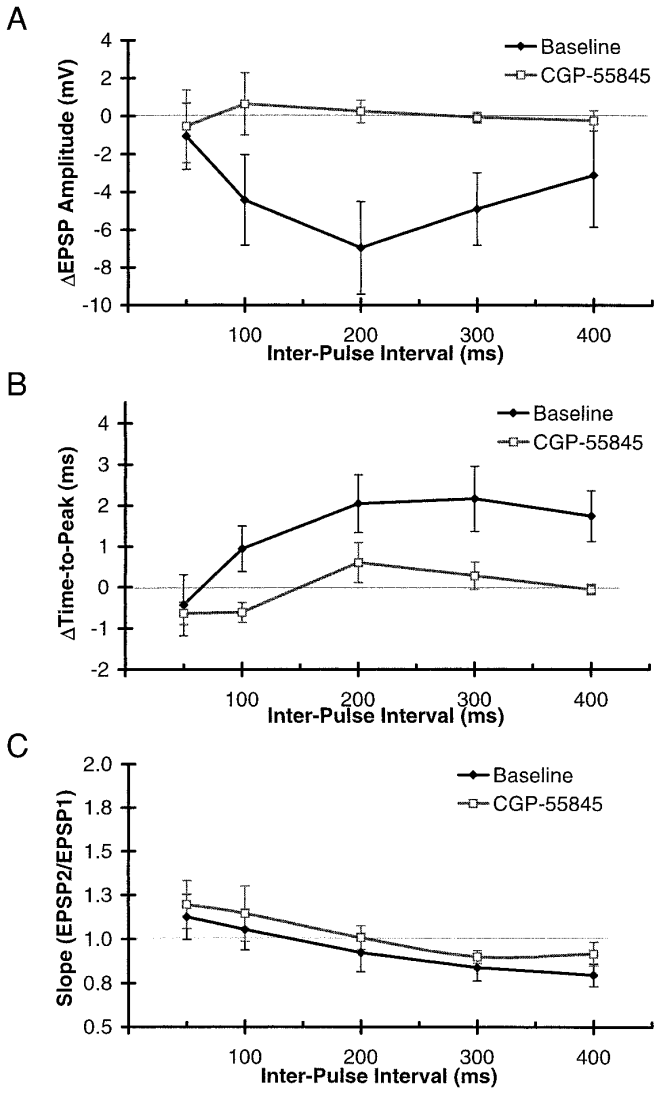

FIG. 8. Average effects of CGP-55845 on IPI functions for EPSP amplitude, TTP, and slope for neocortical neurons. *A*: ΔEPSP amplitude. In the control condition (black) ΔEPSP was ~0 at the 50-ms IPI, and depression was observed at all other intervals. CGP-55845 flattened the IPI function and abolished any depression of peak EPSP amplitude. *B*: ΔTTPs were positive at all IPI, reflecting the increased TTP and broadening of the 2nd EPSP in relation to the 1st. CGP-55845 blocked the increases in TTP and again flattened the IPI function. *C*: EPSP slope ratio was ~1 at all IPIs, with a small degree of facilitation at short IPI and a small degree of depression at long IPIs. CGP-55845 did not significantly alter the shape or magnitude of the IPI function.

Figure 7 shows the IPI function for EPSP amplitude of each cell. At the 50-ms IPI both facilitation and depression were observed. Depression was predominant at all other IPIs. CGP-55845 blocked the depression and revealed facilitation in some cells at the 100-ms IPI. Figure 8*A* shows the average results for EPSP amplitude. A two-way ANOVA revealed a significant interaction ($F_{4,32} = 4.67$, $P < 0.01$), indicating that CGP-55845 significantly altered ΔEPSP at some IPIs but not all. The F tests for simple effects showed that CGP-55845 significantly increased the ΔEPSP at the 100-, 200-, and 300-ms IPI. One-way analysis revealed that, although

in the absence of CGP-55845 there was a significant dependence of ΔEPSP on IPI ($F_{4,16} = 9.9$, $P < 0.001$), the IPI function in the presence of CGP-55845 was flat ($F_{4,16} = 0.2$, $P > 0.9$). The effects of CGP-55845 on the TTP measure are shown in Fig. 8*B*. TTP was longer for the second EPSP than the first ($\Delta TTP > 0$ ms) for all intervals, peaking at 3 ms at the 300-ms IPI. The two-way ANOVA did not reveal a significant interaction ($F_{4,32} = 2.93$, $P = 0.071$) between CGP-55845 and IPI, although there was a trend in that direction. However in the control condition there were significant differences in the ΔTTP at different IPIs ($F_{4,16} = 4.8$, $P < 0.01$), whereas in the presence of CGP-55845 there was no significant dependence of ΔTTP on IPI, in which the ΔTTP values were ~0 ms.

In contrast to CA3 neurons, auditory cortex neurons exhibited relatively little change in the EPSP slopes across different IPIs, resulting in slope ratios ~1, both in the presence and absence of CGP-55854. The two-way ANOVAs revealed no significant interaction ($F_{4,32} = 0.11$) or effect of CGP ($F_{1,8} = 0.4$). The slope ratio was significantly affected by the IPI ($F_{4,32} = 15.8$). The finding that the slope ratios were close to one both in the control and CGP-55845 conditions is consistent with the notion that the slope measure is relatively unaffected by $GABA_B$-dependent properties. It is also consistent with the observation that the influence of hyperpolarization on the slope measure was not significant and with previous observations that monosynaptic PPF is often not observed in cortex. CGP-55845 did not produce any changes in the EPSP versus IPI function (Fig. 8*C*).

As in hippocampal cells, CGP-55845 did not significantly alter the parameters of the first EPSP: amplitude (control 12.7 ± 1.79 mV, CGP-55845 11.7 ± 1.73 mV), TTP (7.16 ± 0.55 ms, 6.7 ± 0.28 ms), or slope (5.46 ± 0.55 ms/mV, 5.6 ± 0.55 ms/mV) of the first EPSP. Thus, as in the hippocampus, the $GABA_B$-dependent properties almost exclusively affect time-dependent responses.

DISCUSSION

Short-term plasticity in hippocampus and auditory cortex

When different time-dependent properties are operating in parallel in pharmacologically intact slices, the first pulse of a stimulus can dramatically alter the postsynaptic response to the second pulse. Depending on whether the net effect of these different processes on the second postsynaptic response is to move it closer or farther from threshold than the first response, short-term facilitation or depression is said to have occurred. In the CA3 region of the hippocampus, the second PSP was generally facilitated at intervals <100 ms and generally depressed at longer intervals. The temporal profile of short-term plasticity was different for auditory cortex cells. Although individual cells could exhibit facilitation or depression at short intervals, on average there was little effect, and depression was predominant at long intervals.

In addition to facilitation or depression of the peak EPSP amplitude, the postsynaptic response to the first and second pulse also differ in the width and or duration of the PSP. The changes in width were generally reflected in the TTP measure. Broader EPSPs represent a form of facilitation because broadening should facilitate temporal summation and decrease the requirement for input synchronization. We have shown here that short-term plasticity of EPSP amplitude and EPSP width can be independent; at long intervals depression of the EPSP amplitude is generally observed, but the EPSPs are also broader.

The presence of the $GABA_B$ antagonist CGP-55845 did not generally produce significant changes in the response to the first EPSP, suggesting that, at least in slices, $GABA_B$-dependent mechanisms are primarily involved not in modulating the response to an isolated action potential but instead in modulating responses to temporal patterns of action potentials. In the presence of CGP-55845 there were no significant differences in either ΔEPSP or ΔTTP values between different IPIs both in the hippocampus and auditory cortex. The finding that blocking $GABA_B$-dependent properties did not generally effect responses at an IPI of 50 ms is consistent with data showing that paired-pulse plasticity of the fast EPSP is the main form of short-term plasticity being expressed at these intervals and with data showing that $GABA_B$-dependent mechanisms are slower. Together these results show that different forms of facilitation and depression can occur in parallel, that $GABA_B$-dependent mechanisms play an important role in short-term plasticity, and that in the range of a few hundred milliseconds $GABA_B$-dependent mechanisms may be the principal contributor to paired-pulse plasticity.

Paired-pulse plasticity of EPSPs

The goal in this paper was to address the interaction among different forms of short-term synaptic plasticity that were previously characterized. We thus did not isolate fast EPSPs and IPSPs; however, our use of EPSP slope and TTP to obtain indirect measures of the fast EPSP and IPSPs produced results that are consistent with previous studies that analyzed isolated plasticity of EPSPs or IPSPs. Previous studies reported that monosynaptic EPSPs generally exhibit strong PPF in CA3 neurons (Xiang et al. 1994; Zalutsky and Nicoll 1990). Our analyses of the EPSP slope are in agreement with these results. Any facilitation of peak amplitude observed at the 50- and 100-ms IPI in the presence of CGP-55845 is likely to be due homosynaptic PPF. Although an increase in driving force produced by the fast IPSP can result in an increase in slope, it cannot account for an increase in the peak EPSP amplitude. The PPF of the slope peaked at the shortest interval examined here (50 ms) and returned to baseline within a few hundred milliseconds. This time course is in agreement with previous reports in which homosynaptic PPF is reported to peak at intervals of ≤50 ms.

In neocortical slices, both PPF and PPD of monosynaptic EPSPs were reported (Markram and Tsodyks 1997; Ramoa and Sur 1996; Thomson and Deuchars 1994). Indeed, there were some discrepancies regarding PPP in the neocortex. A recent study shed some light on this issue by showing that different excitatory synapses exhibit different PPP characteristics (Stratford et al. 1996). In visual cortex slices Stratford et al. (1996) found that the thalamocortical to L-IV projection exhibited PPD; the L-VI → L-IV projection exhibited PPF, and L-IV → L-IV synapses did not exhibit PPP. Gil et al. (1997) also report PPP differences among different

synapses in the rat somatosensory cortex. In agreement with Stratford et al. (1996) they reported that the thalamocortical synapse onto L-III neurons exhibited PPD, whereas intracortical synapses exhibited PPD or PPF. The slope analysis and the lack of facilitation of the peak amplitude in our study are consistent with the absence of PPP or a small degree of PPD in the excitatory synapses onto LII/III pyramidal cells.

Paired-pulse depression of fast IPSPs

Although PPP of the monosynaptic EPSP is generally considered to be the primary form of short-term synaptic plasticity, PPD of the fast IPSP is likely to be as important in generating short-term synaptic plasticity. Although our results and those of others indicate that the PPP of EPSPs differs between brain regions and synapse types, the PPD of fast IPSPs seems to be similar in both CA3 and neocortex. Indeed robust PPD of fast IPSPs was observed in CA3 (Lambert and Wilson 1993), CA1 (Davies et al. 1990; Lambert 1991; Nathan and Olpe et al. 1994), and neocortex (Deisz and Prince 1989; Fukuda et al. 1993; Metherate and Ashe 1994). These studies generally report robust PPD of the fast IPSP with a similar time course and magnitude. Although there is general agreement that PPD is dependent on presynaptic $GABA_B$ receptors, it was suggested that there is also a non–$GABA_B$-dependent component to PPD of the fast IPSP (Deisz et al. 1997; Lambert and Wilson 1994).

In this study monosynaptic EPSPs and fast IPSPs were not isolated, reflecting normal physiological conditions in which EPSPs and IPSPs are jointly activated. The fast IPSP generally cuts off or truncates the fast EPSP. Thus a decrease in the magnitude of the fast IPSP can produce an apparent increase in the magnitude of the EPSP. This ''apparent PPF'' is sometimes mistaken for homosynaptic PPF of the EPSP. However, in addition to the $GABA_B$ sensitivity, this indirect form of facilitation can often be distinguished from monosynaptic PPF on the basis of its time course. PPF, which seems to be caused by residual Ca^{2+} in the presynaptic terminal (Kamiya and Zucker 1994; Wu and Saggau 1994), generally peaks $<$50 ms, whereas the time course of PPF of the fast IPSP is similar to that of the slow IPSP and peaks between 100 and 200 ms.

Presynaptic $GABA_B$-mediated inhibition of excitatory transmission was also reported. However, this appears to be much weaker than the presynaptic inhibition of the fast IPSP. $GABA_B$-dependent presynaptic inhibition of EPSPs is not observed in response to single pulse stimulation (Davies and Collingridge 1996; Davies et al. 1991) and seems to require a train of stimuli to be observed (Isaacson et al. 1993; Solís and Nicoll 1992; for an exception see Gil et al. 1997).

The facilitation produced by PPD of the fast IPSP generally takes the form of broadening of the EPSP rather than increases in the peak amplitude. Nevertheless, this form of facilitation is likely to enhance temporal summation and should be taken into account in computational models of neural information processing.

Functional role of $GABA_B$-dependent mechanisms

With the recent cloning of $GABA_B$ receptors (Kaupmann et al. 1997) and considerable data regarding the pharmacology and biophysics of $GABA_B$-dependent mechanisms (for reviews see Mody et al. 1994; Mott and Lewis 1994), there is a rapidly accumulating amount of information regarding the molecular biology and biophysics of the $GABA_B$ receptor. Lacking are both hypotheses and studies that attempt to address the functional role of $GABA_B$ receptors, which are widely distributed throughout most cortical and subcortical areas (Chu et al. 1990; Kaupmann et al. 1997). Such hypotheses should address both the inhibitory and facilitatory role of $GABA_B$ receptors as well as the potential importance of the time course of these events.

Various pharmacological studies suggested some functional roles for $GABA_B$-dependent processes. Counterintuitively, given that $GABA_B$ receptors are generally thought to primarily mediate inhibition, $GABA_B$ antagonists were shown to protect rats from absence seizures (Hosford et al. 1992; Klebs et al. 1992). Because epilepsy is associated with a decrease in excitation to inhibition ratio, the protection by $GABA_B$ antagonists suggests that the net effect of $GABA_B$-dependent processes may be facilitatory. $GABA_B$ antagonists were also reported to enhance the performance of rats in passive avoidance tasks in rats (Mondadori et al. 1996) and of monkeys on spatial color tests (Mondadori et al. 1993). However, the generality of these results is not yet clear nor is it known whether the behavioral effects can be directly attributed to blockade of $GABA_B$ receptors rather than nonspecific effects such as peripheral drug actions or arousal. $GABA_B$ antagonists were also reported to block the induction of LTP when using a primed-burst paradigm (Davies et al. 1991) but not with a tetanic stimulation protocol (Davies and Collingridge 1996). The dependence of LTP on $GABA_B$ receptors, when using a primed-burst paradigm, seems to be due to the PPD of the fast IPSPs. Again this result suggests that the net effect of $GABA_B$-mediated processes is facilitatory. Related to the functional role of $GABA_B$ receptors is the important issue of which conditions activate these receptors because slice experiments generally rely on fairly high-intensity stimulation to activate $GABA_B$ receptors. Future research will have to determine whether $GABA_B$ receptors are consistently activated during behavioral tasks.

We have shown that $GABA_B$-dependent processes are likely to be the main mechanism underlying short-term plasticity in the range of a few hundred milliseconds. It is thus possible that the role of $GABA_B$-dependent processes relates to the functional role of short-term plasticity. Various hypotheses regarding the function of short-term plasticity were suggested. Carew and colleagues (Fisher et al. 1997, 1997) have shown that short-term synaptic enhancement between *Aplysia* interneurons provides a mechanism for ''online'' modulation of the siphon withdrawal reflex. It was also suggested that PPD of cortical synapses plays a role in gain control by amplifying transient changes in firing rates (Abbott et al. 1997; Tsodyks and Markram 1997). These last studies examined temporal dynamics in response to more complex temporal patterns, including random trains of electrical stimulation (Abbott et al. 1997; Varela et al. 1997). Indeed more complex temporal patterns are likely to be more relevant than paired-pulse stimulation for certain types of sensory processing. However, we believe paired-pulse stimulation provides a good facsimile of certain auditory tasks

and experiments, i.e., interval discrimination tasks, in which two very brief tones are presented 50–500 ms apart (Wright et al. 1997), and in vivo experiments where two tones are presented at different intervals (Brosch and Schreiner 1997). Consistent with our findings in slice, in vivo experiments from the auditory cortex of anesthetized cats have shown that the response to the second of a pair of tones is generally inhibited; however, facilitation is also observed (Brosch and Schreiner 1997).

We suggested that a computational role of short-term forms of plasticity, such as PPP of EPSPs, PPD of fast IPSPs, as well as slow synaptic events such as the slow IPSP, may be to process temporal information on the time scale of tens to hundreds of milliseconds (Buonomano and Merzenich 1995; Buonomano et al. 1997). Specifically, if a brief input such as a tone arrives in the cortex, it will activate a given population of neurons and initiate a series of time-dependent properties. If the same input arrives again 100 ms later, it will arrive in a different network state or environment; functionally some connections will be facilitated (e.g., as a result of PPD of fast IPSPs) and some cells will be hyperpolarized. As a result of these changes in the network state the same input may activate a different but overlapping population of neurons. The differences in population responses can be used to code for temporal features of stimuli, such as duration, interval, and order. Recent experimental results in hippocampal slices have shown that different populations of neurons respond to the first and second of a pair of pulses (Buonomano et al. 1997).

The results described here are consistent with the hypothesis that the net inhibitory action of postsynaptic $GABA_B$ receptors and the net facilitatory action of presynaptic $GABA_B$ receptors significantly change the state of networks of neurons in a time-dependent manner and could contribute to the generation of temporally selective neural responses. Furthermore, our results stress that, to understand how time-dependent properties affect neuronal firing, it is necessary to consider that many different opposing properties are operating in parallel and that it is the relative balance among these properties that will determine whether the net effect is facilitatory or depressive.

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