

# Dendritic Sodium Spikes Are Variable Triggers of Axonal Action Potentials in Hippocampal CA1 Pyramidal Neurons

Nace L. Golding and Nelson Spruston\*

Department of Neurobiology  
and Physiology  
Institute for Neuroscience  
Northwestern University  
Evanston, Illinois 60208

## Summary

Several early studies suggested that spikes can be generated in the dendrites of CA1 pyramidal neurons, but their functional significance and the conditions under which they occur remain poorly understood. Here, we provide direct evidence from simultaneous dendritic and somatic patch-pipette recordings that excitatory synaptic inputs can elicit dendritic sodium spikes prior to axonal action potential initiation in hippocampal CA1 pyramidal neurons. Both the probability and amplitude of dendritic spikes depended on the previous synaptic and firing history of the cell. Moreover, some dendritic spikes occurred in the absence of somatic action potentials, indicating that their propagation to the soma and axon is unreliable. We show that dendritic spikes contribute a variable depolarization that summates with the synaptic potential and can act as a trigger for action potential initiation in the axon.

## Introduction

Most neurons in the central nervous system (CNS) function by generating action potentials in response to appropriate synaptic inputs, yet little is known about the actual steps leading to action potential initiation. Are synaptic inputs summed passively in the dendrites, or can voltage-gated channels, which are known to be present in the dendritic membrane of many neurons, contribute substantially to the membrane potential change required to produce an action potential in the axon? Alternatively, can dendrites themselves serve as the site of action potential initiation in response to some synaptic inputs? Answers to questions like these have been elusive, in large part owing to the technical difficulty of probing dendritic function directly. Indeed, the question of whether voltage-gated channels in dendrites can amplify synaptic potentials or generate action potentials is a controversial one. Many experiments have indicated that the axon is the usual site of action potential initiation in several types of neurons, but some studies have indicated a role for the dendrites in the process of spike initiation (reviewed by Johnston et al., 1996; Yuste and Tank, 1996; Stuart et al., 1997a).

The controversy regarding the site of action potential initiation in CA1 neurons is rooted in a long history of experiments on these neurons. Early *in vivo* work using

field potential recordings in CA1 indicated that spikes could be generated in the proximal apical dendrites of CA1 neurons and subsequently propagate in both directions away from this dendritic site of initiation (Cragg and Hamlyn, 1955; Andersen, 1960; Fujita and Sakata, 1962; Andersen and Lomo, 1966). Almost three decades later, by combining *in vitro* field potential recordings with local tetrodotoxin (TTX) application, Turner and colleagues substantiated these conclusions, finding that active dendritic conductances precede somatically recorded population spikes (Turner et al., 1989). Using current source density analysis *in vivo*, Herreras arrived at the similar conclusion that active dendritic conductances preceded axonal action potential generation in CA1 neurons (Herreras, 1990). Finally, Turner and colleagues used a variety of observations to conclude that a gradual transition from synaptic amplification to all-or-none dendritic spike generation proceeded as synaptic stimulus intensity was increased (Turner et al., 1989).

Support for the idea of excitable dendrites has also come from microelectrode recordings. In the early 1960s, Spencer and Kandel, using intracellular microelectrode recordings *in vivo*, identified small amplitude, fast, all-or-none spikes (fast prepotentials) that occurred either in isolation or in association with full size action potentials (Spencer and Kandel, 1961). Because these fast prepotentials were absent during antidromic stimulation, they were attributed to dendritically initiated spikes, an interpretation that received support in several subsequent studies (Schwartzkroin, 1977; Wong and Stewart, 1992; Turner et al., 1993). Intradendritic recordings also indicated that CA1 dendrites are active (Wong et al., 1979; Benardo et al., 1982; Poolos and Kocsis, 1990; Wong and Stewart, 1992; Andreasen and Lambert, 1995b), and several studies showed that dendrites retained these active properties when isolated from the soma either mechanically or pharmacologically (Benardo et al., 1982; Turner et al., 1991, 1993; Colling and Wheal, 1994). Other studies have shown that the threshold and timing of action potentials differ for proximal versus distal synaptic stimulation, leading to the conclusion that distal synaptic inputs may result in dendritic spike initiation, while proximal inputs lead to axonal spike initiation (Andersen et al., 1987; Andreasen and Lambert, 1998).

Despite this wealth of data suggesting that spikes may be generated in CA1 dendrites, the question has remained controversial. For example, in contrast to the studies cited above, some field potential studies concluded that action potentials are generated near the soma and subsequently invade the dendrites actively (Miyakawa and Kato, 1986; Richardson et al., 1987). This notion has gained support from recent patch-clamp studies which suggest that the threshold for action potential initiation is lowest in the axon of CA1 neurons (Spruston et al., 1995; Colbert and Johnston, 1996; Hoffman et al., 1997). Furthermore, the role of dendritic voltage-gated channel activation need not be limited to spike generation. Sodium and calcium channels present in CA1 dendrites (Magee and Johnston, 1995a) may be activated during subthreshold synaptic stimulation

\* To whom correspondence should be addressed (e-mail: spruston@nwu.edu).

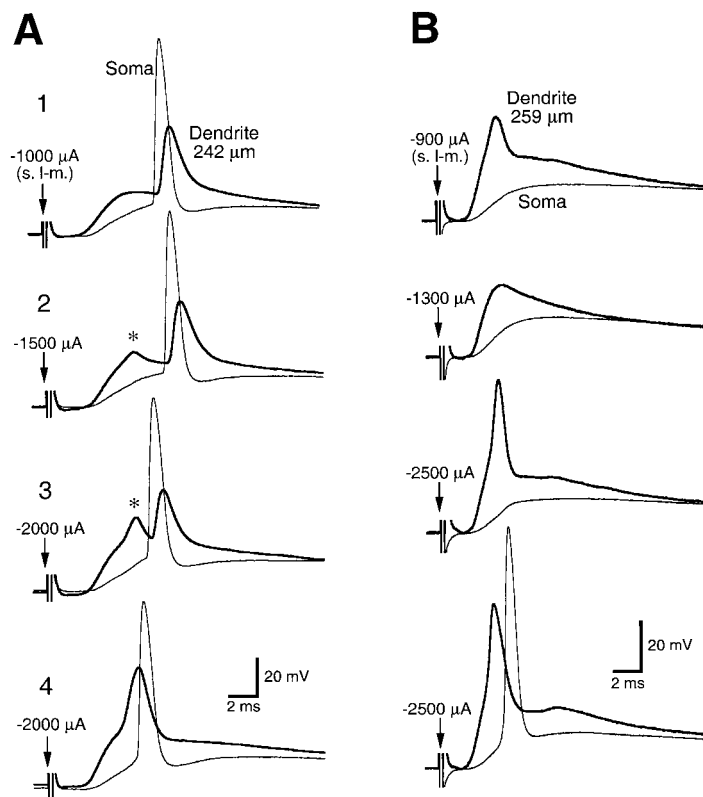


Figure 1. Initiation of Dendritic Spikes Occurs in Vitro

(A) Responses of a pyramidal cell recorded simultaneously from the soma (thin traces) and the dendrite (thick traces, distance = 242  $\mu\text{m}$ ) to synaptic stimuli of different intensities in stratum lacunosum-moleculare (arrows). A threshold stimulus gave rise to an EPSP that triggered an action potential that was detected first in the soma and subsequently in the dendrite (A1). However, stronger stimuli elicited EPSPs with graded, active electrogenic components (asterisks, [A2] and [A3]) and also could give rise to a dendritic spike (A4).

(B) In a different pyramidal cell, dendritic spikes of graded amplitude were elicited at lower stimulus intensities than somatic action potentials. These isolated dendritic spikes, regardless of amplitude, appear strongly attenuated at the soma. Note the lack of monotonicity in the relationship between the amplitude of the dendritic spike and stimulus strength.

(Magee and Johnston, 1995b). As blocking these channels results in a reduction in the amplitude of the somatic excitatory postsynaptic potential (EPSP) (Lipowsky et al., 1996; Gillissen and Alzheimer, 1997), it remains possible that the excitable properties of dendrites identified in some studies may serve to amplify synaptic potentials without actually generating dendritic spikes. Even if spikes can be generated in CA1 neurons, it is unclear which patterns of synaptic activation are most effective at evoking them and how dendritic spikes propagate to the soma.

Here, we use simultaneous patch-pipette recordings from the soma and a dendrite of the same neuron to address these questions directly. We demonstrate that sodium spikes can be generated in the dendrites of CA1 neurons in response to specific patterns of synaptic stimulation. Furthermore, we find that the propagation of these spikes to the soma is unreliable, suggesting that dendritic spikes are functionally distinct from action potentials propagating via the axon. These results help to reconcile many contentious results obtained over four decades of research and provide insight into the steps leading to action potential initiation in CA1 neurons.

## Results

### Dendritic Spikes in Response to Synaptic Stimulation

Simultaneous patch-pipette recordings were obtained from the soma and primary apical dendrite of CA1 pyra-

midal neurons in hippocampal slices maintained at physiological temperature (32°C–36°C). Most slices were prepared from 6- to 11-week-old rats, but similar results were observed in slices from 4-week-old rats. A stimulating electrode was placed in either the distal third of the stratum radiatum or in stratum lacunosum-moleculare; similar results were observed with both of these stimuli, which activate axons impinging on approximately the middle and outer thirds of the apical dendrites, respectively.

In the majority of neurons, synaptic stimulation just above threshold for spike initiation produced action potentials that occurred first in the soma and later in the dendrite ( $n = 22$  of 30 recordings in which a somatic action potential could be evoked by a single stimulus; Figure 1A1), presumably reflecting action potential initiation in the axon and active back-propagation into the dendrites, with significant amplitude attenuation (Spruston et al., 1995). In some cells, however, increasing the synaptic stimulus intensity resulted in a dendritic spike that preceded the somatic action potential ( $n = 4$  of 10 recordings tested in this way; Figure 1A4). Furthermore, stimuli at or near the intensity that evoked a dendritic spike occasionally evoked partial dendritic regenerative responses that preceded the somatic action potential but were later followed by a back-propagating action potential (Figures 1A2–1A3). In a minority of recordings ( $n = 8$  of 30), threshold stimulation resulted in dendritic spikes that preceded the somatic action potential. In two of these eight cases, threshold stimulation resulted in dendritic spikes that occurred in isolation of a somatic

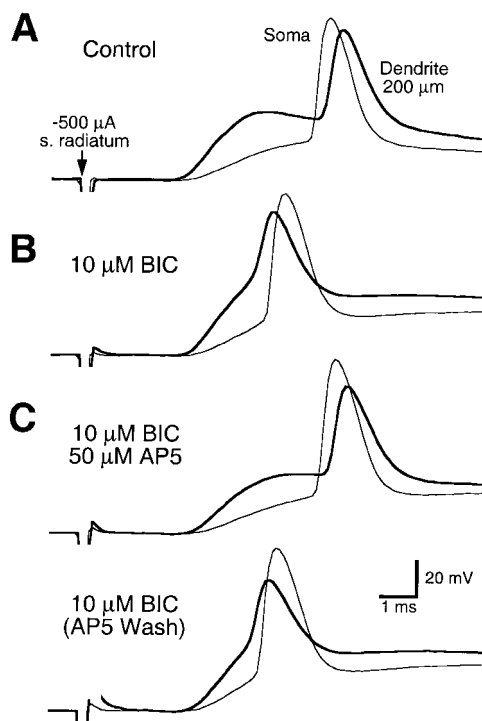


Figure 2. The Site of Spike Initiation Is Sensitive to the Strength of Excitation

(A) Threshold activation of synaptic inputs in stratum radiatum triggers an action potential that is observed first in the soma (thin traces) and subsequently in the dendrite (thick traces, distance = 200  $\mu$ m). (B) Blockade of inhibition mediated by GABA<sub>A</sub> receptors with bicuculline caused the site of spike initiation to shift from the axon to the dendrite.

(C) Reducing the strength of excitation by blocking NMDA receptors with D-AP5 reversibly shifted spike initiation back to the axon.

action potential (Figures 1B1–1B3), but as stimulus intensity was further increased, the dendritic spike eventually gave rise to a somatic action potential (Figure 1B4).

These results constitute a direct demonstration of dendritic spike initiation in CA1 pyramidal neurons. By dendritic spike initiation, we mean only that a spike occurred in the dendrite first and not necessarily that it was the sole cause of the action potential in the soma. These results are in accord with previous suggestions that stronger excitatory synaptic inputs can trigger dendritic spikes in CA1 cells (Turner et al., 1989, 1991). To further test the idea that synaptic strength can modulate the site of spike initiation, EPSP amplitude was altered pharmacologically, rather than by changing stimulus intensity. In control, threshold synaptic stimulation triggered an action potential that occurred first in the soma and later in the dendrite (Figure 2A). Blocking GABA<sub>A</sub>-mediated inhibition increased the overall synaptic depolarization associated with the same stimulus and caused the dendritic spike to occur first ( $n = 4$  for 10  $\mu$ M bicuculline,  $n = 3$  for 5–50  $\mu$ M SR95531; Figure 2B). The subsequent addition of 50  $\mu$ M D-AP5 reduced the overall synaptic depolarization by blocking NMDA receptors and reversibly shifted the site of spike initiation from the

dendrite to the soma ( $n = 2$ ; Figures 2C and 2D). Dendritic spikes were promoted in a similar manner by blocking GABA<sub>B</sub>-mediated inhibition with 1  $\mu$ M CGP55845A. These results provide further confirmation that dendritically generated spikes occur preferentially when the excitatory component of a synaptic potential is strong.

#### Dendritic Spikes in Response to Trains of Synaptic Stimuli

An important question is whether excitatory synaptic inputs capable of triggering dendritic spikes actually occur *in vivo*. Two observations *in vitro* presented so far suggest that they could. First, in some cells, dendritic spikes were observed in the absence of corresponding somatic action potentials (Figure 1B). Second, even in those cells in which dendritic spikes only occurred at a stimulus intensity larger than that required to evoke somatic spikes, the necessary increase in stimulus intensity was modest (as little as 1.5 $\times$  the threshold stimulus for a somatic spike; see Figure 1A). Perhaps the most compelling suggestion that dendritic spikes may occur in response to synaptic inputs of physiological relevance, however, is the observation that dendritic spikes occurred almost invariably during trains of synaptic stimuli. In 30 of 36 neurons, trains of five synaptic stimuli (20–66 Hz) resulted in at least one spike that occurred first in the dendrite. In the cell shown in Figure 3, the action potential was initiated in the axon on the first stimulus (Figure 3B1), in the dendrite on the second stimulus (Figure 3B2), and in the axon again on the third and subsequent stimuli (Figures 3B3 and 3B4; fifth response not shown). This example is typical in that the second synaptic stimulus was the most effective trigger of dendritic spikes ( $n = 30$  of 30 recordings exhibiting dendritic spikes), even if the first postsynaptic potential (PSP) was below action potential threshold (Figure 3C). Additional dendritic spikes sometimes occurred in response to stimuli other than the second in a train, but the occurrence of more than two dendritically initiated spikes in a train of five stimuli was infrequent ( $n = 9, 9, 6, 2,$  and 4 for 1–5 spikes, respectively).

A major factor underlying the prevalence of dendritic spikes during trains is the facilitation of the EPSP that occurs during repetitive synaptic stimulation. When the synaptic stimulus intensity was reduced to produce trains of subthreshold PSPs, the second and third responses in the train were usually the largest (Figure 4A), suggesting that dendritic spike initiation is correlated with the size of the PSP. In support of this hypothesis, the initial slope of the EPSPs giving rise to dendritic spike initiation was larger than the slope of EPSPs resulting in somatic initiation (Figures 4B and 4C). Nevertheless, facilitated EPSPs late in the train rarely gave rise to dendritic spikes, suggesting that other factors contribute to whether a strong synaptic input can trigger a dendritic spike (see Discussion).

Isolated dendritic spikes (i.e., in the absence of a corresponding somatic action potential) were also prevalent in response to trains of synaptic stimuli ( $n = 11$  of 30 cells that exhibited dendritic spikes). Figure 5 shows examples from three recordings in which isolated dendritic spikes were recorded in response to repetitive

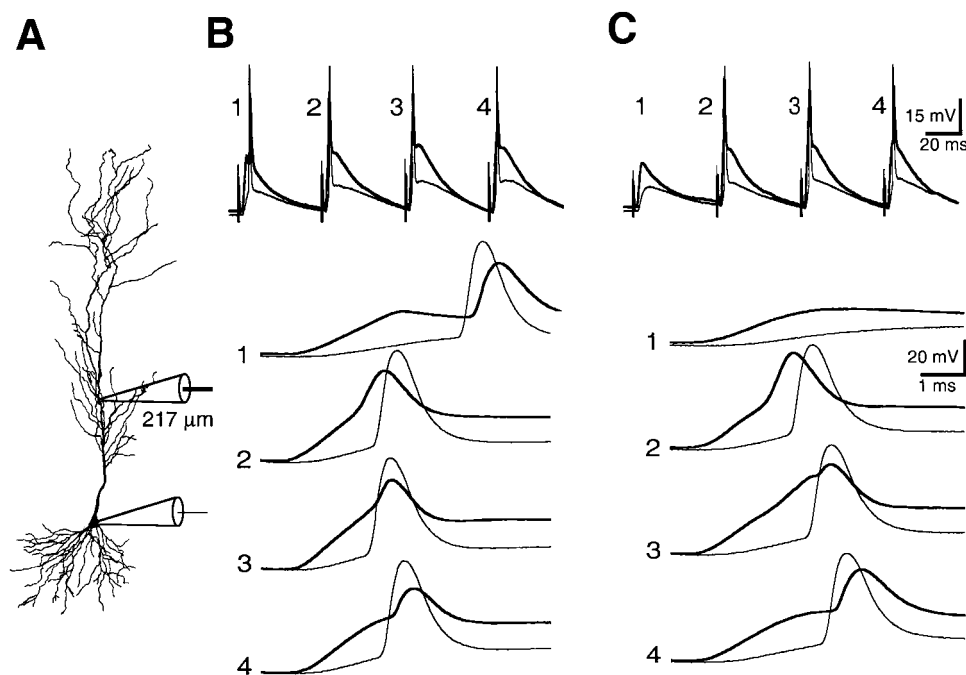


Figure 3. Dendritic Spike Initiation Is Prominent during Brief Trains of Synaptic Stimuli

(A–C) Responses of a CA1 pyramidal cell (shown in [A]) to 20 Hz trains of PSPs recorded simultaneously from the soma (thin traces) and the dendrite (thick traces, distance = 217  $\mu$ m). The stained neuron provides morphological confirmation that the recordings were from a CA1 pyramidal neuron.

(B) Responses to a train of four synaptic stimuli are shown at the top, and each response is expanded below. Spike initiation occurred near the soma in the first response, shifted to the dendrite in the second response, and shifted back near the soma in the third and fourth responses. (C) The shift in the site of spike initiation to the dendrite occurred independent of prior spike initiation, as the second response produced a dendritically initiated spike even though the first response fell below threshold.

synaptic stimulation. Isolated spikes elicited in response to trains of synaptic stimuli had variable amplitudes in different responses but were usually smaller than those associated with somatic action potentials (Figure 5B). Similar isolated dendritic spikes were also observed in the presence of 10  $\mu$ M bicuculline or 50  $\mu$ M SR95531 ( $n = 3$  and 1, respectively), indicating that inhibition mediated by GABA<sub>A</sub> receptors was not responsible for the failure of dendritic spikes to trigger action potentials at the soma.

One technical concern in these experiments was that the cytoplasmic dialysis or capacitance load associated with whole-cell patch-pipette recordings could itself change the site of action potential initiation. To address this issue, experiments were performed in the cell-attached configuration (Figure 6). As in whole-cell recordings, trains of action potentials evoked by synaptic stimulation usually resulted in dendritic spike initiation in response to at least one stimulus in the train ( $n = 7$  of 10 recordings), most often in response to the second stimulus (Figure 6A). In a few cases, isolated dendritic spikes were also observed in dual cell-attached recordings ( $n = 3$  of 10; Figure 6A2). In four of seven cells showing dendritic spikes in cell-attached recordings, the soma was repatched in the whole-cell configuration to confirm that both recordings were from the same cell (Figure 6B). These results alleviate the concern that dendritic spike initiation is an artifact of whole-cell recording.

We also examined the dependence of dendritic spike generation on the temperature and age of the animal. We found that the stimulus intensity required to elicit dendritic spikes was higher at room temperature than at physiological temperature ( $n = 4$ ). This observation potentially explains why dendritic spike initiation was not observed in a previous study in which most experiments were performed at room temperature (Spruston et al., 1995). In the present study, dendritic spikes were observed in slices from animals as young as 26 days old (the youngest age examined).

#### Dendritic Spikes Are Mediated by Sodium Channels and Are Sensitive to Previous Action Potential Firing

Dendritic spikes could also be evoked by injecting large, brief current pulses directly via the dendritic electrode (Figure 7). In some cases, these current-evoked dendritic spikes appeared first in isolation (Figure 7, middle) but were associated with somatic action potentials when the amplitude of the injected current was increased (data not shown). Current-evoked dendritic spikes were blocked by TTX, indicating that dendritic spikes require activation of dendritic sodium channels (Figure 7). Because these current-evoked dendritic spikes appear almost identical in half width to dendritic spikes evoked by synaptic stimulation (Figure 7), it is likely that the synaptically evoked dendritic spikes are also primarily sodium-dependent. By contrast, dendritic spikes

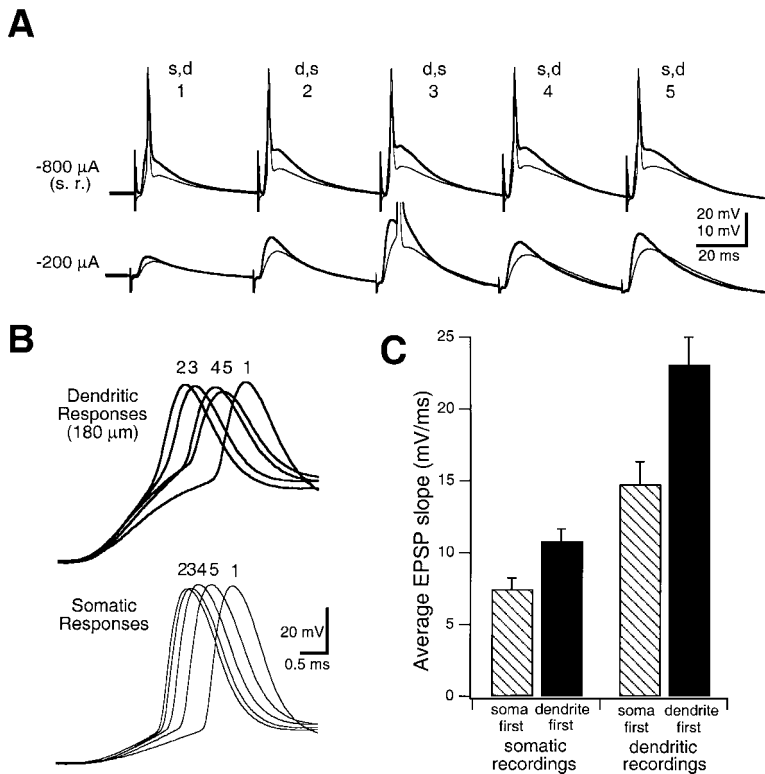


Figure 4. Strong Synaptic Excitation Favors Dendritic Spike Initiation

(A) (Upper traces) Responses of a pyramidal cell to a train of synaptic stimuli recorded simultaneously from the soma (thin traces) and the apical dendrite (thick traces, distance = 180  $\mu$ m). The second and third action potentials occurred first in the dendrites (d,s), whereas the first, fourth, and fifth action potentials occurred first in the somatic recording (s,d). (Lower traces) A train of largely subthreshold PSPs reveals substantial frequency potentiation in the responses.

(B) Superposition of all five dendritic and all five somatic traces reveals a clear correlation between the time of the spike and the initial slope of the EPSP. The dendritically initiated spikes (2 and 3) arose earlier, from the fastest rising EPSPs.

(C) Summary graph comparing the slopes of EPSPs triggering spikes initiated in the soma or the dendrite. Differences between the slopes of the EPSPs giving rise to somatically versus dendritically initiated spikes are statistically significant (paired sample t test,  $p < 0.00001$  for somatic EPSPs and  $p < 0.00004$  for dendritic EPSPs,  $n = 10$  cells).

evoked by current injection were insensitive to 200  $\mu$ M CdCl<sub>2</sub> and 50  $\mu$ M NiCl<sub>2</sub>, which blocked synaptic transmission, indicating that voltage-activated calcium channels are not required for dendritic spike initiation ( $n = 4$ ; data not shown). Nevertheless, it is likely that the depolarization associated with the dendritic sodium spike induces some calcium influx through voltage-activated calcium channels under physiological conditions.

Since synaptically evoked dendritic spikes appear to require dendritic sodium channel activation, and dendritic sodium channels are known to be inactivated for prolonged periods by prior depolarization (Colbert et al., 1997; Jung et al., 1997), we examined whether dendritic spikes are sensitive to recent action potential firing (Figure 8). A train of three to six action potentials evoked

by a somatic current step attenuated subsequent, synaptically evoked dendritic spikes ( $n = 8$ ; Figure 8B). In general, synaptic responses evoked less than 500 ms after the conditioning train gave rise to highly attenuated dendritic spikes, which in many cases failed to trigger action potentials at the soma. At progressively longer intervals, dendritic spikes recovered in amplitude in a graded manner, with full recovery apparent at intervals of 500–1500 ms. When the duration of the conditioning train was extended, however, dendritic spikes evoked following short recovery periods had larger amplitudes than those following a brief conditioning train (compare Figures 8B and 8C). This result suggests that although the first few back-propagating spikes can alter dendritic excitability, subsequent spikes have considerably less

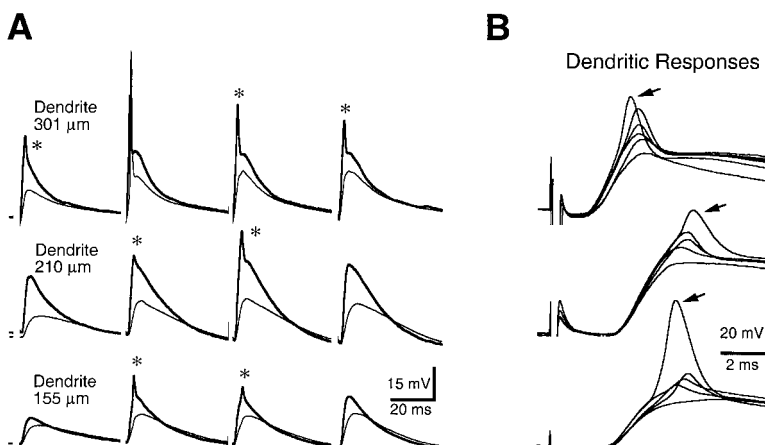


Figure 5. Variable Amplitude, Isolated Dendritic Spikes Are Prominent during Trains of Synaptic Stimuli

(A) Isolated dendritic spikes (asterisks, thick traces), elicited with 20 Hz trains of synaptic stimuli, recorded simultaneously at the soma and at different distances in the dendrites of three different cells. The voltage contribution of these spikes is barely detectable at the soma (thin traces).

(B) Superimposed dendritic traces recorded from the examples shown at the left (and others) reveal that isolated dendritic spikes are graded in amplitude. Arrows indicate dendritic spikes that triggered action potentials in the soma.

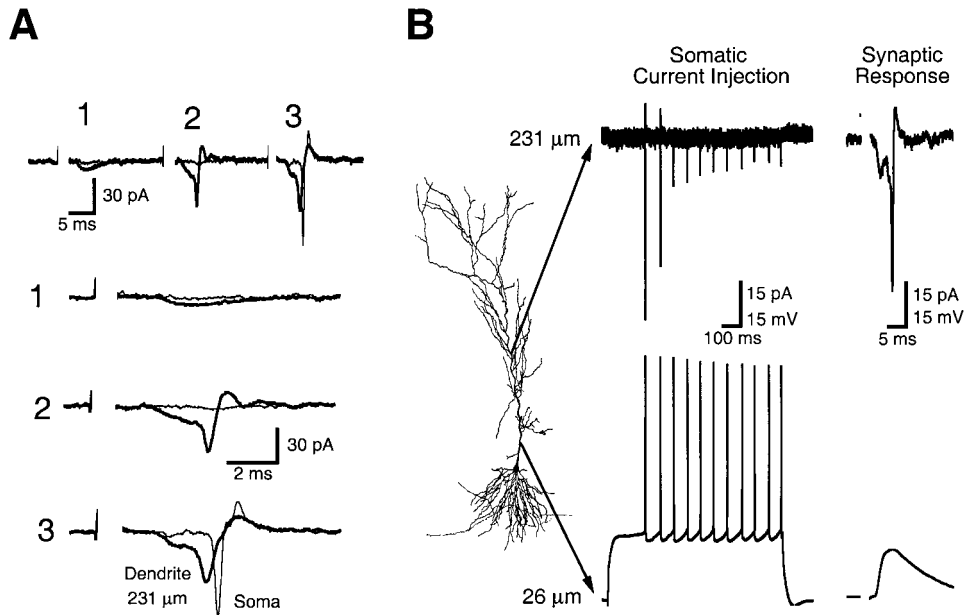


Figure 6. Dendritic Spikes Can Be Detected by a Noninvasive Recording Technique

(A) Currents measured in simultaneous cell-attached patch recordings from a proximal dendrite (near the soma, thin traces) and a distal apical dendrite (thick traces, distance = 231  $\mu\text{m}$ ) of the same cell in response to a train of synaptic stimuli (three shocks, 66 Hz). Individual responses are shown expanded below. Note the isolated dendritic spike in response to the second stimulus and the dendritically initiated spike in response to the third stimulus.

(B) Electrophysiological confirmation that the paired recordings in (A) were from the same cell. The somatic cell-attached patch-pipette was replaced by a whole-cell patch-pipette 26  $\mu\text{m}$  from the soma. Currents recorded in cell-attached configuration at the distal dendritic location were correlated with spikes elicited by a 300 pA current step injected into the proximal dendritic site. The synaptic response elicited in this configuration reveals a spike in the dendrite that does not propagate to the soma. The stained neuron provides morphological confirmation that the recordings were from a CA1 pyramidal neuron.

effect. This can be understood by realizing that the later spikes in a train propagate to the distal dendrites, with significant amplitude attenuation (Spruston et al., 1995), largely as a result of sodium channel inactivation in the proximal dendrites (Colbert et al., 1997; Jung et al., 1997). Because these later spikes do not substantially depolarize the distal dendrites (depolarizations even smaller than those shown in Figure 8C will occur at dendritic locations distal to this recording site), the sodium channels there can recover from inactivation to some extent, even while the more proximal dendritic sodium channels remain inactivated, owing to the larger depolarization associated with each spike in the proximal dendrites. The ability of dendritic spikes to recover

during sustained spike back-propagation therefore suggests that the dendritic spikes are generated in distal regions of the dendrites that are relatively insulated from the effects of attenuated back-propagating action potentials.

#### Dendritic Spikes Can Trigger Axonal Action Potentials

The observation that dendritic spikes have variable amplitudes and can occur in isolation from action potential firing in the soma and axon raises the question of what function is served by these dendritic spikes. One possibility is that they serve a local function, perhaps related to synaptic plasticity (see Discussion). Alternatively, or

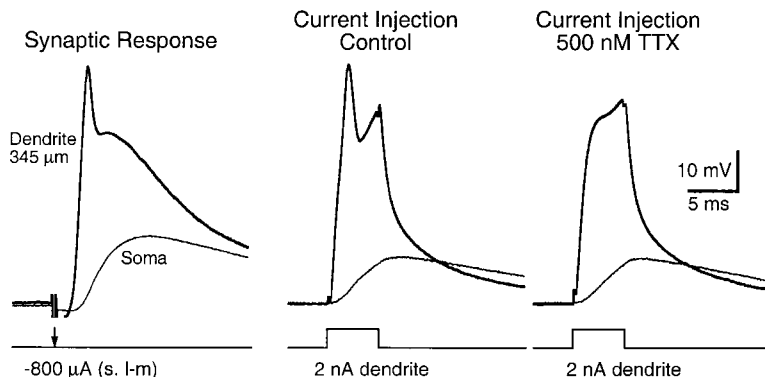


Figure 7. Dendritic Spikes Are Dependent on Activation of Voltage-Gated Sodium Channels

An EPSP elicited with a shock to stratum lacunosum-moleculare triggered a spike in the dendrite (thick traces, distance = 345  $\mu\text{m}$ ) that failed to propagate to the soma (thin traces). The amplitude and time course of the synaptically triggered dendritic spike was mimicked by a 5 ms depolarizing current pulse injected into the dendritic electrode, and this spike was eliminated in the presence of 500 nM TTX.

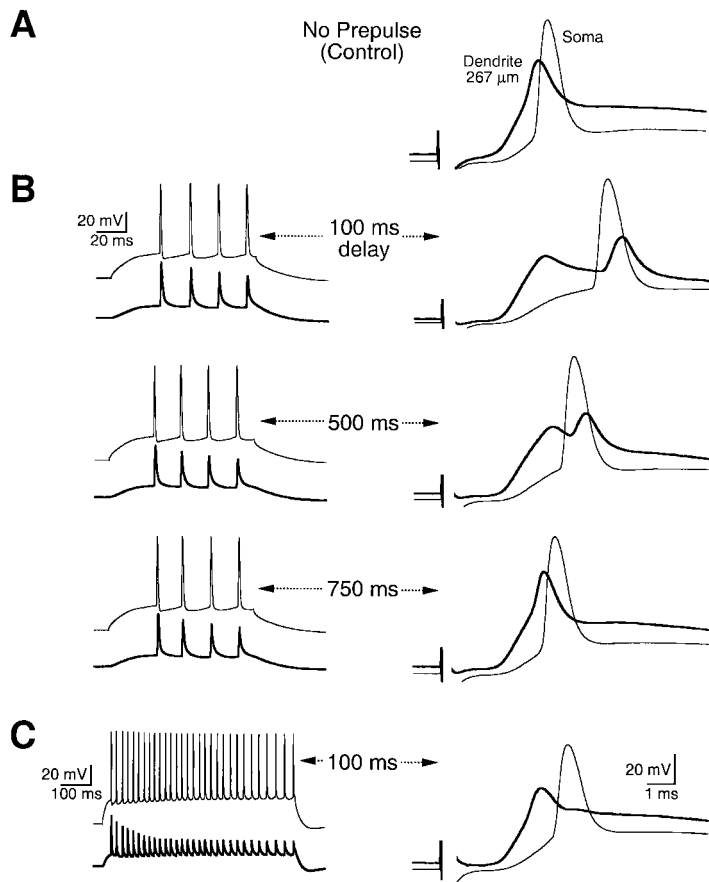


Figure 8. The Amplitude of Dendritic Spikes Is Sensitive to Prior Action Potential Firing

(A) Synaptically elicited dendritic spike recorded simultaneously from the soma (thin traces) and the apical dendrite (thick traces, distance = 267  $\mu\text{m}$ ). (B) When the same synaptic stimulus followed 100 ms after a train of four action potentials elicited by a 100 ms, 550 pA depolarizing prepulse injected into the soma, the dendritic spike was absent, and a delayed back-propagating spike followed the somatic action potential. Partial recovery from activity-dependent attenuation of dendritic spikes was apparent when the synaptic stimulus followed the prepulse by 500 ms. Full recovery of dendritic spike amplitude occurred when the synaptic stimulus followed the prepulse by 750 ms, and active back-propagation of the somatic action potential to the dendritic recording site is not detectable. (C) Substantial recovery of dendritic spike amplitude occurred when the synaptic stimulus was given 100 ms after an extended, 650 ms train of action potentials that showed activity-dependent amplitude attenuation of back-propagating action potentials.

in addition, they could function as an active form of synaptic integration, which might serve to increase the probability of a synaptic input triggering axonal action potentials. Some observations in our recordings support this idea. As illustrated in Figure 9, dendritic spikes can provide an additional depolarization at the soma. Whether

or not an action potential is triggered in the axon depends on the magnitude of the additional depolarization provided by the dendritic spike. In Figure 9A1, the PSP is subthreshold, but in Figure 9A2, an additional depolarization contributed by a small dendritic spike (about 20 mV at 155  $\mu\text{m}$ ) increases the somatic membrane

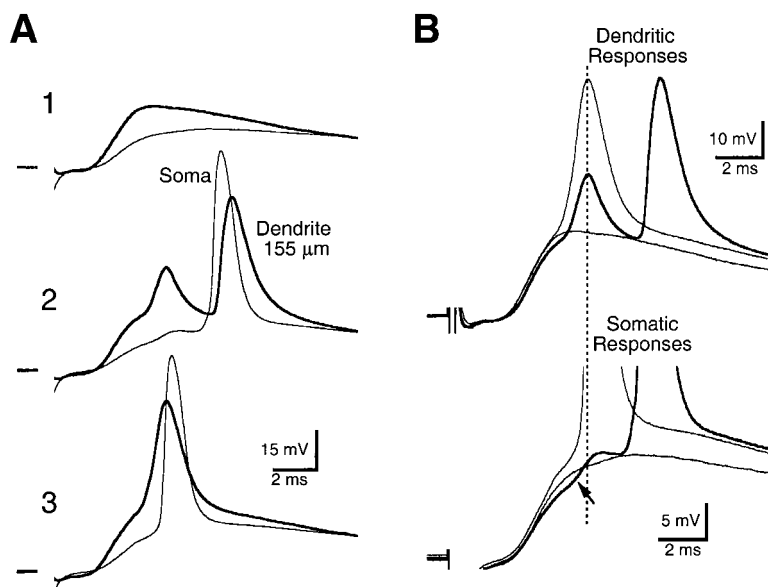


Figure 9. Dendritic Spikes Summate with Postsynaptic Potentials

(A) Threshold synaptic stimuli of identical intensity elicit responses consisting of a subthreshold PSP (A1), a PSP that gives rise to a weak dendritic spike followed by a back-propagating somatic action potential (A2) and a full dendritic spike that triggers a non-back-propagating somatic action potential (A3). (B) Comparison of the dendritic (top) and somatic (bottom) voltage changes in the three responses in (A). The response in (A2) is shown as thick traces in (B). The dashed line indicates the peak of the dendritic spikes in the dendritic responses at the top. Below, an inflection (arrow) is apparent in the somatic PSP of the thick trace, just prior to the peak of the dendritic spike. This inflection, which appears to be due to the dendritic spike, provides just enough additional depolarization to the somatic PSP to allow it to trigger a full size action potential.

potential by a few millivolts, causing it to trigger an action potential in the axon. This recording provides a clear example of active dendritic integration that precedes axonal action potential initiation and back-propagation into the dendrites (see also Figures 1A2 and 1A3). In cases such as this, the dendritic spike has not propagated regeneratively along the dendrite to the soma and axon; rather, the dendritic spike has propagated semiactively (or passively) along the dendrite and provided only a small additional depolarization to the somatic PSP. In other cases, the depolarization provided by the dendritic spike is presumably larger than that shown in Figure 9A2, and the somatic action potential occurs without delay, as shown in Figure 9A3. In these cases, no back-propagating action potential is observed, presumably because the larger dendritic spike has left the dendrite in a refractory state, owing to the inactivation of a larger fraction of dendritic sodium channels.

## Discussion

The simultaneous somatic and dendritic recordings presented here provide definitive evidence that sodium-dependent spikes can be initiated in the dendrites of CA1 neurons in response to specific patterns of synaptic stimulation. These spikes were observed with a single synaptic stimulus at the threshold for a spike in 27% of our recordings, but 83% revealed dendritic spikes in response to a train of stimuli at the same intensity. Isolated dendritic spikes were observed in some trials in ~40% of the recordings showing dendritic spikes. Equally importantly, the present recordings provide information about the properties of dendritic spikes and their propagation to the soma. In contrast to the large, all-or-none action potentials that occur in the axon and soma, dendritic spikes are variable in amplitude and are regulated by the neuron's recent history of synaptic and action potential activity; short-term facilitation during brief bursts of synaptic input promotes dendritic spike initiation, whereas sodium channel inactivation prevents sustained dendritic spike generation following repetitive firing. Dendritic spikes attenuate drastically as they propagate to the soma, where they sometimes fail to trigger axonal action potentials. Dendritic spikes can thus be viewed as influential but not absolute determinants of action potential generation in the axon.

### Synaptic Inputs Can Trigger Dendritic Sodium Spikes in CA1 Neurons

The steps leading to action potential initiation in CA1 neurons are likely to proceed as follows. Synaptic potentials propagate from the dendrites of CA1 neurons toward the soma and trigger an action potential if the PSP is above threshold in the axon. Some patterns of synaptic input, particularly those that have a strong excitatory component, such as during brief, high-frequency inputs, trigger spikes in the dendrites. Dendritic spikes have variable amplitudes at a given dendritic recording location. The smallest dendritic spikes fail to provide enough depolarization to trigger a spike in the axon, resulting in isolated dendritic spikes (see Figures

1, 5 and 6). Somewhat larger dendritic spikes provide just enough additional depolarization to the somatic PSP that an action potential does occur, but with some delay (see Figure 9). The largest and most reliably propagating dendritic spikes will always trigger full size action potentials in the axon. Dendritic spikes may therefore be viewed as a form of amplification for some synaptic inputs, since the variable-amplitude depolarization they contribute to the somatic PSP increases the probability of action potential initiation in the axon (see also Stuart et al., 1997a).

Our results are then consistent with the view that a low threshold action potential initiation zone exists in the axon of CA1 cells (Spruston et al., 1995; Colbert and Johnston, 1996). Though many factors may contribute to the higher threshold for spike initiation in the dendrites, Hoffman and colleagues have shown that an important one is the high density of A-type potassium channels in the apical dendrites of CA1 neurons (Hoffman et al., 1997). Our results indicate, however, that in response to some synaptic stimuli, the effects of these dendritic potassium channels can be overcome, and the higher threshold spike initiation zone(s) in the dendrites can be activated, before threshold is reached in the axon.

The synaptically triggered dendritic spikes described here likely require the activation of dendritic voltage-activated sodium channels, as these spikes have half widths similar to TTX-sensitive spikes evoked by direct current injection (Figure 7). The dependence of dendritic spikes on sodium channels is also consistent with the sensitivity of dendritic spikes to previously occurring back-propagating spikes, which induce a prolonged form of inactivation in dendritic sodium channels. As the time course of dendritic spike recovery is similar to that of the recovery of sodium channels from prolonged inactivation reported previously (Colbert et al., 1997; Jung et al., 1997), this correlation strongly suggests that the cumulative inactivation of dendritic sodium channels caused by back-propagating action potentials reduces the amplitude and/or extent of the propagation of dendritic spikes. Longer trains of action potentials, however, had less effect on dendritic spikes than did the shorter trains (Figure 8C). This is an important result, because it supports the interpretation that dendritic spikes are likely to be generated in the distal dendrites, where less sodium channel inactivation will occur, since back-propagating action potentials are smaller during repetitive spiking.

Although strong excitatory inputs promote their occurrence, dendritic spikes can be generated at or near the threshold for spiking (Figure 1), especially during the facilitation associated with repetitive synaptic activation (Figure 3). During repetitive activation of a population of presynaptic axons, however, dendritic spike generation cannot be sustained, presumably owing to the inactivation of dendritic sodium channels. The inability of dendritic spikes to be sustained during extended trains of synaptic stimuli cannot be explained by a progressive recruitment of inhibition, as the same result was obtained when GABA<sub>A</sub><sup>-</sup> or GABA<sub>B</sub><sup>-</sup> mediated inhibition was blocked.

Direct evidence that synaptic activation can trigger dendritic spikes in vivo comes from dendritic recordings

performed in the anesthetized rat. Kamondi and colleagues have shown that dendritic spikes are observed during sharp waves, which are extracellular events associated with defined behavioral states (Kamondi et al., 1998). Interestingly, these authors find that during a single sharp wave, many more spikes are observed in dendritic recordings than in somatic recordings during similar events. Their observations are therefore in accord with our finding that dendritic spikes can occur in isolation of somatic action potentials. On the surface, however, their observation of multiple dendritic spikes during a single sharp wave would seem to contradict our finding that sustained dendritic spiking cannot be supported in CA1 neurons. However, our experiments differ considerably from the *in vivo* situation in that the same population of presynaptic axons is activated on every trial, so a limited number of dendritic spike initiation zones may be recruited in our experiments. In the *in vivo* experiments, more dendritic spike initiation zones may be activated, provided that each dendritic trigger zone is sufficiently distant from the others so as to be relatively insulated from the refractory effects of a spike generated in another zone. This possibility may explain the apparent absence of a refractory period during dendritic spiking *in vivo* (Kamondi et al., 1998). In addition, the isolation of dendritic spike initiation zones from one another and from the soma may be more prominent *in vivo* than *in vitro*, as dendritic spikes observed *in vivo* are smaller than their counterparts *in vitro* (Kamondi et al., 1998), perhaps in part owing to the effects of increased background synaptic activity *in vivo* (Rapp et al., 1996).

#### **Dendritic Spike Amplitude Is Variable and Propagation to the Soma Is Unreliable**

The amplitude of dendritic spikes recorded at a given location can vary considerably. There are several possible explanations for this observation. First, it is possible that there are several sites where dendritic spikes can be generated. The site activated may vary from trial to trial, especially considering the low probability of release at individual synapses (Murthy et al., 1997), so each stimulus may activate a unique set of synapses. Since each dendritic spike initiation zone may be at a different location, variable dendritic spike amplitude could reflect spikes that are attenuated differently as they propagate from each site to the dendritic recording location and the soma. Second, it is possible that spike amplitude at any given trigger zone varies from trial to trial, owing to the stochastic gating of voltage-activated sodium and potassium channels. Third, the degree to which any given dendritic spike propagates from its distal site of generation to the somatic and dendritic recording sites could vary from trial to trial, owing to the variable activation of voltage- and/or ligand-gated channels.

The observation of dendritic spikes in the absence of corresponding somatic action potentials indicates that the propagation of these events from the dendrites to the soma is unreliable. Even for a spike generated at a very distal location, it is somewhat surprising that it would fail to propagate to the soma altogether, especially considering that back-propagating action potentials have considerable amplitudes at distances up to

400  $\mu\text{m}$  from the soma (Andreasen and Lambert, 1995b; Callaway and Ross, 1995; Spruston et al., 1995). Several possible explanations exist for the apparent difference between soma-to-dendrite and dendrite-to-soma spike propagation. One possibility is that dendritic spikes are never as large as somatic spikes, even at their site of generation. This would be in accord with the high density of A-type potassium channels in the dendrites of CA1 neurons, which cause attenuation in the amplitude of back-propagating action potentials (Hoffman et al., 1997) and could similarly limit the amplitude of dendritic spikes. Another factor may simply be dendritic geometry, since propagation from a region of low-impedance (the soma) to a region of higher impedance (the dendrites) is biophysically more favorable than the reverse (Goldstein and Rall, 1974; Jack et al., 1983; Rall and Segev, 1987). Another possibility is that a proximal region of high-potassium channel density shunts out dendritic spikes, which may already be attenuated by the time they reach this zone. Somatic spikes, by contrast, may propagate through such a shunt because of their larger amplitude in this proximal region of the dendrites. Direct recordings of potassium channels from the dendrites of CA1 neurons have not revealed any such proximal zone of high-potassium channel density (Hoffman et al., 1997); however, Andreasen and Lambert have reported a high density of calcium-activated potassium channels in CA1 dendrites, a finding that deserves further study (Andreasen and Lambert, 1995a). A final consideration is the role of inhibition, which has been suggested to affect dendritic spike generation and back-propagation (Turner et al., 1989; Kim et al., 1995; Buzsáki et al., 1996; Miles et al., 1996; Tsubokawa and Ross, 1996). Appropriately targeted inhibition could be responsible for causing spikes to be generated in dendrites (perisomatic inhibition) or for causing spikes to vary in amplitude or fail to propagate to the soma (dendritic inhibition). Though inhibition may alter the overall strength of the synaptic input, it cannot fully explain the variability of dendritic spike amplitude or the isolated dendritic spikes, as we observed both phenomena in the presence of GABA<sub>A</sub> or GABA<sub>B</sub> antagonists. However, all of these factors could contribute to the initiation and propagation of dendritic spikes and warrant further study.

#### **Dendritic Spikes in Other Neurons**

Dendritic spikes have also been reported in cerebellar Purkinje cells (Llinás and Sugimori, 1980); however, these spikes are mediated by calcium electrogenesis and are therefore fundamentally different from the dendritic sodium spikes described here. Microelectrode recordings from the dendrites of layer V pyramidal neurons of the neocortex have indicated that spikes can be generated in the dendrites of these neurons (Pockberger, 1991; Kim and Connors, 1993), as have interpretations of somatic microelectrode responses to glutamate iontophoresis and synaptic stimulation (Schwindt and Crill, 1997, 1998) and somatic voltage-clamp experiments (Regehr et al., 1993). These findings have been extended recently by the direct observation of dendritic spikes with multiple patch-pipette and calcium-imaging experiments in neocortical pyramidal neurons (Schiller et al., 1997; Stuart et al., 1997b).

The dendritic sodium spikes observed in layer V neocortical pyramidal neurons show some similarity to those described here in hippocampal CA1 pyramidal neurons. Importantly, Stuart et al. used combined recording from the soma, dendrite, and axon to demonstrate directly that full size action potentials occur in the axon before the soma, even when dendritic spikes precede the somatic action potential (Stuart et al., 1997b). This occurs because dendritic spikes in layer V neurons also attenuate severely as they propagate to the soma. This important finding is in accord with our data suggesting that the axon is the final site of synaptic integration in CA1 neurons, even when spikes are generated in the dendrites.

Some differences are apparent in the dendritic spikes of layer V versus CA1 neurons. First, dendritic spikes in layer V neurons required high-intensity stimulation, whereas dendritic spikes were generated in some CA1 neurons even with threshold synaptic stimulation (see Figure 1B). Second, a clear relationship was observed between dendritic-to-somatic spike latency in layer V neurons (Stuart et al., 1997b); no such relationship was apparent in our data from CA1 neurons (data not shown), suggesting that the site of dendritic spike initiation may be more labile in CA1 neurons. Finally, calcium spikes have also been reported to occur in response to synaptic stimulation of the distal apical dendrites of layer V cortical pyramidal neurons (Yuste et al., 1994; Schiller et al., 1997; Seamans et al., 1997). Though we did not observe calcium spikes in CA1 neurons with the synaptic stimuli used in this study, stronger synaptic stimuli can evoke calcium spikes in CA1 dendrites (N. L. G. and N. S., unpublished data), a finding that has been reported by others, both in vitro and in vivo (Fujita and Sakata, 1962; Schwartzkroin and Slawsky, 1977; Miura et al., 1997; Kamondi et al., 1998).

Dendritic spikes have also been recently reported in mitral cells of the olfactory bulb (Chen et al., 1997). Like the dendritic spikes reported here, these spikes can fail to propagate to the soma; however, the conditions leading to dendrosomatic spike propagation failures differ in mitral cells and CA1 cells. In mitral cells, isolated dendritic spikes occurred when the soma was hyperpolarized either by direct current injection or activation of perisomatic inhibition (Chen et al., 1997). In CA1 cells, direct hyperpolarization of the soma did not alter dendritic spike propagation (data not shown). Another difference between these cell types is the reliability of spike back-propagation. Unlike CA1 neurons, back-propagating spikes in mitral cells show little amplitude attenuation (Bischofberger and Jonas, 1997; Chen et al., 1997), probably reflecting a higher density of dendritic sodium channels and/or a lower density of dendritic potassium channels in mitral cells as compared with CA1 neurons (Bischofberger and Jonas, 1997).

#### Functional Relevance of Dendritic Spikes

The fact that dendritic spike initiation in CA1 neurons occurs in vitro during coincident excitatory input from several presynaptic axons and is sensitive to prior action potential activity raises the possibility that dendritic spikes might promote the transmission of specific, behaviorally relevant patterns of synaptic activity. Indeed,

the recent finding that dendritic spikes occur during sharp wave activity in vivo suggests that dendritic spikes can be initiated during natural, highly synchronized network activity in the hippocampus (Kamondi et al., 1998). Because dendritic spikes do not propagate reliably to the soma, their function may be distinct from action potentials sending a signal via the axon to the cell's postsynaptic targets. Here, we show that one important function of dendritic spikes may be to increase the probability that selected synaptic inputs result in an action potential in the axon. In addition, however, dendritic spikes may have important local functions in the dendrites, such as providing the postsynaptic depolarization necessary for the induction of long-term potentiation (Gustafsson et al., 1987; Magee and Johnston, 1997; Markram et al., 1997). Such a mechanism may be particularly important at distal dendritic locations, where action potential back-propagation may be ineffective, especially during repetitive action potential firing (Spruston et al., 1995). In light of several reports that dendritic voltage-gated channels and action potential propagation in dendrites can be modulated by neurotransmitter receptor activation (Chen and Lambert, 1997; Tsubokawa and Ross, 1997; Colbert and Johnston, 1998; Hoffman and Johnston, 1998), it will be important to examine how these neurotransmitters may influence synaptic integration and plasticity by altering dendritic spike initiation and propagation.

#### Experimental Procedures

Simultaneous patch-pipette recordings were obtained from the soma and apical dendrites of CA1 pyramidal neurons in hippocampal slices from 4- to 11-week old male Wistar rats (average = 7 weeks,  $n = 72$ ). Brains were removed following halothane anesthesia and cardiac perfusion with ice-cold, oxygenated physiological solution. Hippocampal slices (300  $\mu\text{m}$ ) were prepared in ice-cold solution with a vibrating tissue slicer (Campden Instruments) and then transferred to an incubation chamber containing warm ( $34^\circ\text{C} \pm 2^\circ\text{C}$ ), oxygenated solution. For recording, slices were transferred to a chamber on the fixed stage of an Axioscop FS microscope (Zeiss) and visualized by infrared differential interference videomicroscopy (Stuart et al., 1993). All recordings were performed at  $34^\circ\text{C} \pm 2^\circ\text{C}$ . The extracellular physiological solution for cardiac perfusion, slice preparation, incubation, and recording contained 125 mM NaCl, 25 mM glucose, 25 mM  $\text{NaHCO}_3$ , 2.5 mM KCl, 1.25 mM  $\text{NaH}_2\text{PO}_4$ , 2 mM  $\text{CaCl}_2$ , and 1 mM  $\text{MgCl}_2$  (pH 7.4, bubbled with 95%  $\text{O}_2$ , 5%  $\text{CO}_2$ ). Intracellular solution used in the patch-pipettes contained 115 mM potassium gluconate, 20 mM KCl, 10 mM sodium phosphocreatine, 10 mM HEPES, 4 mM magnesium adenosine triphosphate (MgATP), 0.3 mM guanosine triphosphate (GTP), 0.1% biocytin, and either 2 mM EGTA alone or a combination of 10 mM EGTA and 0.5 mM  $\text{CaCl}_2$ . Similar results were obtained with an intracellular solution containing 115 mM potassium methylsulfate instead of potassium gluconate ( $n = 7$ ). Bicuculline methiodide and TTX were obtained from Sigma, SR95531 was obtained from RBI, D-AP5 was obtained from Precision Biochemicals, and CGP55845A was a gift from Ciba-Geigy. All recordings were obtained using identical bridge and voltage-clamp amplifiers (BVC-700, Dagan). Simultaneous whole-cell voltage recordings from the soma and an apical dendrite were obtained in bridge mode ( $n = 62$  dendritic recordings 102–378  $\mu\text{m}$  from the center of the soma; mean  $\pm$  SD =  $211 \pm 58 \mu\text{m}$ ). Patch electrodes were fabricated from thick walled borosilicate glass (EN-1, Garner Glass) and had tip resistances of 4–11 M $\Omega$  in saline. Bridge balance and capacitance compensation were performed for all whole-cell recordings, which were terminated if series resistance exceeded 80 M $\Omega$ . Synaptic stimulation of Schaffer collaterals was achieved by placing a broken patch-pipette filled with extracellular

solution or a bipolar stainless steel electrode (Frederick Haer) in the outer third of the stratum radiatum or in stratum lacunosum-moleculare. The occurrence of an inflection in the membrane potential of either the somatic or dendritic recording was taken to indicate the occurrence of a spike. The time of action potential initiation was measured from this inflection point, which was quantitatively determined as the point at which a local increase in the second derivative of the membrane potential exceeded 150 mV/ms<sup>2</sup> (i.e., the time corresponding to a large increase in the slope of the membrane potential). The locus of spike initiation is defined as the recording site (soma or dendrite) where the spike inflection occurs first. Simultaneous extracellular recordings were obtained from the soma and dendrite in the cell-attached patch configuration ( $n = 10$  dendritic recordings 220–299  $\mu\text{m}$  from the soma; mean  $\pm$  SD =  $243 \pm 26$   $\mu\text{m}$ ). The pipette potential was held at  $-65$  mV in voltage-clamp mode, such that the transmembrane potential (about 0 mV) was sufficiently depolarized to inactivate voltage-gated ionic conductances. Consequently, the currents recorded reflect capacitive currents proportional to  $dV/dt$ .

#### Acknowledgments

We thank György Buzsáki, David Ferster, and Catherine Woolley for comments on the manuscript. This work was supported by grants from the National Institutes of Health (NS-35180) and the Human Frontiers in Science Program and by fellowships from the Klingenstein and Sloan Foundations.

Received May 27, 1998; revised October 10, 1998.

#### References

- Andersen, P. (1960). Interhippocampal impulses. II. Apical dendritic activation of CA1 neurons. *Acta Physiol. Scand.* **48**, 178–208.
- Andersen, P., and Lomo, T. (1966). Mode of activation of hippocampal pyramidal cells by excitatory synapses on dendrites. *Exp. Brain Res.* **2**, 247–260.
- Andersen, P., Storm, J., and Wheal, H.V. (1987). Thresholds of action potentials evoked by synapses on the dendrites of pyramidal cells in the rat hippocampus *in vitro*. *J. Physiol. (Lond)* **383**, 509–526.
- Andreasen, M., and Lambert, J.D.C. (1995a). The excitability of CA1 pyramidal cell dendrites is modulated by a local  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$  conductance. *Brain Res.* **698**, 193–203.
- Andreasen, M., and Lambert, J.D.C. (1995b). Regenerative properties of pyramidal cell dendrites in area CA1 of the rat hippocampus. *J. Physiol. (Lond)* **483**, 421–441.
- Andreasen, M., and Lambert, J.D.C. (1998). Factors determining the efficacy of distal excitatory synapses in rat hippocampal CA1 pyramidal neurons. *J. Physiol. (Lond)* **507**, 441–462.
- Benardo, L.S., Masukawa, L.M., and Prince, D.A. (1982). Electrophysiology of isolated hippocampal pyramidal dendrites. *J. Neurosci.* **2**, 1614–1622.
- Bischofberger, J., and Jonas, P. (1997). Action potential propagation into the presynaptic dendrites of rat mitral cells. *J. Physiol. (Lond)* **504**, 359–365.
- Buzsáki, G., Penttonen, M., Nádasdy, Z., and Bragin, A. (1996). Pattern and inhibition-dependent invasion of pyramidal cell dendrites by fast spikes in the hippocampus *in vitro*. *Proc. Natl. Acad. Sci. USA* **93**, 9921–9925.
- Callaway, J.C., and Ross, W.N. (1995). Frequency-dependent propagation of sodium action potentials in dendrites of hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* **74**, 1395–1403.
- Chen, H., and Lambert, N.A. (1997). Inhibition of dendritic calcium influx by activation of G protein-coupled receptors in the hippocampus. *J. Neurophysiol.* **78**, 3484–3488.
- Chen, W.R., Mitgaard, J., and Shepherd, G.M. (1997). Forward and backward propagation of dendritic impulses and their synaptic control in mitral cells. *Science* **278**, 463–467.
- Colbert, C., Magee, J.C., Hoffman, D.A., and Johnston, D. (1997). Slow recovery from inactivation of  $\text{Na}^+$  channels underlies the activity-dependent attenuation of dendritic action potentials in hippocampal CA1 pyramidal neurons. *J. Neurosci.* **17**, 6512–6521.
- Colbert, C.M., and Johnston, D. (1996). Axonal action-potential initiation and  $\text{Na}^+$  channel densities in the soma and axon initial segment of subicular pyramidal neurons. *J. Neurosci.* **16**, 6676–6686.
- Colbert, C.M., and Johnston, D. (1998). Protein kinase C activation decreases activity-dependent attenuation of dendritic  $\text{Na}^+$  current in hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* **79**, 491–495.
- Colling, S.B., and Wheal, H.V. (1994). Fast sodium action potentials are generated in the distal apical dendrites of rat hippocampal CA1 pyramidal cells. *Neurosci. Lett.* **172**, 73–76.
- Cragg, B.G., and Hamlyn, L.H. (1955). Action potentials of the pyramidal neurones in the hippocampus of the rabbit. *J. Physiol. (Lond)* **129**, 608–627.
- Fujita, Y., and Sakata, H. (1962). Electrophysiological properties of CA1 and CA2 apical dendrites of rabbit hippocampus. *J. Neurophysiol.* **25**, 209–222.
- Gillessen, T., and Alzheimer, C. (1997). Amplification of EPSPs by low  $\text{Ni}^{2+}$ - and amiloride-sensitive  $\text{Ca}^{2+}$  channels in apical dendrites of rat CA1 pyramidal neurons. *J. Neurophysiol.* **77**, 1639–1643.
- Goldstein, S.S., and Rall, W. (1974). Changes of action potential shape and velocity for changing core conductor geometry. *Biophys. J.* **14**, 731–757.
- Gustafsson, B., Wigström, H., Abraham, W.C., and Huang, Y.-Y. (1987). Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials. *J. Neurosci.* **7**, 774–780.
- Herreras, O. (1990). Propagating dendritic action potential mediates synaptic transmission in CA1 pyramidal cells *in situ*. *J. Neurophysiol.* **64**, 1429–1441.
- Hoffman, D.A., and Johnston, D. (1998). Downregulation of transient  $\text{K}^+$  channels in dendrites of hippocampal CA1 pyramidal neurons by activation of PKA and PKC. *J. Neurosci.* **18**, 3521–3528.
- Hoffman, D.A., Magee, J.C., Colbert, C.M., and Johnston, D. (1997).  $\text{K}^+$  channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. *Nature* **387**, 869–875.
- Jack, J.J.B., Noble, D., and Tsien, R.W. (1983). *Electrical Current Flow in Excitable Cells* (Oxford: Oxford University Press).
- Johnston, D., Magee, J.C., Colbert, C.M., and Christie, B.R. (1996). Active properties of neuronal dendrites. *Annu. Rev. Neurosci.* **19**, 165–186.
- Jung, H., Mickus, T., and Spruston, N. (1997). Prolonged sodium channel inactivation contributes to dendritic action potential attenuation in hippocampal pyramidal neurons. *J. Neurosci.* **17**, 6639–6646.
- Kamondi, A., Acsády, L., and Buzsáki, G. (1998). Dendritic spikes are enhanced by cooperative network activity in the intact hippocampus. *J. Neurosci.* **18**, 3919–3928.
- Kim, H.G., and Connors, B.W. (1993). Apical dendrites of the neocortex: correlation between sodium- and calcium-dependent spiking and pyramidal cell morphology. *J. Neurosci.* **13**, 5301–5311.
- Kim, H.G., Beierlein, M., and Connors, B.W. (1995). Inhibitory control of excitable dendrites in neocortex. *J. Neurophysiol.* **74**, 1810–1814.
- Lipowsky, R., Gillessen, T., and Alzheimer, C. (1996). Dendritic  $\text{Na}^+$  channels amplify EPSPs in hippocampal CA1 pyramidal cells. *J. Neurophysiol.* **76**, 2181–2191.
- Llinás, R., and Sugimori, M. (1980). Electrophysiological properties of *in vitro* Purkinje cell dendrites in mammalian cerebellar slices. *J. Physiol. (Lond)* **305**, 197–213.
- Magee, J.C., and Johnston, D. (1995a). Characterization of single voltage-gated  $\text{Na}^+$  and  $\text{Ca}^{2+}$ -channels in apical dendrites of rat CA1 pyramidal neurons. *J. Physiol. (Lond)* **487**, 67–90.
- Magee, J.C., and Johnston, D. (1995b). Synaptic activation of voltage-gated channels in the dendrites of hippocampal pyramidal neurons. *Science* **268**, 301–304.
- Magee, J.C., and Johnston, D. (1997). A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* **275**, 209–213.

- Markram, H., Lubke, J., Frotscher, M., and Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 275, 213–215.
- Miles, R., Toth, K., Gulyas, A.I., Hajos, N., and Freund, T.F. (1996). Differences between somatic and dendritic inhibition in the hippocampus. *Neuron* 16, 815–823.
- Miura, M., Yoshioka, M., Miyakawa, H., Kato, H., and Ito, K.-I. (1997). Properties of calcium spikes revealed during GABA<sub>A</sub> receptor antagonism in hippocampal CA1 neurons from guinea pigs. *J. Neurophysiol.* 78, 2269–2279.
- Miyakawa, H., and Kato, H. (1986). Active properties of dendritic membrane examined by current source density analysis in hippocampal CA1 pyramidal neurons. *Brain Res.* 399, 303–309.
- Murthy, V.N., Sejnowski, T.J., and Stevens, C.F. (1997). Heterogeneous release properties of visualized individual hippocampal synapses. *Neuron* 18, 599–612.
- Pockberger, H. (1991). Electrophysiological and morphological properties of rat motor cortex neurons in vivo. *Brain Res.* 539, 181–190.
- Poolos, N., and Kocsis, J.D. (1990). Dendritic action potentials activated by NMDA receptor-mediated EPSPs in CA1 hippocampal pyramidal cells. *Brain Res.* 524, 342–346.
- Rall, W., and Segev, I. (1987). Functional Possibilities for Synapses on Dendrites and Dendritic Spines. In *Synaptic Function*, G.M. Adelman, W.E. Gall, and W.M. Cowan, eds. (New York: John Wiley & Sons), pp. 605–636.
- Rapp, M., Yarom, M., and Segev, I. (1996). Modeling back propagating action potentials in weakly excitable dendrites of neocortical pyramidal cells. *Proc. Natl. Acad. Sci. USA* 93, 11985–11990.
- Regehr, W., Kehoe, J., Ascher, P., and Armstrong, C. (1993). Synaptically triggered action potentials in dendrites. *Neuron* 11, 145–151.
- Richardson, T.L., Turner, R.W., and Miller, J.J. (1987). Action-potential discharge in hippocampal CA1 pyramidal neurons: current source-density analysis. *J. Neurophysiol.* 58, 981–996.
- Schiller, J., Schiller, Y., Stuart, G., and Sakmann, B. (1997). Calcium action potentials restricted to distal apical dendrites of rat neocortical pyramidal neurons. *J. Physiol. (Lond)* 505, 605–616.
- Schwartzkroin, P.A. (1977). Further characteristics of hippocampal CA1 cells in vitro. *Brain Res.* 128, 53–68.
- Schwartzkroin, P.A., and Slawsky, M. (1977). Probable calcium spikes in hippocampal neurons. *Brain Res.* 135, 157–161.
- Schwindt, P.C., and Crill, W.E. (1997). Local and propagated dendritic action potentials evoked by glutamate iontophoresis on rat neocortical pyramidal neurons. *J. Neurophysiol.* 77, 2466–2483.
- Schwindt, P.C., and Crill, W.E. (1998). Synaptically evoked dendritic action potentials in rat neocortical pyramidal neurons. *J. Neurophysiol.* 79, 2432–2446.
- Seamans, J.K., Gorelova, N.A., and Yang, C.R. (1997). Contributions of voltage-gated Ca<sup>2+</sup> channels in the proximal versus distal dendrites to synaptic integration in prefrontal cortical neurons. *J. Neurosci.* 17, 5936–5948.
- Spencer, W.A., and Kandel, E.R. (1961). Electrophysiology of hippocampal neurons. IV. Fast prepotentials. *J. Neurophysiol.* 24, 272–285.
- Spruston, N., Schiller, Y., Stuart, G., and Sakmann, B. (1995). Activity-dependent action potential invasion and calcium influx into hippocampal CA1 dendrites. *Science* 268, 297–300.
- Stuart, G., Spruston, N., Sakmann, B., and Häusser, M. (1997a). Action potential initiation and backpropagation in neurons of the mammalian central nervous system. *Trends Neurosci.* 20, 125–131.
- Stuart, G., Schiller, J., and Sakmann, B. (1997b). Action potential initiation and propagation in rat neocortical pyramidal neurons. *J. Physiol. (Lond)* 505, 617–632.
- Stuart, G.J., Dodt, H.-U., and Sakmann, B. (1993). Patch-clamp recordings from the soma and dendrites of neurons in brain slices using infrared video microscopy. *Pflügers Arch.* 423, 511–518.
- Tsubokawa, H., and Ross, W.N. (1996). IPSPs modulate spike backpropagation and associated [Ca<sup>2+</sup>]<sub>i</sub> changes in the dendrites of hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* 76, 2896–2906.
- Tsubokawa, H., and Ross, W.N. (1997). Muscarinic modulation of spike backpropagation in the apical dendrites of hippocampal CA1 pyramidal neurons. *J. Neurosci.* 17, 5782–5791.
- Turner, R.W., Meyers, D.E., and Barker, J.L. (1989). Localization of tetrodotoxin-sensitive field potentials of CA1 pyramidal cells in the rat hippocampus. *J. Neurophysiol.* 62, 1375–1387.
- Turner, R.W., Meyers, D.E., Richardson, T.L., and Barker, J.L. (1991). The site for initiation of action potential discharge over the somato-dendritic axis of rat hippocampal CA1 pyramidal neurons. *J. Neurosci.* 11, 2270–2280.
- Turner, R.W., Meyers, D.E., and Barker, J.L. (1993). Fast pre-potential generation in rat hippocampal CA1 pyramidal neurons. *Neuroscience* 53, 949–959.
- Wong, R.K.S., and Stewart, M. (1992). Different firing patterns generated in dendrites and somata of CA1 pyramidal neurones in guinea-pig hippocampus. *J. Physiol. (Lond)* 457, 675–687.
- Wong, R.K.S., Prince, D.A., and Basbaum, A.I. (1979). Intradendritic recordings from hippocampal neurons. *Proc. Natl. Acad. Sci. USA* 76, 986–990.
- Yuste, R., and Tank, D.W. (1996). Dendritic integration in mammalian neurons, a century after Cajal. *Neuron* 16, 701–716.
- Yuste, R., Gutnick, M.J., Saar, D., Delaney, K.R., and Tank, D.W. (1994). Ca<sup>2+</sup> accumulations in dendrites of neocortical pyramidal neurons: an apical band and evidence for two functional compartments. *Neuron* 13, 23–43.