# Pyramidal Cells and Stratum Lacunosum-Moleculare Interneurons in the CA1 Hippocampal Region Share a GABAergic Spontaneous Input

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ABSTRACT:    Patch-clamp technique was used in the CA1 region of the hippocampal rat slice preparation in order to perform a comparison between synaptic GABAergic spontaneous postsynaptic currents (sPSCs) recorded from pyramidal cells (PCs) of stratum pyramidale (SP) and interneurons of stratum-lacunosum moleculare (SL-M INs). GABAergic sPSCs from PCs and from SL-M INs displayed similar frequency (0.75 ± 0.26 Hz vs. 0.53 ± 0.11 Hz, respectively), amplitude (34.6 ± 5.0 pA vs. 39.6 ± 4.1 pA), rise-time (2.9 ± 0.4 ms vs. 3.2 ± 0.3 ms), and decay-time (31.7 ± 1.5 vs. 32.3 ± 2.4). Agonists of receptors for endogenously released transmitters were bath-applied to induce variations in the frequency of sPSCs. Spontaneous PSC frequency increased after carbachol and trans-1-aminocyclopentane-1,3-dicarboxilic acid (t-ACPD), whereas it decreased after 5-hydroxy-tryptamine (5-HT) and baclofen in both classes of cells. Cross-correlation analysis of double-patch recordings (one PC and one SL-M IN) revealed 4.4 times as many coincident events as would be expected at random. The ratio between measured and random coincidences did not vary when the sPSCs frequency was increased. These results suggest that the same class of spontaneously active GABAergic cells impinge both on PCs and on SL-M INs, exerting control over them by varying the level of released GABA.    © 1996 Wiley-Liss, Inc.

KEY WORDS:    synaptic activity, inhibition, double-patch, hippocampal circuitry, cross-correlation

## INTRODUCTION

The entire hippocampus is infiltrated by a wide network of GABAergic interneurons with various morphological and membrane properties. Indeed, pyramidal cells (PCs) receive an extensive GABAergic input (Miles and Wong, 1987; Lambert and Wilson, 1993; Pearce, 1993). Similarly, hippocampal interneurons (INs) express GABA receptors and receive a GABAergic synaptic termination (Lacaille et al., 1989; Fraser and MacVicar, 1991; Williams et al., 1994). Do different types of GABAergic interneurons impinge separately on PCs and INs, or are there two distinct sets of GABAergic interneurons that project separately to PCs and interneurons? Spontaneous GABAergic activity was studied in order to address this question. Young pyramidal cells of the rat hippocampal CA1 re-

gion receive spontaneous GABAergic input (Ropert et al., 1990) whose function is still unknown. Similarly, interneurons in the stratum lacunosum moleculare (SL-M INs) and the inner border of stratum radiatum receive a spontaneous GABAergic input (Lacaille and Schwartzkroin, 1988a,b; Kunkel et al., 1988; Williams and Lacaille, 1992; Williams et al., 1994), which has not been investigated in detail. In the present investigation the general characteristics of the spontaneous GABAergic input to PCs and SL-M INs in the CA1 hippocampal region were analyzed and compared to each other. In principle, different types of hippocampal interneurons could be subjected to differential modulation by neurotransmitters coming from the afferents. Thus, metabotropic agonists for glutamate, GABA, acetylcholine, and serotonin were used in order to modulate sPSCs. Two-electrode patch recording was thus performed on PC–SL-M IN pairs. If PCs and SL-M INs share some common afference, the resulting spontaneous GABAergic events on the two recorded cells should be nearly simultaneous. It was in fact found that spontaneous GABAergic input to SL-M interneurons statistically, kinetically, and pharmacologically resembles the spontaneous GABAergic input to PCs, indicating that some GABAergic interneurons terminate on both PCs and SL-M INs.

## MATERIALS AND METHODS

Wistar rats 6 to 14 days old were anesthetized with a solution of 5% urethane and decapitated. After decerebration the brain was immersed in oxygenated (95% $O_2$, 5% $CO_2$) Krebs solutions containing (mM) NaCl 126, KCl 3.5, $NaH_2PO_4 \cdot H_2O$ 1.2, $MgCl_2 \cdot 6H_2O$ 1.3, $CaCl_2 \cdot 2H_2O$ 2, $NaHCO_3$ 25, glucose 11. Slices 300 $\mu$m thick were cut (FTB Vibrocut 3, Frankfurt, Germany) in a refrigerated solution, kept at 32°C, and moved to the recording chamber where they were perfused at a constant rate of 2–3 mL/min at room temperature (20–22°C). PCs and SL-M INs were selected

under visual control with an Axioscope Zeiss microscope with Nomarski optics and a water-immersion lens (400× total magnification). Patch electrodes of about 4 MΩ resistance were pulled from borosilicate tubings (2 mm o.d.). Intracellular solution was composed of (mM) KCl 126, NaATP 1.5, HEPES 10, $MgCl_2$ 2, EGTA 1. pH was adjusted to 7.35 with KOH. Voltage- and current-clamp experiments were performed with EPC-7 amplifiers (LIST Electronics, Germany) driven by pClamp 6.0.2. system (Axon Instruments, Burlingame, CA). Cells with series resistance of >30 MΩ were discarded. Drugs were bath-applied via the superfusate. Kynurenic acid (1 mM) was applied in all experiments to eliminate the ionotropic glutamatergic drive. Voltage-clamp holding potential was −70 mV. In current clamp experiments the holding current was selected to maintain the resting potential at about −70 mV. Signal was recorded on videotape at 10 kHz sampling rate with a two-channel interface (VR10B, Instrutech, VT) and then analyzed off-line. One-channel signals were digitized at 4 kHz and then analyzed with the program N05 generously supplied by Dr. S. Traynelis. Only non overlapping synaptic events were considered for analysis of amplitude, rise time, and decay time. Frequency was evaluated over 2- to 3-minute-long records. Two-channel correlation analysis was performed on data sampled at 1 kHz using an in-house program. Results are reported as mean ± SEM. Comparisons between different groups were performed using paired or unpaired Student $t$-tests, accepting as significant differences with $P < .05$.

## RESULTS

### General Features of Spontaneous Synaptic Activity

Visually identified cells in SP or SL-M were classified as pyramidal cells or interneurons on the basis of their firing response to a current step in current clamp mode. Twenty-six cells recorded in SP displayed the accomodating firing pattern typical of pyramidal cells (Fig. 1a, left), whereas 20/24 cells recorded in the SL-M displayed the non-accomodating firing pattern characteristic of interneurons (Fig. 1a, right). In 4 cells recorded by patch clamp in SL-M, current pulses produced a firing pattern that was neither clearly accomodating nor non-accomodating, and these were discarded from further analysis. Input resistance in PCs and SL-M INs had different values (232 ± 32 MΩ, n = 24, and 363 ± 92 MΩ, n = 18, respectively; $P < .05$). Under voltage clamp, both PCs and SL-M INs displayed sustained, spontaneous synaptic activity detected as post-synaptic inward currents (Fig. 1b). PSCs reversed at a holding potential of about 0 mV, close to Cl⁻ reversal potential (−1 mV). Bicuculline methochloride (10 μM) completely and reversibly abolished sPSCs. Application of tetrodotoxin (TTX) decreased by 88 ± 32% the frequency of sPSCs recorded from SL-M INs (n = 3). Mean frequency, amplitude, rise-time, and decay-time of sPSCs in PCs and SL-M INs in control conditions are reported in Table 1. Comparisons of these parameters in PCs and INs showed no significant differences. Analysis of the inter-    interval distribution was per-

formed on 5 PCs and 5 SL-M INs. To eliminate dependency on the bin size, histograms of cumulative inter-event interval were calculated as shown in Figure 1c for a PC (left) and a SL-M IN (right). In all cases it was possible to represent the histogram with a function $A(\Delta t) = [1 - e^{-(\Delta t/\tau)}]$, as shown in the example of Figure 1c (continuous lines) where $\Delta t$ is the event interval and $\tau$ is the inverse of the mean frequency. This description is equivalent to the distribution of inter-event intervals by a 0-order Poisson distribution with time constant $\tau$.

### Modulation of sPSCs Frequency

Neurotransmitter receptor agonists were used to reveal possible differences between PCs and INs in the modulation of sPSCs. Among those agents tested, the most effective in changing sPSCs frequency were carbachol, t-ACPD, baclofen, and serotonin (5-HT). When bath-applied to the preparation, the drugs produced variations in sPSCs frequency with a time lag ranging from 30 to 180 s. Carbachol (10 μM) and t-ACPD (10 μM) significantly enhanced sPSCs frequency, whereas 5-HT (10 μM) and baclofen (10 μM) produced the opposite effect. This was true regardless of the cell type from which sPSCs were recorded (Fig. 2a–d). The results are reported in Table 2 as percent variation in frequency after pharmacological treatment. Postsynaptic effects were also found. Input resistance was altered by carbachol (+32 ± 18% in PCs, n = 5, and 33 ± 5% in SL-M INs, n = 5), 5HT (−80 ± 55% in PCs, n = 3 and −60 ± 37% in SL-M INs, n = 3), and baclofen (−25 ± 4% in PCs, n = 3 and 20 ± 6 in SL-M INs, n = 3), whereas it was not significantly altered by t-ACPD.

### Paired Recording From a Pyramidal Cell and a SL-M Interneuron

GABAergic neurons producing sPSCs could in principle establish synapses with different cell types. To address the question of whether a single GABAergic cell eliciting sPSCs on a PC could also contact a neighboring SL-M IN, paired patch-clamp recording of sPSCs was performed on PC–SL-M IN pairs. The presence of correlated sPSCs in the two traces would indicate a common afference. A distance of about 150–200 μm separated the PC and IN in each pair. Cross-correlation analysis in a window of 50 ms was performed determining the latencies between events in one channel with respect to events in the other. The results are shown in latency histograms for the simultaneous and for the displaced traces. In Figure 3 a series of double-recorded traces are shown (left) together with the related correlogram (right). The activity of a neuron pair was taken to be significantly correlated when histograms from simultaneous traces displayed a clear peak around the origin. By visual inspection, a notable cross-correlation was found for 10 out of 12 neuron pairs examined, suggesting the presence of a common input. As a control, for 3 of the 10 pairs, the cross-correlograms were recalculated after displacing one trace by 500 ms. In no case did the resulting cross-correlogram display any clear peak.

The frequency of coincident events was used to quantify the degree of cross-correlation for those 10 neuron pairs that exhibited a distinct peak in the cross-correlogram. For this analysis, two
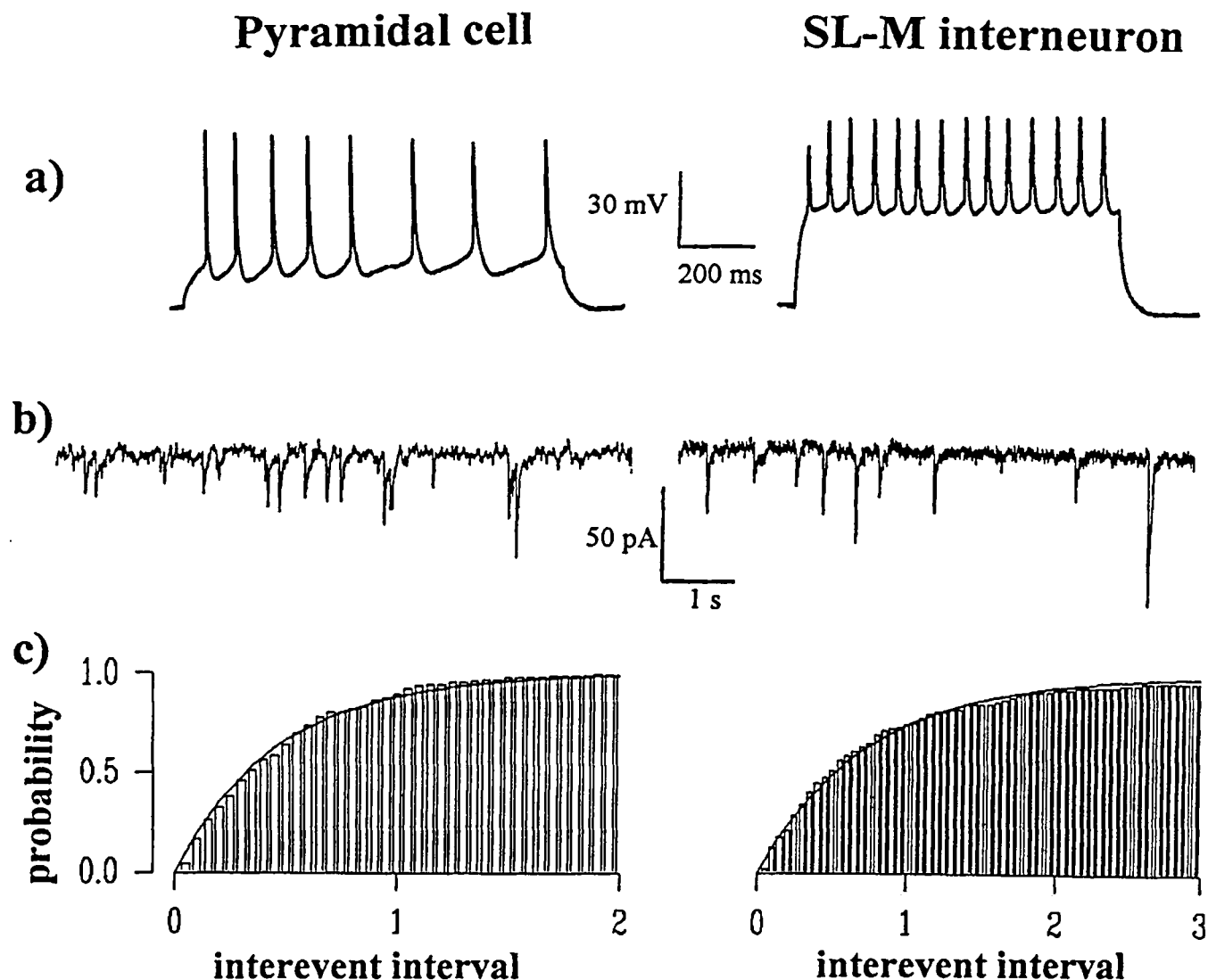
# Pyramidal cell

# SL-M interneuron



**FIGURE 1.** Comparison between properties of pyramidal cells and SL-M interneurons. a: Current clamp recording. Response to a depolarizing current pulse of 80 (pyramidal) and 50 pA (interneuron) lasting about 1 s. Membrane potential was −70 mV in both cells. Pyramidal cell and SL-M interneuron displayed, respectively, the typical accomodating and non-accomodating pattern. b: Voltage-clamp recording (−70 mV holding potential). In 1 mM kynurenic acid and symmetrical $Cl^-$ concentration pyramidal cells as well as SL-M interneurons displayed spontaneous, bicuculline-sensitive inward currents whose cumulative interevent latency (c) was described by an exponential curve: $A(t) = 1 - e^{-(t/\tau)}$ (solid line), where $\tau$ is the reciprocal of the mean frequency. The bin width is 50 ms for both histograms. The value of $\tau$ is 0.46 ± 0.06 s for the pyramidal cell and 0.74 ± 0.13 s for the SL-M interneuron.

*TABLE 1.*

*Comparison Between Kinetic Characteristics of GABAergic Synaptic Currents in Pyramidal Cells or in SL-M Interneurons**

| Mean ± SEM | Pyramidal cells | n | SL-M interneurons | n |
|---|---|---|---|---|
| Frequency (Hz) | 0.75 ± 0.26 | 26 | 0.53 ± 0.11 | 20 |
| Amplitude (pA) | 34.6 ± 5.0 | 21 | 39.6 ± 4.1 | 14 |
| Rise time (ms) | 2.9 ± 0.4 | 8 | 3.2 ± 0.3 | 13 |
| Decay time (ms) | 31.7 ± 1.5 | 8 | 32.3 ± 2.4 | 13 |

*Characteristics of sPSCs from pyramidal cells and SL-M interneurons. Frequency, amplitude, and rise and decay time of sPSCs were evaluated for the samples indicated. Sampling rate was 4 kHz. No variations were detected in any of the parameters using a non-paired Student t-test at 5% of significance.

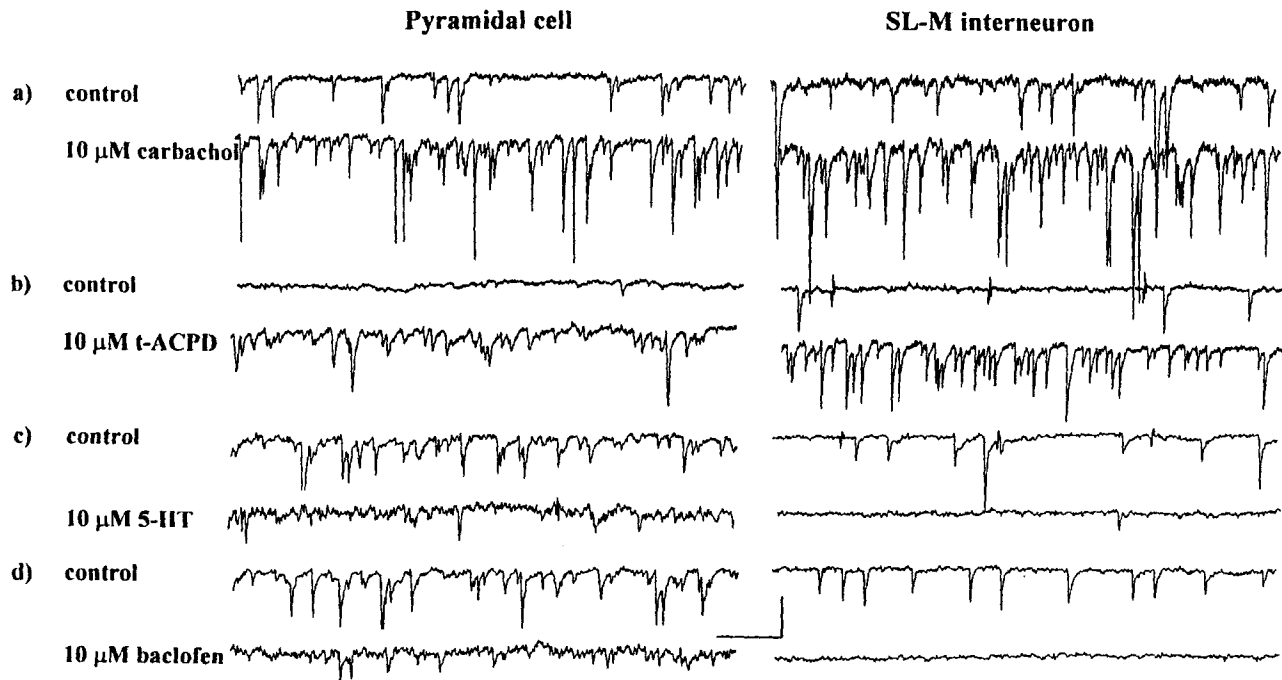**Pyramidal cell**          **SL-M interneuron**



FIGURE 2.     a–d: Effect of different drugs on sPSC frequency. Voltage-clamp recording of sPSCs from pyramidal cells (left) and SL-M interneurons (right). In each pair of traces the upper one was recorded in control conditions and lower one starts 30–150 s after pharmacological treatment. Carbachol (10 μM) and t-ACPD (10 μM) increase the frequency of sPSCs, whereas 5-HT (10 μM) and baclofen (10 μM) decrease sPSC frequency in pyramidal cells as well as in SL-M cells. Calibration bar-1 s, 20 pA.

events were classified as coincident if they showed a latency difference $|\Delta t| \leq 4$ ms. For the 10 correlated cell pairs the average frequency of coincident events was (0.088 ± 0.041 Hz). This frequency was then compared to the frequency derived from three other conditions. First, the frequency of paired coincident events was compared to the frequency paired *non-coincident* events. Non-coincident events were defined as those occurring outside 12 ms interval before or after the central peak. The frequency of non-coincident, or "background," events was calculated as the mean value for all bins outside the defined interval. The average frequency of background events (0.021 ± 0.010 Hz, n = 10) was

significantly lower ($P < .05$) than the average frequency of coincident events. Second, the frequency of actual coincident events was compared to the frequency of coincident events produced by displacing two simultaneous traces by 500 ms (0.020 ± 0.010 Hz, n = 3, $P ± .05$). Third, the frequency of paired coincident events was compared to the frequency of randomly expected coincidences, given by $\nu_{random} = \Delta t \cdot \nu_1 \cdot \nu_2$, where $\Delta t$ is the maximum accepted latency for two correlated events (4 ms here), and $\nu_1$ and $\nu_2$ are the sPSCs frequencies in the two cells. This condition yielded a significantly lower frequency of "chance" coincident events (0.017 ± 0.014 Hz, n = 10, $P < .05$) than that

TABLE 2.

Increase in PSC Frequency in Pyramidal Cell or in SL-M Interneurons After Pharmacological Treatment†

| Frequency variation (%) after treatment | Pyramidal cells | n | SL-M interneurons | n |
|---|---|---|---|---|
| 10 μM carbachol | +309 ± 118 | 5 | +257 ± 70 | 5 |
| 10 μM t-ACPD | +160 ± 100 | * | +371 ± 179 | 4 |
| 10 μM baclofen | −97 ± 22 | 3 | −94 ± 34 | 3 |
| 10 μM 5-HT | −57 ± 30 | 3 | −44 ± 29 | 3 |

†Modulation of sPSCs frequency by different drugs. The percentage of variation in sPSC frequency was calculated from the samples indicated. Bath-applied carbachol and t-ACPD increase sPSC frequency, whereas 5-HT and baclofen reduce frequency in pyramidal cells as well as in SL-M interneuron. Statistical significance within each group is assessed with the paired Student t-test. The asterisk (*) indicates data taken from Sciancalepore et al. (1995).
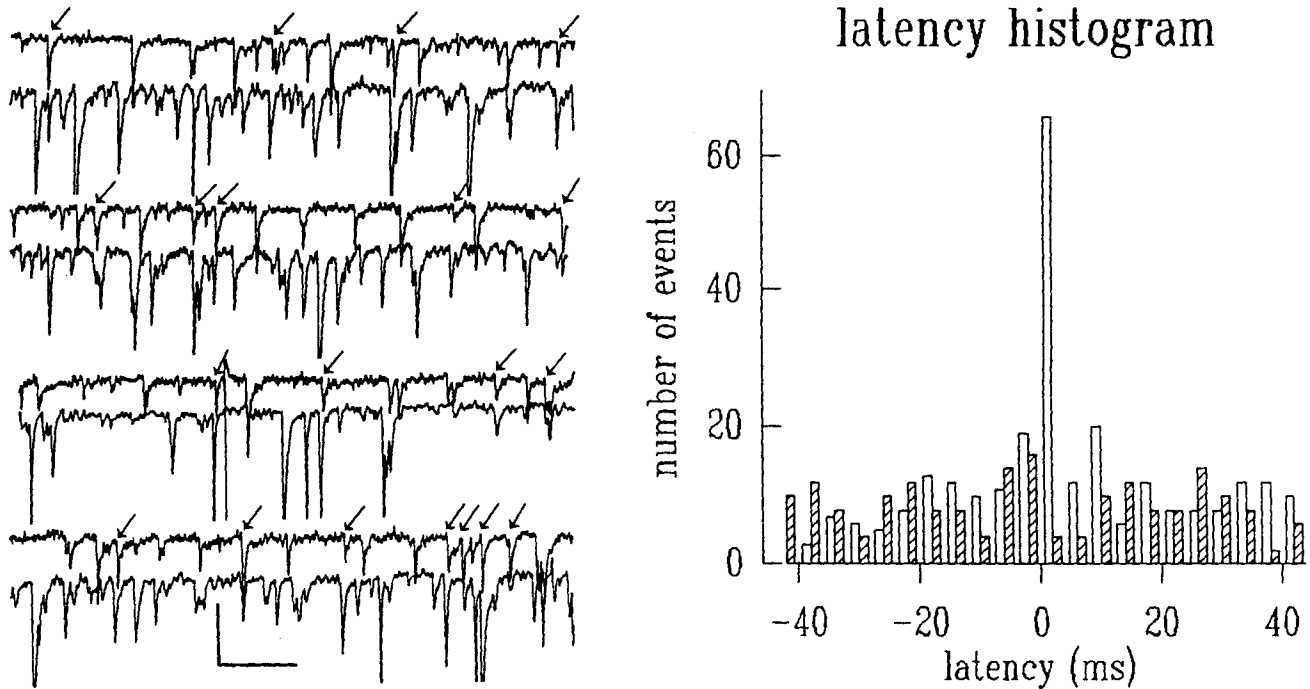
## latency histogram

**FIGURE 3.** Double whole-cell patch-clamp recording. Left: Four records of two-electrode patch recording from a pyramidal cell and a SL-M interneuron (upper and lower traces of each pair) in which numerous coincident events are present. The arrows indicate pairs of events at a time lag (t) ≤4 ms. Calibration bar-1 s, 100 pA. Right: latency histogram of the two cells. The number of events at a given latency from each other was evaluated over a 500-s-long record sampled at 1 kHz. The bin width was 4 ms. The histogram with hatched bars was calculated shifting the traces by 500 ms; open bars represent the histogram from the simultaneous traces. The amplitude of the correlated events at 0 ms latency is about sixfold the average amplitude at the other latencies.

found in real neuron pairs. The frequency of real detected coincident events was thus on average 4–5 times larger then the frequency of events yielded by three different analysis procedures.

In 2 cases carbachol was applied to increase sPSCs frequency. The ratio between measured and randomly expected coincidences $(\nu_{measured}/\nu_{random})$ was not significantly changed by the treatment $(\nu_{measured}/\nu_{random} = 6.2 \pm 1.3$ in control conditions and $5.8 \pm 2.8$ after treatment). A finer analysis of the delay between the correlated events was then performed to see whether any timing relationships were present among "coincident" events. Classifying events with latency difference $|\Delta t| \leq 4$ ms as coincident (see above), it was found that the absolute value of the delay between coincident events (0.70 ± 0.91 ms, n = 10) was not significantly different from 0. Thus, events recorded in neuron pairs and classified as "coincident" were, for statistical purposes, simultaneous.

## DISCUSSION

Cells in SP and in SL-M were patch-clamped under visual control. Their position within the slice, firing pattern, and input resistance allowed a clear-cut distinction between the two cell types. Spontaneous PSCs from SL-M interneurons persisted in the presence of the glutamate receptor blocker kynurenate but were blocked by bicuculline. Furthermore, they inverted close to the reversal potential for chloride, and their frequency was strongly depressed by TTX, indicative of $GABA_A$-mediated currents mostly due to presynaptic action potential activity. Recording from PCs reveals sPSCs with similar characteristics (Atzori, 1994; Sciancalepore et al., 1995). The resemblance of mean amplitude, rise time, and decay time between PCs and SL-M INs indicated no major differences at postsynaptic $GABA_A$ receptors. Furthermore, inter-event interval histograms were adequately fitted by a first-order Poisson function for recordings from PCs as well as from SL-M INs. Do PCs and SL-M INs receive a common input from a distinct class of as yet unidentified interneurons? If so, GABAergic activity recorded from PCs or SL-M INs should display similar modulation by exogenously applied agonists. To test this hypothesis, we selected carbachol, t-ACPD, and baclofen as agonists. These agents activate metabotropic receptors for acetylcholine, glutamate, and GABA, respectively, in rat hippocampus (Bianchi and Wong, 1994; Gerber and Gawhiler, 1994; Sciancalepore et al., 1995). 5-HT affects membrane excitability mainly through $5-HT_{1A}$ receptors (Andrade and Nicoll, 1987; Freund et al., 1990). In the present report, when applied to both PCs and SL-M INs, carbachol and t-ACPD elicited an increase, whereas baclofen and 5-HT caused a decrease in the frequency of sPSCs, indicating an effect on the afferent presynaptic GABAergic interneurons. Such a behavior could not be ascribed to the variation in postsynaptic cell input resistance since t-ACPD application did not vary input resistance while it produced a sPSCs frequency increase. In summary, bath application of agonists failed to reveal any differential modulation of sPSCs char-

acteristics in the two classes of neurons. Differences in the drug-induced change in frequency can be accounted for by the limited sample size. Unpaired Student *t*-test comparing the variation of frequency in PCs and in SL-M interneurons was in fact non-significant in all cases.

It was thus impossible to identify any evidence for two distinct sources of sPSCs in PCs and SL-M INs; our interpretation is that the same set of GABAergic neurons is probably responsible for both responses. Simultaneous recording from a PC and a SL-M interneuron revealed a number of synchronous events significantly larger than the number of randomly expected synchronous events. The average time lag between correlated events from the two cell types was a fraction of the mean event rise time, indicating that the observed deviation from absolute synchronicity was compatible with sampling error. The continuous presence of a glutamate receptor blocker suggests that simultaneous events were not caused by co-activation of two distinct GABAergic neurons by a glutamatergic input, but rather by the same GABAergic interneuron or set of interneurons. PCs and SL-M INs thus appear to share an input not only from a single class of GABAergic neuron, but even from a single cell or group of cells.

Whereas the frequency of coincident events registered from neuron pairs was much greater than could be explained by chance, coincident events still occurred at the relatively low frequency of <0.1 Hz. The low frequency of the synchronous events may be explained by assuming that an action potential in the presynaptic neuron did not always elicit exocitosis at all synaptic boutons, either because of failure of the action potential to invade the axon terminal, or by failure of GABA release at the synapse.

The existence of several types of GABAergic interneurons is widely accepted (Freund et al., 1990; Buhl et al., 1994). Morphologically distinct types of interneurons are present in the three layers of the hippocampal CA1 region: oriens-alveus interneurons (O-A INs), basket and vertical cells in or close to stratum pyramidale (SP INs), and SL-M INs. A body of evidence indicates that SL-M INs are GABAergic: Cells identified as stellate, horizontal, and short-axon neurons in stratum radiatum/stratum lacunosum moleculare are positive for GAD staining (Ribak et al., 1978). However the low level of their spontaneous firing (Lacaille and Schwartzkroin, 1988a) suggests that they give a modest contribution to spontaneous GABAergic activity in a slice preparation.

Electrophysiological evidence for the GABAergic nature of interneurons in O-A and SP is also available (Lacaille et al., 1987; Lacaille and Schwartzkroin 1988a). These cells show a resting potential more positive than that of SL-M INs (−51 mV and −55 mV, respectively, vs. −58 mV). Moreover, O-A INs in CA1 display spontaneous firing (Lacaille and Williams, 1990) and show processes crossing SP and stratum radiatum reaching SL-M (Lacaille and Williams, 1990). Biocytin injections in O-A stain cells electrophysiologically identified as interneurons that send their axons to stratum radiatum and further, up to the CA3 dentate gyrus areas (Sik et al., 1994). A type of O-A IN sensitive to t-ACPD whose axon cross stratum pyramidale and reach SL-M has been described (type II interneurons, McBain et al., 1994), although no confirmation of this projection was achieved by elec-

trophysiologic means. Such observations suggest O-A INs as one of the principal sources for the spontaneous GABAergic activity recorded in PCs and SL-M INs. O-A INs are believed to exert the feed-forward and feed-back inhibition elicited by activation of the primary afferents in the hippocampal slice preparation (Miles and Wong, 1987; Lacaille et al., 1987; Lacaille and Schwartzkroin, 1988a; Lacaille and Williams, 1990; Lacaille, 1991; Williams and Lacaille, 1992). The present results suggest the existence of a class of GABAergic interneurons with bifurcating projections to PCs and to SL-M INs. Such a circuit could spatially and temporally shape neuronal behavior, mediating simultaneous recurrent inhibition of PCs and SL-M INs immediately after a phasic activation of pyramidal cells. According to this view, tonic GABAergic spontaneous release per se could play a role in regulating the excitability of PCs and SL-M INs. A rise in spontaneous activity might set an upper limit to the activity of PCs as well as INs by shunting cell membrane during periods of elevated excitatory input. Analogously, a decrease in spontaneous GABAergic activity could enhance cellular excitability during periods of decreased excitability. Since frequency is a continuous parameter, cellular excitability could thus be varied by spontaneous GABAergic activity in a non-quantal fashion, allowing a flexible control by different neuromodulators. Such a hypothesis does not exclude the possibility that spontaneous GABA release might also have a role in neuronal axon guidance or synaptic plasticity during the formation of hippocampus functional units during development (Barbin et al., 1993; Berninger et al., 1995).

## Acknowledgments

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