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Intradendritic recordings from hippocampal neurons

(dendritic spikes/burst generation/synaptic potentials)

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ABSTRACT **Dendritic activity in guinea pig hippocampal CA_1 and CA_3 pyramidal neurons was examined by using an *in vitro* preparation. Histologically confirmed intradendritic recordings showed that dendrites had an average input resistance of 47.0 MΩ and average membrane time constant of 33.3 msec. Active spike responses could be evoked by intracellular injection of outward current or by the activation of synaptic inputs. The predominant activity was burst firing. A typical intracellularly recorded dendritic burst consisted of spikes on a slowly increasing depolarizing potential. The spike components of the burst were of two distinct types: low threshold, fast spikes; and high threshold, slow spikes. Tetrodotoxin (1 μg/ml) blocked the fast spikes, but slow spikes could still be evoked with direct intracellular stimulation. In contrast to dendritic responses, direct depolarization of CA_1 somata did not give rise to burst generation. Orthodromic stimuli evoked large-amplitude excitatory postsynaptic potentials, followed by inhibitory postsynaptic potentials in dendrites of CA_1 and CA_3 neurons. In two instances, simultaneous recordings were obtained from coupled pairs of elements that were presumed to be soma and dendrite of the same CA_3 pyramidal neuron. Depolarization of either element led to burst generation at that site, and the underlying slow depolarization appeared to evoke a burst at the other site. This potential postsynaptic amplifying mechanism was not ordinarily functional because even suprathreshold orthodromic activation did not normally evoke bursting in dendrites.**

Although dendrites in the mammalian central nervous system are of obvious anatomical and physiological importance as areas for signal reception and generation, until recently, little direct information has been available regarding the properties of dendritic membranes. Most studies of dendritic function have, of necessity, relied upon data obtained from intrasomatic or extracellular recordings (1–3). Such experiments have provided evidence suggesting that voltage-dependent active responses can be generated in some nerve cell dendrites. Direct evidence for regenerative responses has recently been obtained from intradendritic recordings in Purkinje cells (4–6). One brief report of recordings from procion-stained neocortical dendrites has also appeared (7).

Recordings in alligator Purkinje cell dendrites show that two types of spike responses are generated—namely, short-duration, low-threshold, small-amplitude spikes; and high-threshold larger-amplitude spikes with a longer duration (4). It has been proposed that the long-duration action potentials are a result of electronic summation of small spikes (2, 4). Recent investigations into the ionic mechanisms of dendritic spike generation in pigeon and rat Purkinje cells reveal that at least part of the electroresponsiveness is resistant to tetrodotoxin (TTX) and probably is mediated by Ca^{2+} (5, 6).

In hippocampal neurons of the guinea pig, certain types of spike activities have been assumed to be of dendritic origin on the basis of indirect evidence from intrasomatic recordings. These consist of small spike-like potentials of short duration (8, 9) that resemble the fast prepotentials of Spencer and Kandel (10) and prolonged TTX-resistant spikes that are probably mediated by Ca^{2+} (11–13).

By making use of the *in vitro* slice preparation (14, 15) and techniques for intracellular labeling with horseradish peroxidase (HRP), we have been able to record these two forms of spikes directly from identified dendrites. The data obtained are relevant to questions about the site of origin, the mode of generation, and the significance of such spikes for signal transmission within the neuron. Our interest in the properties of dendrites has also been stimulated by data suggesting that dendritic electrogenesis may play a significant role in normal and epileptiform burst firing in the hippocampal pyramidal cells (1, 2, 16).

MATERIALS AND METHODS

Experiments were performed on transverse slices of guinea pig hippocampus maintained *in vitro*. Details of this technique have been described (14, 15). Microelectrodes were pulled from microfiber capillary stock (Frederick Haer and Co., Ann Arbor, MI) and filled with 4 M K acetate or 4% Sigma type VI HRP dissolved in Tris, pH 8.6/0.2 M KCl. These electrodes had impedances of 100–150 MΩ (measured at 130 Hz) after being beveled.

Stimulation of the stratum radiatum and the hilum of the dendate gyrus with monopolar tungsten electrodes was used to produce orthodromic activation of CA_1 neurons via Shaeffer collaterals and of CA_3 neurons via mossy fibers, respectively. Intracellular current pulses were delivered via a Wheatstone bridge. Elements selected for analysis had a stable resting potential >50 mV; impalements of dendrites could be maintained for up to 1 hr.

The unique layered architecture of the hippocampus is easily appreciated in the transverse slice preparation (17). The microelectrode tip can be positioned under direct observation, by using a dissecting microscope at ×50 magnification, to make penetrations into the stratum pyramidale where the predominant elements are cell bodies of hippocampal pyramidal neurons or into the stratum lucidum or radiatum which contains the apical dendrites of these neurons (18). During attempts to impale dendrites, electrode penetrations in the stratum lucidum or radiatum were made normal to the slice cut surface and at least 150 μm from the margin of the stratum pyramidale (measured with a calibrated eyepiece at ×50 magnification). Although penetrations in these areas would most likely yield intradendritic recordings, it was necessary to rule out the possibility that intracellular recordings in dendritic layers might be from interneurons or displaced pyramidal cell bodies. We therefore used the intracellular HRP labeling technique (19) to verify that the cell body of the recorded element was remote from the site of microelectrode penetration.

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Abbreviation: TTX, tetrodotoxin; HRP, horseradish peroxidase.

Iontophoresis of HRP was accomplished by applying 350-msec-duration positive pulses of 0.75–1 nA at 350-msec intervals for at least 20 min. Intracellular activities could be recorded throughout the injection period. After the HRP injection, slices were maintained in the chamber for at least 1 hr. The slices were fixed overnight in 3% glutaraldehyde and 1% paraformaldehyde and then transferred to phosphate-buffered 30% sucrose for 6 hr. Individual slices were embedded in a 5% gelatin/20% egg albumin block which was hardened for 3 hr in phosphate-buffered 30% sucrose/4% glutaraldehyde. One hundred-micrometer transverse sections were cut on a freezing microtome. HRP-injected cells were "intensified" with 5% $CoCl_2$ and developed by using diaminobenzidine and H_2O_2 (20).

In two instances we made simultaneous impalements in the stratum pyramidale and stratum radiatum of the CA_3 region and were successful in recording from pairs of electronically coupled elements. Portions of the experimental data were analyzed by using a PDP-12 computer programmed to measure the amplitude and the duration of selected spikes.

RESULTS

Intracellular records could be obtained most easily from a light band traversing the slice in the CA_1 and CA_3 regions. When Evans blue dye was added to the perfusate to stain the preparation, this light band region was observed to correspond to a densely packed cell body region (stratum pyramidale). Stable intradendritic recordings were obtained in 57 instances. In each case it was possible to visualize the microelectrode and determine that a given penetration was made into the stratum radiatum, at least 150 μm from the margin of the stratum pyramidale. In a few instances, visual observations were confirmed in enlarged photographs of the slice with the microelectrode in place (e.g., Fig. 1 *inset*). Two criteria were used to identify dendrites as sites of recording.

(*i*) In seven successful penetrations with HRP-filled microelectrodes, cells were labeled by using iontophoretic injections after electrophysiological observations had been made. In each instance the cell body of the labeled neuron was located in the stratum pyramidale, at least 150 μm from the site of microelectrode penetration (Fig. 1). All filled neurons were pyramidal type cells. From this finding we concluded that cell processes (dendrites) in the stratum radiatum had been impaled.

(*ii*) Elements impaled in the stratum radiatum, including the 7 described above and 50 others, had electrophysiological properties that differed unambiguously from those of CA_1 or CA_3 pyramidal cell somata. In CA_1 stratum pyramidale (somatic) impalements, spike bursts were rarely elicited by brief (10–20 msec) depolarizing pulses (0.1–0.3 nA) (8). By contrast, bursts such as those in Fig. 3 were regularly evoked by similar stimuli in stratum radiatum (dendritic) impalements. In the CA_3 region, bursts could be elicited by direct depolarization of elements in both the stratum pyramidale (13) and the stratum radiatum. In both CA_1 and CA_3 pyramidal neurons, dendritic and somatically evoked bursts had distinctly different features (see below, Fig. 2, and Table 1).

The input resistance and membrane time constant of the dendrites and somata of neurons in the CA_3 region were determined by their responses to intracellular, long-duration (150 msec), inward current pulses. For input resistance determination, the maximal membrane potential changes (V) in response to the current pulses (I) (0.1–0.5 nA) were measured. The slope of a straight line calculated by least-squares linear fit of V vs. I gave the input resistance of the neuron. Mean (±SD) values of 39.7 ± 12.1 MΩ (n = 8) and 48.6 ± 11.6 MΩ (n = 8) were

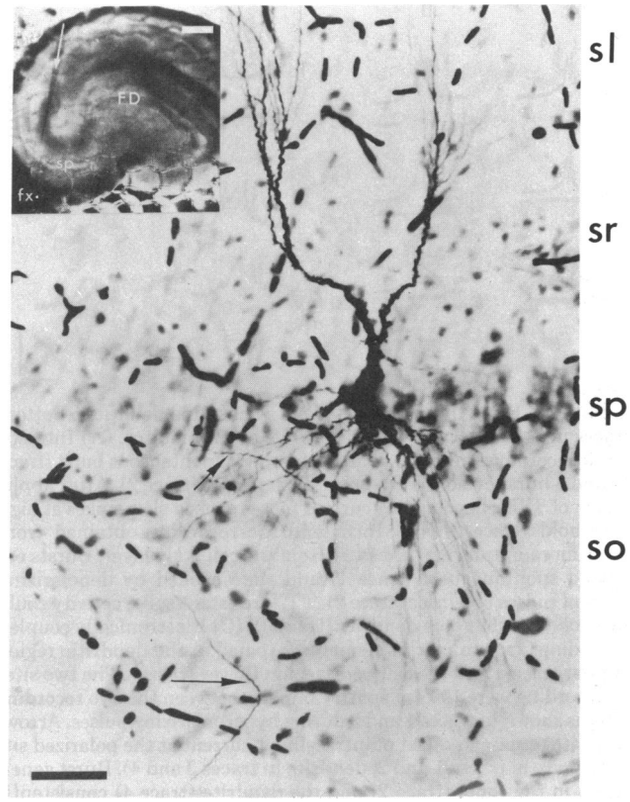

FIG. 1. HRP-filled CA_3 pyramidal cell. The apical dendrites are located in the stratum radiatum (sr); the basilar dendrites are in the stratum orien (so). The arrow in so points to the axon of the cell. The HRP-filled electrode penetrated a dendrite of this neuron in the sr, about 170 μm away from the near margin of the stratum pyramidale (sp), where the cell body was located. Note that erythrocytes were also stained. Scale = 50 μm. (*Inset*) Hippocampal slice preparation. The light band in the slice (sp) corresponds to the pyramidal cell body layer. A microelectrode is shown (arrow) positioned in the sr during an attempt to record from an apical dendrite. sl, Stratum lacunosum; FD, fascia dentate; fx, fornix. Scale = 500 μm.

obtained for somata and dendrites, respectively (the difference between these two values was not statistically significant, $P >$ 0.25). The time course of the soma membrane potential response to the current pulse could be closely fitted to a single exponential with a mean (±SD) time constant of 31.8 ± 4.8 msec (n = 8). The time course of the dendritic response, however, could be resolved into two exponentials with time constants of 4.0 ± 0.12 msec (n = 8) and 33.3 ± 11.8 msec (n = 8). By analogy with the model neuron (21) the longer of these two dendritic time constants is probably the same as the membrane time constant. These results suggest that the membrane time constants of the different regions of the soma–dendritic complex might have similar values.

Typical recordings of spike bursts from somata and dendrites of CA_3 pyramidal cells are illustrated in Fig. 2. In both intrasomatic and intradendritic impalements, bursts arose spontaneously (*A* 1 and *B* 1) and could be evoked at threshold by intracellular depolarizing pulses of 2- to 20-msec duration (e.g., Fig. 2, *B* 2, Fig. 3, *B* 2). Burst spikes typically arose from an underlying slow depolarizing envelope. The first spikes of the burst were of short duration ("fast"). At the peak of the depolarizing envelope, one or more long-duration ("slow") spikes were generated before the termination of the burst (Fig. 2, *A* 1 and 2, *B* 1 and 2). These frequently had inflections and double peaks (Fig. 2 *A* and *B*). Long-duration hyperpolarizations (up to 1 sec) associated with increased conductance were often

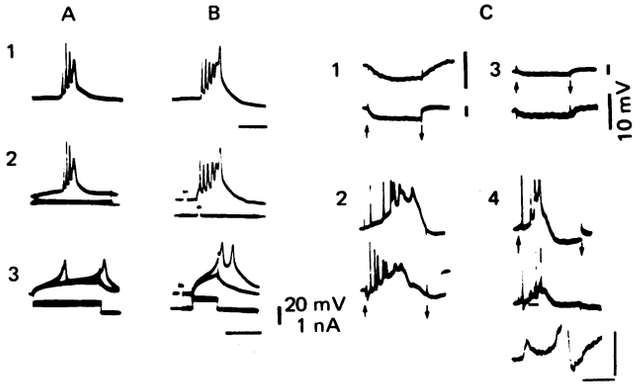

FIG. 2. Burst firing recorded from somata and dendrites. Bottom traces in *A* 2 and 3 and *B* 2 and 3 are current monitor. (*A*) Intrasomatic recordings from one neuron, showing a spontaneous burst (trace 1) and a burst evoked by depolarizing current (trace 2). After application of TTX, depolarizing current pulses evoked slow spikes at high threshold (trace 3). (*B*) Intradendritic recording obtained from stratum radiatum, 200 μm away from the cell body layer. Bursts occurred spontaneously (trace 1) and were evoked by depolarizing current pulses of 5 msec (trace 2). TTX-resistant spike activity could be evoked in the same dendrite (trace 3). (*C*) Electronically coupled recordings from a pair of elements impaled in the dendritic region (upper traces) and the cell body region (lower traces). The two sites of recording were 100 μm apart. Coupling between the two recording sites is shown in traces 1 and 3 during hyperpolarizing pulses. Arrows indicate onset and offset of intracellular current at the polarized site (cell body in traces 1 and 2; dendrite in traces 3 and 4). Burst generation in the soma (trace 2) and the dendrite (trace 4) consistently evoked a burst at the other site. Trace 4 shows small fractionated spikes resembling fast prepotentials recorded in the soma simultaneously with the occurrence of fast spikes in the dendrite. The bottom part of trace 4 shows an expanded fraction of the middle trace indicated by the black bar. An isolated fast prepotential and a full spike (top chopped off) arising from a second fast prepotential are shown. The slow spikes in the burst evoked at the peak of the slow depolarization reached higher amplitudes in the dendritic than in the somatic record. Time calibration in *B* 1 for *A* 1 and *B* 1 and in *B* 3 for *A* 2 and 3 and *B* 2 and 3, 50 msec. Voltage calibration bars in *C* 1 and 3, 10 mV. Calibrations in *C* 4, 50 mV and 100 msec for *C* 2 and 4, except 100 mV and 10 msec for bottom trace of *C* 4. Spikes have been retouched for clarity.

observed following the bursts. Although the temporal pattern of the fast and slow spikes in dendrites was similar to that recorded in cell bodies (cf. Fig. 2, *A* 1 and *A* 2), intrasomatically and intradendritically recorded spike bursts differed in a number of parameters (Table 1). The fast spikes of bursts recorded in dendrites were of lower amplitude than those in somata. In intradendritic recordings, partial responses, similar in appearance to the "fast prepotentials" described by Spencer and Kandel (10), were often intermixed with the fast spikes during the initial phase of burst firing (e.g., Fig. 3, *B* 2). Slow spikes were always of lower amplitude than fast spikes in somatic recordings, whereas in dendrites this relationship was reversed. In addition it may be noted that the average amplitude of slow spikes recorded in dendrites was about 60% greater than in somata. TTX (1μg/ml) blocked both the fast spikes and those partial responses that resembled fast prepotentials in both regions, but slow spikes could still be elicited by increasing the intensity of depolarizing current pulses (Fig. 2, *A* 3 and *B* 3). The largest TTX-resistant spike recorded in the soma had an amplitude of about 44 mV. Those recorded from the dendrites showed an average amplitude of about 56 mV. In both intrasomatic and intradendritic recordings, the thresholds and amplitudes of slow spikes associated with spontaneous or evoked bursting were comparable to those of TTX-resistant spikes.

Table 1. Spike parameters during bursts

	Soma	Dendrite
Fast spike amplitude, mV	64.3 ± 6.0 (20)	52.5 ± 10.2 (15)
Fast spike duration,* msec	1.1 ± 0.5 (20)	1.3 ± 0.5 (15)
Slow spike amplitude, mV	39.9 ± 3.3 (13)	65.8 ± 11.5 (12)
Slow spike duration, msec	2.6 ± 0.8 (13)	3.4 ± 1.4 (12)
TTX-resistant spike amplitude, mV	39.6 ± 4.9 (16)	55.7 ± 11.0 (10)
TTX-resistant spike duration, msec	6.3 ± 2.1 (16)	3.6 ± 1.0 (10)

Values tabulated are the mean ±SD (number of observations).
* Duration of spikes measured at half amplitude.

Another variety of electrogenic activity, previously noted in intrasomatic recordings (unpublished data), also was present in CA_1 and CA_3 dendrites. In TTX-poisoned preparations, depolarizing current pulses subthreshold for spike generation evoked slow depolarizing potentials whose amplitudes showed time-dependent increases that deviated from the time course of passive charging in these neurons. These appeared to be active membrane events (Figs. 3, *B* 3 and 2, *B* 3). This electroresponsiveness was only seen with outward current pulses and was related to the slow onset of TTX-resistant spikes at threshold. When pairs or trains of such spikes were triggered, these slow potentials appeared to summate into a more prolonged depolarizing envelope (Fig. 2, *B* 3). These responses may contribute to the slow envelope underlying burst generation in dendrites and somata of hippocampal pyramidal neurons.

Because the somata of the pyramidal cells generated Na^+ spikes with average amplitudes of 64.3 mV, it might be proposed that the fast spikes recorded in the dendrites are electronically propagated soma spikes. Our data do not support this interpretation. Dendritic fast spikes recorded at a distance of at least 150 μm from the cell body had an average amplitude of 52.5 mV. If these dendritic spikes were the electrotonic reflection of soma spikes with amplitudes averaging 63.4 mV, the length constant of the dendrite for the spike (λf) would have to be 800 μm (assuming that the amplitude of the electronically spreading soma spike decreased exponentially with distance). Based on this value, a direct current length constant (λ) of 3.2 mm would be expected.‡ Because this is an improbably high value, it is likely that active dendritic responses are involved in the generation of fast spikes. This suggestion was also supported by the observation that amplitude and duration of the intradendritically recorded fast spikes did not vary systematically with distance from the margin of stratum pyramidale (range, 150–350 μm), although lower-amplitude fractionated fast spikes were more often encountered in distal dendritic recordings.

To examine further the relationships between spike activities in the soma and dendrite, we attempted to make simultaneous intracellular recordings from these sites in the same neuron. Impalements of elements in the stratum pyramidale and stratum radiatum of the CA_3 region were obtained with two independently manipulated microelectrodes. In two instances, intracellular recordings were made from pairs of electrotonically coupled elements (Fig. 2*C*). The electrotonic spread from

‡ The equation for conversion of frequency-dependent length constant to direct current length constant in the case of an infinitely long cable was applied (22):

$$\lambda = \lambda f \Big/ \left[\frac{2}{1 + (1 + \omega^2\tau^2)^{1/2}}\right]^{1/2}$$

in which $\omega = 2\pi f$. For a nerve spike of 3-msec duration, f would be approximately 170 Hz and $\tau = 30$ msec.

a single spike generated at one site did not cause sufficient depolarization to produce full-amplitude spike firing at the other site, although spikelets resembling fast prepotentials were recorded at the remote site (Fig. 2, *C* 4). However, a burst generated by an outward current pulse at one site led to depolarization and burst generation at the second site (Fig. 2, *C* 2 and 4). The slow depolarization underlying the burst at the nonstimulated site was probably actively generated because its amplitude and duration were not obviously related to those at the polarized site. Also, bursts at the unstimulated site could be blocked by hyperpolarizing current pulses (not shown) uncovering a lower-amplitude depolarization that mirrored the slow envelope at the stimulated site.

Recordings such as those shown in Fig. 2*C* could have been obtained from different portions of the same neuron or from two electrotonically coupled cells. The former assumption is supported, but not proved, by two observations. First, we were unable to demonstrate electrical coupling between CA_3 pyramidal cell somata when chemical transmission was blocked by perfusion with medium containing 0.5 mM Ca^{2+} and 8 mM Mg^{2+}. In this medium, electrical stimuli applied to the fornix antidromically activated CA_3 cells and consistently evoked extracellularly recorded population spikes. Intracellular recordings showed that, when sufficient hyperpolarizing current was applied to a given neuron during antidromic stimulation, the antidromic spike could be blocked without uncovering short-latency depolarizing potentials. If the somata of CA_3 cells were electrically coupled, antidromically evoked spike activity in neighboring coupled cells might have been reflected as depolarizing potentials in the hyperpolarized cell (23, 24). Second, charging curves obtained from somata of CA_3 neurons could be closely fitted to a single exponential. If functional coupling through low-resistance junctions were present to explain results such as those of Fig. 3, *C* 1 and 3, both short and longer time constants would be expected (see especially figure 6 of ref. 25).

Spontaneous and directly evoked activities in dendrites of CA_1 neurons also consisted predominantly of burst firing (e.g., Fig. 3, *B* 1 and 2). In contrast, spontaneous activity in somata of CA_1 neurons consisted mainly of solitary spikes (8); typical burst firing was not evoked by short-duration depolarizing pulses. We examined the responses of CA_1 dendrites to orthodromic synaptic activation produced by stimulation of the stratum radiatum to determine whether more "natural" excitation would generate dendritic bursts. Fig. 3 contrasts the responses of a CA_1 dendrite to orthodromic and direct stimulations. Orthodromic stimuli evoked a large excitatory postsynaptic potential in this element (Fig. 3*A*), but no bursts were generated even at supramaximal stimulus intensities. At the resting membrane potential the excitatory postsynaptic potential triggered a single fast spike that could be fractionated into several components and blocked when it fell during increasing dendritic hyperpolarization (Fig. 3*A*). The same element generated both spontaneous (Fig. 3, *B* 1) and current-evoked (Fig. 3, *B* 2) bursts. The difference between the effectiveness of orthodromic and direct stimulations in evoking bursts could not be attributed to a threshold phenomenon because excitatory postsynaptic potentials elicited by stimuli might exceed both the amplitude and duration of the depolarization evoked by intracellular current pulses (cf. Fig. 3, *A* 2 and *B* 2). This result was consistently observed in 30 other stable intradendritic recordings in which the effect of orthodromic input was examined. Other data (unpublished) suggest that this is the consequence of the orthodromically evoked dendritic inhibitory postsynaptic potential which serves to eliminate dendritic burst activity in a manner comparable to that described for spike responses in alligator Purkinje cell dendrites (4).

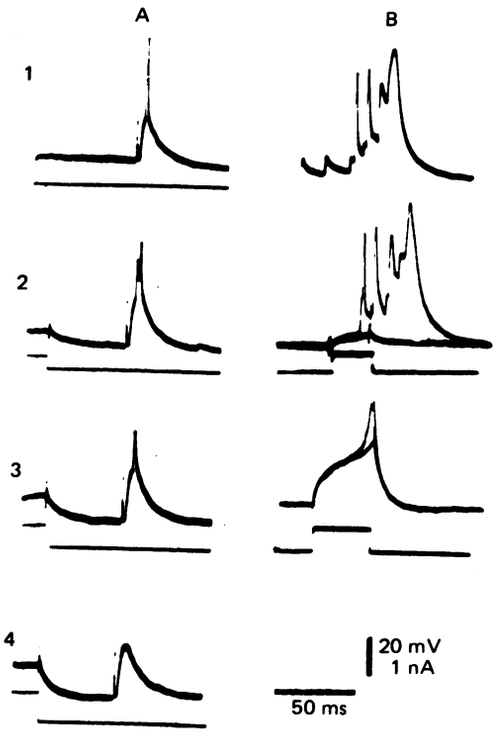

FIG. 3. Intradendritic recordings from a CA_1 pyramidal cell. Bottom traces are the current monitor. (*A*) Postsynaptic activities evoked by stratum radiatum stimulation. Control dendritic spike (in trace 1) was recorded in penetration 350 μm away from the cell body layer. In traces 2–4, hyperpolarizing current applied during orthodromic stimulation blocked the spike in steps and uncovered an excitatory postsynaptic potential (trace 4). (*B*) Spontaneous (trace 1) and directly evoked burst (trace 2) in the same dendrite as in *A*. TTX-resistant activity of this dendrite is shown in trace 3. Whereas short-duration (20 msec) depolarizing pulses could evoke depolarizations that triggered bursts (trace 2), excitatory postsynaptic potential of comparable duration that produced even larger depolarizations only evoked a spike (cf. *A* 1 and *B* 2). Membrane potential, 60 mV. Calibrations in *B* 4 for all frames.

DISCUSSION

In view of the known differences in dendritic morphology and presumed differences in function in various classes of neurons, caution is required in attempting to generalize with respect to dendritic activities from these data. With this reservation in mind, however, the present experiments do provide additional information regarding dendritic properties. There are three major findings of this study. First, there is evidence that two varieties of spikes are produced in hippocampal pyramidal cell dendrites. Second, there are significant differences between spike generation in dendrites and cell bodies of the same neurons. Third, evidence is provided that spike burst generation in dendrites may have important consequences in terms of somatic activities and the eventual output of the neuron in question.

Previous studies have shown that the somata of hippocampal CA_3 neurons are capable of generating bursts containing high-amplitude fast spikes and high-threshold low-amplitude slow spikes. Fast spikes are sensitive to TTX and are presumably mediated by Na^+, whereas slow spikes are insensitive to TTX, are blocked by Mn^{2+}, and presumably are mediated by Ca^{2+} (12, 13). Recordings from dendrites of both CA_1 and CA_3 cells now reveal similar patterns of bursts containing early fast spikes and late-phase slow spikes which, by analogy to the situation in the cell body, we assume to be mediated by Na^+ and Ca^{2+}, respectively. This conclusion is in part supported by the simi-

larities of threshold, duration, and amplitude between TTX-resistant spikes in dendrites and those of the late-phase slow spikes of dendritic bursts (Table 1 and Fig. 2). There are also significant differences in the amplitudes of these classes of spikes as recorded in the soma and dendrites. One possible interpretation of these findings would attribute amplitude differences to different contributions of voltage-dependent Na^+ and Ca^{2+} conductances to active responses over somatic and dendritic membranes. Other explanations, such as differences in voltage-dependent K^+ conductance in the two regions, cannot be excluded by our data because K^+ conductances were not blocked in these experiments and might well be affecting spike amplitudes and durations. In any case it is clear that both TTX-resistant and spontaneous slow spikes during bursts are significantly larger in amplitude in dendrites than in cell bodies—a finding compatible with their local generation on the dendritic membrane. The data of Table 1 do not clarify the relative contributions of somatic and dendritic membranes to generation of the slow and TTX-resistant spikes recorded in the cell body.

The large amplitude of fast spikes recorded in the dendrites as well as the fractionation of orthodromically evoked fast spikes during hyperpolarizing pulses (Fig. 3*A*) is evidence that fast Na^+ spikes are locally generated on the dendritic membrane. The presence of multiple peaks and inflections (Fig. 3, *A* 2) is consistent with the hypothesis (4) that multiple patches of excitable membrane exist in the dendrites. The stepwise fractionation of the orthodromically evoked spike in Fig. 3, *A* 2–4 during increasingly intense inward current pulses is presumably produced by a sequential block of the responses of excitable membrane patches at increasing electrotonic distances from the recording site. Furthermore, intercalated regions of low electroresponsiveness must be present in the dendrites to account for the fact that single spikes elicited at one site on the neuron do not invade other adjacent sites (see also ref. 4).

The data of Fig. 2*C* either indicate that electrotonic coupling occurs between cells in the CA_3 region of the hippocampus or, more likely from the arguments presented above, that we have successfully impaled the dendrite and soma of the same CA_3 pyramidal cell. Assuming the latter is the case, these data have a direct bearing on the issue of the significance of dendritic spike and burst activity to the output of the neuron. Fast spikes occurring in the dendrite (e.g., Fig. 2, *C* 4, upper trace, second spike) do not readily propagate into the soma, and the same may be said for propagation of somatic fast spikes into dendrites (Fig. 2, *C* 2, first spike, bottom trace). On the other hand, the slow depolarizing envelopes underlying spike bursts that are evoked by direct depolarization appear to serve as generator potentials for regenerative burst responses in remote soma or dendrite. The apparent failure of fast spike propagation in either direction could result from the imposition of areas of low electroresponsiveness with a long membrane time constant between active membrane patches. Under these conditions, slow depolarizing envelopes or slow spikes would be more effective in bringing nearby membrane patches to threshold for spike generation than fast events of a similar amplitude.

The data of Fig. 2, *C* 4 indicate that fast spikes in the dendrite may account for brief low-amplitude spikelets that resemble the fast prepotentials of Spencer and Kandel (10). Our data show that these fast prepotentials are TTX-sensitive and probably are a reflection of Na^+-dependent spike discharges on patches of membrane remote from the recording electrode. TXX-resistant dendritic slow spikes therefore are not generated by summations of small-amplitude fast spikes. The low amplitudes (5–10 mV) together with the short half-amplitude durations (<5 msec) of the fast prepotentials (8) also appear to exclude the possibility that they are the electrotonic reflection of dendritic slow Ca^{2+} spikes.

The unique advantages of the hippocampal slice preparation, together with intracellular labeling techniques, have allowed a more direct approach to the electrophysiology of dendrites of cerebral neurons than was previously possible. It appears from our data that the dendritic membrane of hippocampal pyramidal neurons possesses the capability to generate both Na^+- and Ca^{2+}-mediated spikes. Na^+ spikes may be reflected in somata as fast prepotentials that can evoke spikes and affect cell output. Intrinsic burst generation in dendrites is closely associated with the occurrence of high-threshold Ca^{2+} spikes and development of large-amplitude depolarizations. The somatic membrane is in part electrically isolated from fast dendritic events because of the long membrane time constant; however, the slowly depolarizing envelopes associated with bursts are an effective means by which dendritic events can influence the output of neuronal somata. The extent to which this occurs during orthodromic stimulation depends in part upon the balance between the evoked depolarizing events and concomitant generation of IPSPs on dendrites.

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