Multiple Modes of Action Potential Initiation and Propagation in Mitral Cell Primary Dendrite

WEI R. CHEN,1 GONGYU Y. SHEN,1,3 GORDON M. SHEPHERD,1 MICHAEL L. HINES,2 AND JENS MIDTGAARD4
1Department of Neurobiology, School of Medicine and 2Department of Computer Science, Yale University, New Haven, Connecticut 06520-8001; 3College of Life Science, Zhejiang University, Hangzhou, Zhejiang 310027, China; and 4Department of Medical Physiology, University of Copenhagen, 7400 Copenhagen, Denmark

Received 29 January 2002; accepted in final form 11 June 2002

Chen, Wei R., Gongyu Y. Shen, Gordon M. Shepherd, Michael L. Hines, and Jens Midtgaard. Multiple modes of action potential initiation and propagation in mitral cell primary dendrite. J Neurophysiol 88: 2755–2764, 2002; 10.1152/jn.00057.2002. The mitral cell primary dendrite plays an important role in transmitting distal olfactory nerve input from olfactory glomerulus to the soma-axon initial segment. To understand how dendritic active properties are involved in this transmission, we have combined dual soma and dendritic patch recordings with computational modeling to analyze action-potential initiation and propagation in the primary dendrite. In response to depolarizing current injection or distal olfactory nerve input, fast Na+ action potentials were recorded along the entire length of the primary dendritic trunk. With weak-to-moderate olfactory nerve input, an action potential was initiated near the soma and then back-propagated into the primary dendrite. As olfactory nerve input increased, the initiation site suddenly shifted to the distal primary dendrite. Multicompartamental modeling indicated that this abrupt shift of the spike-initiation site reflected an independent thresholding mechanism in the distal dendrite. When strong olfactory nerve excitation was paired with strong inhibition to the mitral cell basal secondary dendrites, a small fast prepotential was recorded at the soma, which indicated that an action potential was initiated in the distal primary dendrite but failed to propagate to the soma. As the inhibition became weaker, a “double-spike” was often observed at the dendritic recording site, corresponding to a single action potential at the soma. Simulation demonstrated that, in the course of forward propagation of the first dendritic spike, the action potential suddenly jumps from the middle of the dendrite to the axonal spike-initiation site, leaving the proximal part of primary dendrite unexcited by this initial dendritic spike. As Na+ conductances in the proximal dendrite are not activated, they become available to support the back-propagation of the evoked somatic action potential to produce the second dendritic spike. In summary, the balance of spatially distributed excitatory and inhibitory inputs can dynamically switch the mitral cell firing among four different modes: axo-somatic initiation with back-propagation, dendritic initiation either with no forward propagation, forward propagation alone, or forward propagation followed by back-propagation.

INTRODUCTION

Regenerative activity in dendrites has now been well documented in patch recordings from the dendrites of a variety of brain neurons (Golding and Spruston 1998; Larkum et al. 1996, 1999; Magee and Johnston 1995; Martina et al. 2000; Stuart and Sakmann 1994; Stuart et al. 1999; Velte and Masland 1999; Williams and Stuart 2000; for recent review, see Häusser et al. 2000). The mitral cell of the olfactory bulb has been an attractive model for these studies because of its long and mostly unbranched primary dendrite (Mori 1987; Ramón y Cajal 1911), the localization of all afferent excitatory synaptic input to its distal tuft (Price and Powell 1970), the presence of voltage-gated channels along both primary and secondary dendrites (Bischofberger and Jonas 1997; Xiong and Chen 2002), and the relation of action potential spread to dendrodendritic inhibitory feedback (Jahr and Nicoll 1982; Rall and Shepherd 1968; Xiong and Chen 2002).

The mitral cell primary dendrite provides a flexible complement of active properties in which the site of action potential initiation varies with excitatory input to the distal tuft and inhibitory input to the secondary dendrites (Chen et al. 1997). Depending on these input conditions, the action potential can be initiated at the soma or distal dendrite and can either back propagate or forward propagate. These experimental results are most easily understood with the aid of computer simulations that are tightly constrained by the simple geometry of the cell and the dual electrode recordings. In simulations of action-potential initiation in response to injected current, shifts in action-potential initiation between different sites and changes in the direction of propagation can be reproduced very accurately (Shen et al. 1999). In that model, the shifting site of initiation depends on a complex interaction between spatial gradients of electrotonic current along the soma-dendritic axis and a lower threshold for spike generation in the axon.

A first goal of the present study was to explore action-potential initiation in relation to synaptic inputs, comparing experimental results and the significant change in model behavior when current injection stimulation is replaced by olfactory nerve synaptic stimulation. A second goal was to explore the mechanism of some complex spiking properties revealed in the mitral cells, including fast prepotentials and dendritic “double spikes” (Chen et al. 2000). Here we analyze these properties in terms of their possible ionic basis, the conditions for their occurrence, and the dendritic sites involved in their elec-
trogenesis, using a combined experimental and computational approach. We show how the experimental findings can be accounted for by complex interactions between the axon initial segment and distal dendritic tuft regions of the mitral cell.

METHODS

Physiological recordings

The experiments were carried out on slices of olfactory bulbs of Sprague-Dawley rats as previously described (Chen and Shepherd 1997). The 400-μm-thick sections were cut horizontally and perfused with oxygenated Ringer solution containing (in mM) 124 NaCl, 3 KCl, 1.3 MgSO₄, 2 CaCl₂, 1.25 NaH₂PO₄, 26 NaHCO₃, and 10 glucose (pH 7.4). Most experiments were carried out at room temperature; several experiments at 37°C gave similar results. Slices were visualized using an Olympus BX50WI microscope with infrared differential interference contrast (IR-DIC) optics and ×40 water-immersion objective. For low-magnification images, a Hamamatsu C2400–07ER camera was used; high-magnification imaging for dendritic recording used a ×3.3 photo-eyepiece with a Dage-MTI CCD-72 camera.

Recording pipettes were fabricated from thick-walled glass capillaries (1.2 mm OD, 0.69 mm ID) and filled with a solution of (in mM) 110 K-glutamate, 2 MgSO₄, 10 HEPES, and 2 K₂-ATP (adjusted to pH 7.4). Most experiments were carried out with recording pipettes filled with the same solution, but experiments were also carried out with the recording pipette containing 0.02% biocytin and 0.02% Lucifer yellow potassium salt to visualize the cell body. For making paired recordings from soma and distal primary dendrite, cells were selected with a characteristic long primary dendrite that could be traced from the cell body to a glomerulus. Dual patch recordings were carried out by patching into the glomerulus. Dual patch recordings were carried out by patching into the glomerulus. Dual patch recordings were carried out by patching into the glomerulus.

Anatomical identification of mitral cells and recording sites

For making paired recordings from soma and distal primary dendrite, cells were selected with a characteristic long primary dendrite that could be traced from the cell body to a glomerulus (Fig. 1A). Often the primary dendrite divided into two smaller branches just before or after entering the glomerulus, after which the dendritic branches were lost in the glomerular neuropil. On occasion, recordings from these smaller dendrites were possible. However, the majority of the recordings were from the main dendritic trunk close to the bifurcation point because this larger compartment was more accessible and robust for patch recordings. The primary dendrite is typically described as unbranched; however, in about one-fifth (8/39) of the cells, a side branch was observed arising from the main trunk at some distance from the cell body.

Ionic nature of dendritic action potentials

In response to depolarizing current injection or distal olfactory nerve excitatory input, action potentials recorded along the primary dendritic trunk generally had a short-duration of 1–3 ms, suggesting that these dendritic spikes were Na⁺ dependent. Bath application of 1 μM tetrodotoxin (TTX), a Na⁺ channel blocker, abolished completely the action potentials recorded simultaneously from the soma and the dendrite (n = 5; Fig. 1B). However, because the action potentials in these TTX experiments were all initiated near the soma, abolishment of the dendritic spikes could be due to a blockade of axo-somatic initiation of action potentials rather than a direct action of TTX on the dendritic spikes. To test further for a critical involvement of Na⁺ channels in dendritic action potentials, 10 mM of an intracellular Na⁺ channel blocker lidocaine N-ethyl bromide (QX-314) was included in the dendritic pipette. After whole cell break-in, the action potential recorded by the dendritic pipette had a smaller amplitude than that recorded by the parameters estimated by fitting the passive charging periods of the experimental data. Uniformly distributed generic Na⁺- and K⁺ channels should be considered as effectively containing all channel contributions that affect the voltage trajectories.

As shown by Shen et al. (1999), there is a substantial volume of parameter space that equally well fits the eight voltage trajectories resulting from dual recordings of high and low current injection into the two electrodes. We chose for this study a set of gating parameters that both fits the data and exhibits the generation of double spikes with ON tuft stimulation and soma hyperpolarization. ON stimulation was modeled by AMPA and N-methyl-D-aspartate (NMDA) type conductance changes consisting of an alpha function with time constant 1.5 ms, and a difference of exponentials with time constants 5 and 80 ms, respectively. Unless otherwise stated, these excitatory synapses were placed at the middle of the tuft branches and the ratio of AMPA to NMDA maximum conductance amplitude was 2.0. Secondary dendrite inhibitory postsynaptic potential (IPSP) was placed at the proximal 20% of these dendrites and modeled as a conductance change with the form of a difference of exponentials with time constants 3 and 80 ms, and a −70-mV reversal potential. However, the results in this paper are not sensitive to either the source of somatic hyperpolarization or the amount of NMDA currents. Complete model code is available on-line at the model database at http://senselab.med.yale.edu and is set up to exhibit the fit to the Shen et al. (1999) data as well as produce Figs. 3, 5, and 6 of this paper.

RESULTS

Computer simulation

The methods for simulating the experimental results from the mitral cell were similar to those already reported (Shen et al. 1999) and were carried out using NEURON simulation environment (Hines and Carnevale 1997). Briefly, the basic morphological features of the mitral cell were incorporated into a canonical compartmental model, consisting of a soma, a primary dendrite with two distal tuft branches, two secondary dendrites, an axon hillock, axon initial segment and myelinated axon. The soma diameter, length and diameter of the primary dendrite, and inter-electrode distance were first estimated from microscopic measurement of the recorded cell. As established previously, the inter-electrode dendritic dimensions are important for constraining the model; the rest of the cell can be regarded as lumped.
somatic pipette, which did not contain QX-314. The further reduction of spike amplitude was much faster in the dendritic site than at the soma (n/H11005/H14; Fig. 1C). These results indicate that QX-314 first acted locally to block the dendritic action potential and gradually diffused to the soma to block action potential generation there. Correspondingly, when QX-314 was instead applied through the somatic recording pipette, the amplitude of somatic action potential reduced faster than dendritically recorded spike (data not shown).

Stepwise shift of action potential initiation site with increasing distal excitatory input

The initiation site for the Na\(^+\) action potential can be made to shift from the soma/axon initial segment to the distal primary dendrite with increase in distal synaptic excitation (Chen et al. 1997). We wished to analyze this shift in greater detail. As shown in Fig. 2, with low levels of excitatory synaptic input to the tuft, the action potential was initiated at the soma/axon initial segment and back-propagated into the dendrite (Fig. 2A). With higher stimulus intensities, the initiation site shifted to the distal primary dendrite, as previously reported. To rule out a possible effect of patch electrodes on the action-potential-generating mechanism, the same experiments were performed using cell-attached recording configuration for both the soma and dendrite electrodes (Fig. 2B). In these recording conditions, comparable differences in spike-peak timing between the soma and the dendritic recording site were observed, both for low and high stimulus intensities (n = 8). This indicates that the whole cell recording conditions had little influence on the observed changes in action-potential initiation.

To study the shift of action-potential initiation site in greater detail, the action-potential peak-delay difference between the soma and the dendrite was plotted as a function of the ON stimulus intensity (Fig. 2C). In all cells tested (n = 6), this resulted in a stepwise change in the relative peak timing, indicating that as the distal excitatory input increased, the initiation site shifted suddenly from the soma/axon initial segment to the distal dendrite. The maximum time difference by which the dendritic action-potential peak could lead the soma was relatively large compared with the current injection experiments (Shen et al. 1999). This suggested that synaptic depolarization of the more distal dendritic tuft was particularly effective in generating the stimulus-response curve in Fig. 2C.

To test this hypothesis, whole cell recordings from the fine tuft branches are needed but appear to be quite difficult experiments. We therefore used computational simulations to gain...
insight into this question. The methods for modeling the mitral cell and obtaining concurrent simulations for eight experimental traces (soma and distal sites, weak and strong excitation) are fully described in Shen et al. (1999). Because AMPA and NMDA receptors are present at the olfactory nerve synapses (Berkowitz et al. 1994; Chen and Shepherd 1997; Ennis et al. 1996), we added those types of conductance to the distal branches of the primary dendritic tuft to simulate excitatory olfactory nerve input (see Methods). In all simulations shown here, the ratio of NMDA to AMPA maximum conductance was set to 0.5. Because action-potential responses we analyze here generally occurred quite early, varying this ratio over a large range did not affect the results in a way that could not be compensated for by slightly adjusting the magnitude of AMPA and inhibitory conductances. Figure 3A illustrates the simulated action potentials at the soma, distal primary dendritic trunk, and the middle of the tuft branch, in response to three different levels of synaptic excitation delivered to the middle of the tuft branches. The simulations showed a stepwise change similar to the experimental results (see the middle curve in Fig. 3B). The simulations further showed that the shape of the curve was sensitive to the placement of the synaptic conductances in the tuft branches. When the synapses were located close to the tips of the tuft branches, a rather steeper shift in spike-peak timing difference was observed (the trace in Fig. 3B labeled with “distal”). Conversely, moving the synapses close to the primary dendritic trunk resulted in a dramatically shallower stimulus-response curve (the trace in Fig. 3B labeled with “proximal”). Results for a uniform distribution of synaptic conductance in the tuft were almost identical to the case where they are localized at the middle of the tuft.

Evidence regarding the site of generation of distal dendritic action potentials was sought by comparing the voltage trajectories in the simulations from the tuft, the distal dendritic trunk and the soma (Fig. 3A). The results showed that at low synaptic intensity (Fig. 3A, 3 nS), the soma action potential was initiated prior to that in the dendrite, and the action potential in the distal dendrite occurred before that in the tuft. As synaptic intensity increased (Fig. 3A, 6.5 nS), the latency of the action potential responses was decreased, but the sequence and relative timing remained unchanged. With a further slight increase in synaptic excitation (Fig. 3Ac, 7 nS) action-potential initiation shifted rather abruptly to the tuft.

Dendritic double spikes

In some mitral cells (n = 8), two closely spaced action potentials were recorded from the distal primary dendrite. This occurred under conditions that favored dendritic action potential initiation, such as relatively strong synaptic excitation of the tuft while soma excitability was reduced by hyperpolarizing current injection or by an IPSP evoked in the secondary
dendrites by stimulating the EPL laterally (Fig. 4). At short latencies for the ON stimulation after an EPL-IPSP, the soma action potential was suppressed, leaving a somatic fast prepotential reflecting the isolated dendritic action potential (Chen et al. 1997; Eccles et al. 1958; Mori et al. 1982; Spencer and Kandel 1961). At longer stimulus intervals, the dendritic action potential became “double spikes;” the initial spike preceded a somatic action potential, whereas the second spike followed the second occurrence of the somatic action potential.

Considering the inactivation properties of Na\(^+\) channels that underlie action potential generation, it is intriguing how the distal primary dendrite could fire two fast action potentials so closely to each other. To understand this behavior, we again simulated the computer model with a protocol similar to that of the experiment. An IPSP was evoked at the proximal 20% of the secondary dendrites, prior to the ON-evoked EPSP in the middle of the primary dendritic tuft (Fig. 5A). By varying the delay of the ON-EPSP, the model qualitatively reproduced our experimental recordings. It showed that the EPSP evoked an action potential in the primary dendritic tuft branches (see plot of activation parameter m in Fig. 5B, a–c), which propagated half way into the primary dendritic trunk (traces c–f). An action potential was then triggered at the axon initial segment (traces f–h), which then back-propagated through the soma and into the primary dendrite (Fig. 5C, h–n). Analysis of the Na\(^+\) inactivation parameter (h) distribution along the primary dendrite at different times during the first dendritic action potential showed that the Na\(^+\) channels in the proximal part of the primary dendrite were little inactivated during the forward propagation of the first action potential and were thus ready to contribute to membrane excitability during the back-propagation that generated the second dendritic spike. In other words, the first dendritic action potential “jumped” over the proximal dendritic membrane to elicit a full action potential in the much more excitable axon initial segment after which it propagated further down the axon as well as backwards into the primary dendrite. Following the onset of the axonal action potential, the Na\(^+\) channels in the proximal part of the primary dendrite began to activate to generate the second dendritic spike (Fig. 5C, h–n). When the activation of the primary dendritic trunk had declined below maximum, the tuft Na\(^+\) channels still displayed some activation (m parameter, traces h–l). When the activation of the primary dendritic trunk had declined below maximum, the tuft Na\(^+\) channels still displayed some activation (m parameter, traces m and n), but much less than the full level reached during the first action potential (m parameter, traces c and d).

This was accompanied by most of the Na\(^+\) channels still being inactivated in the tuft during the second action potential, thus not allowing a full tuft activation during the second dendritic spike (h parameter, traces h–n). Another possibility is that the second dendritic action potential could be purely due to passive electrotonic spread of the soma action potential. To analyze this in the model, the Na\(^+\) conductances in the whole primary dendrite were suddenly set to zero at the end of the first dendritic spike (Fig. 6, arrow). This allowed only the passive spread of the somatic action potential back into the dendrite. This manipulation reduced the somatic action potential only slightly (Fig. 6, - - - -), while the second dendritic response was reduced by more than 50% (Fig. 6, - - - -). Similar results were obtained when the Na\(^+\) channel m and h parameters were kept constant at their instantaneous values from the time indicated by the arrows. Thus the Na\(^+\) current generated at least in the proximal part of the dendrite is
DISCUSSION

The experimental findings support the previous report (Chen et al. 1997) that weak synaptic excitatory input to the distal dendrite leads to action potential initiation in the axon initial segment, in accordance with the classical model (Eccles 1957; Edwards and Ottoson 1958; Fuortes et al. 1957; Stuart et al. 1997), showing that dendritic voltage-gated Na⁺ channels support back-propagation into the dendrites. With moderate to strong excitatory input to the distal dendrite, the site of action potential initiation shifts to the distal dendrite so that there is forward propagation from the distal dendrite to the axon initial segment. This is a full-blown, all-or-nothing, rapid action potential very similar in amplitude and time course to that generated at the soma. These results support previous evidence for forward propagating action potentials in dendrites (Andersen 1960; Golding and Spruston 1998; Herreras 1990; Larkum et al. 1999; Turner et al. 1991). Thus the classical model of action potential generation in the neuron appears to be oversimplified. A rich diversity is observed among different dendrites, which includes both forward and back-propagating action potentials in the dendritic tree (Häusser et al. 2000).

Importance of the methodological advantages of the mitral cell and its inputs

Why does the mitral cell give clearer evidence for dendritic spike initiation and forward propagation compared with many other neurons? We suggest several reasons. First, the restriction of all excitatory afferent input of olfactory axons to the distal tuft of the primary dendrite means that there is no complication of excitatory inputs at other levels of the dendritic tree, as there is in many other types of neurons. Second, the primary dendrite is unusually long, retaining its diameter throughout its length, and being mostly un-branched.
Third, the density of Na\(^+\) channels in the primary dendrite is higher (90 pS/\(\mu\)m\(^2\)) (Bischofberger and Jonas 1997) compared with the apical dendrite of other cells, such as 40 pS/\(\mu\)m\(^2\) for cortical pyramidal neurons (Magee 1999; Stuart and Sakmann 1994). This means that the Na\(^+\) action potential threshold is somewhat lower, and action-potential propagation when it occurs is correspondingly more robust. A similarly high density of Na\(^+\) channels (113 pS/\(\mu\)m\(^2\)) is reported in the dendrites of oriens-alveus interneurons in hippocampus, which also support dendritic initiation and nondecremental propagation of action potentials (Martina et al. 2000).

**Modeling constraints and considerations**

The model used in this study was similar to that used by Shen et al. (1999) with the substitution of a depolarizing synaptic conductance in the distal dendritic tuft for the injection of current pulse into the recording sites. The model assumed uniform active and passive membrane properties throughout the somatodendritic membrane. Although the soma and primary dendrite parameter values were constrained by direct recordings from these compartments including estimate of channel densities (Bischofberger and Jonas 1997, Chen et al. 1997), the distal dendrites are not similarly understood. Also, the exact properties and densities of synaptically activated ion channels are not known. Thus the NMDA/AMPA responses were simulated using data from a range of other cell types (Rapp et al. 1996; Traub and Miles 1991). With these caveats, the model was able to reproduce closely the experimental traces. This suggests that active properties in the postsynaptic membrane in the distal tuft dendrites contribute to the experimental findings, such as the shift in action potential sequence with increasing ON-EPSP. The excitatory synaptic inputs were placed at the middle of the tuft branches.

**FIG. 5. Exploring the underlying mechanism of dendritic double spikes.**

A: computer simulation of the experiment shown in Fig. 4. An IPSP was evoked in the proximal 20% of the secondary dendrites, which was followed, at varying delays for different superimposed sweeps, by an ON-EPSP in the distal tuft branches. When the ON-EPSP was close to the onset of the IPSP, the somatic action potential was abolished, leaving a somatic fast prepotential corresponding to an action potential in the dendrite. With longer EPSP latency, an inflection on the rising phase of the somatic membrane potential reflected the transition of the fast prepotential into a full-size action potential in the soma, which corresponded to “double spikes” in the dendrite. The double spikes (*) were further analyzed in B and C. B: spatiotemporal profile of Na\(^+\)-conductance inactivation (\(h\)) and activation (\(m\)) along the primary dendrite during the 1st dendritic action potential. Each trace marked with a–h corresponds to a time point indicated (inset, ●). During the 1st dendritic spike, the Na\(^+\) conductance (\(m\) parameter) was strongly activated in the tuft dendrites, then in the distal primary dendrite, and then in the axon initial segment. The \(h\)-parameter plot shows that the Na\(^+\) conductance in the proximal primary dendrite was negligibly inactivated by the 1st dendritic spike. C: spatiotemporal profile during the 2nd dendritic spike. For the 2nd spike, the Na\(^+\) activation (\(m\) parameter) indicates the back-propagation of the axo-somatic spike into the proximal primary dendrite. The Na\(^+\) conductance in the tuft dendrites remained mostly inactivated (\(h\)) and only showed a small activation (\(m\)) during the 2nd dendritic spike. In this simulation, the excitatory synaptic inputs were placed at the middle of the tuft branches.
appears that the passively spread action potential can still local input resistance and the terminal boundary effects. It the action potential in the proximal dendrite, owing to a higher membrane potential in these distal dendrites can still follow closely the axon of an identical cell, Na⁺ conductance in the primary dendrite was suddenly set to 0 at the end of the 1st dendritic spike (→). This resulted in a large attenuation of the 2nd dendritic spike, although the amplitude of somatic action potential was little affected (−−).

Dendritic double spikes

An important finding of this study is the double spikes observed in the distal primary dendritic trunk. It suggests that the propagation of a fast Na⁺ action potential is not always continuous in a dendrite even with homogeneous membrane properties. It can actually "jump," a phenomenon originally proposed for the dendrites with multiple hot spots (Spencer and Kandel 1961). Such a jump can leave patches of dendritic membrane unexcited and thus available for subsequent spiking activity, which leads to a complex pattern of dendritic electrogenesis. A similar double-spike phenomenon has been noted in the axon of an identified snail neuron (Antic et al. 2000).

Computer modeling suggests that in the case of double spiking, the second action potential in the distal dendrite, especially in the tuft branches, is mainly due to current spread from the proximal primary dendrite because these distal dendrites are in the refractory period of the first action potential. However, even with little Na⁺-channel activation, the membrane potential in these distal dendrites can still follow closely the action potential in the proximal dendrite, owing to a higher local input resistance and the terminal boundary effects. It appears that the passively spread action potential can still activate voltage-gated Ca²⁺ channels to induce Ca²⁺ influx into the tuft dendrites, which might be important both for the plasticity of the ON-mitral cell synapses and the release of neurotransmitter at dendrodendritic synapses.

Summary of action potential initiation and propagation in mitral cell primary dendrite

This study provides experimental evidence supported by computational analysis for four distinct spiking modes of mitral cells (see Fig. 7). With weak to moderate distal synaptic excitation, the action potential is initiated in the axon initial segment and back-propagates into the dendrite (Fig. 7A). Increasing excitatory input causes action potential initiation to shift toward the distal primary dendrite with forward propagation to the axonal initial segment (Fig. 7B). When strong lateral inhibition is imposed to the secondary dendrites by neighboring mitral cells, the soma action potential is blocked as is forward propagation from the distal primary dendrite, leaving the distal dendrite as an isolated active unit (Fig. 7C). At intermediate levels of inhibition, when dendritic initiation occurs, the action potential appears to jump from the distal primary dendrite to the axon initial segment and then back-propagate, causing double spikes in the distal primary dendrite (Fig. 7D). Our results indicate that in a dendrite with homogeneous membrane properties, significant local variations in membrane excitability state may occur; this gives rise to distinctive complex behaviors.

Functional significance of active properties in mitral cell primary dendrite

Why does the mitral cell require robust action potential generation in the primary dendrite? It has been speculated that because of the unusual localization of excitatory synaptic inputs in the distal dendritic terminals, the active properties help to maintain distal dendritic control of axonal output despite dendrodendritic inhibition that occurs near the cell body. Thus the active properties increase the coupling of the distal input to axonal output and in so doing extend the operational range of the mitral cell. The forward and back-propagation of action potentials also provides a mechanism for reciprocal communication between the two spike-initiation sites, which might be critically involved in activity-dependent modulation of synaptic transmission in the olfactory glomerulus.

As the distal dendritic tuft is both presynaptic and postsynaptic (Pinching and Powell 1971; White 1973), another important function for action potential generation in the primary dendrite is to trigger transmitter release for the activation of dendrodendritic synapses in the tuft branches. This function may be of interest for other cell types, given the increasing number of neurons in different brain regions showing dendritic release of neurotransmitters and neuromodulators (Rice et al. 1997; Simmons et al. 1995; Zilberter 2000; Zilberter et al. 1999). One may hypothesize that local spiking in the distal dendrite of cortical pyramidal neurons gives rise to local transmitter release (Zilberter 2000), enabling pyramidal neurons to have "double identities," as would seem to be the case for mitral cells (Fig. 7C): they can function as projection neurons with axonal integration and output, or, when axonal output is

Dendrite

Control

Remove Na⁺ conductance from the primary dendrite at the time indicated by arrows

Soma

FIG. 6. Active back-propagation is involved in generating the 2nd action potential of dendritic double spikes. In the compartmental model of a mitral cell, Na⁺ conductance in the primary dendrite was suddenly set to 0 at the end of the 1st dendritic spike (→). This resulted in a large attenuation of the 2nd dendritic spike, although the amplitude of somatic action potential was little affected (−−).

J Neurophysiol • VOL 88 • NOVEMBER 2002 • www.jn.org
shut down by soma inhibition, function as local interneurons, affecting their immediate environment due to local dendritic action potential generation and transmitter release. In this perspective, the mitral cell may serve as a useful model on the functional distribution of action potential generating sites and their relation to pre- and postsynaptic functions of the dendrite.

W. R. Chen was supported by grants from the National Institutes of Health (NIH) Grant R01-DC-03918 and the Whitehall Foundation; G. Y. Shen received support from the National Natural Science Foundation of China (NSFC 39570183 and 30070190) and PAO YU-KONG Scholarship for Chinese Students Studying Abroad; M. Hines was supported by NIH Grant R01-NS-11613; G. M. Shepherd received support from the Human Brain Project/Neuroinformatics supported by the NIH and NIH Grant R01-DC-00086, by the National Science Foundation, and by the Department of Defense under a Multiple University Research Initiative; and J. Midggaard was supported by the Carlsberg Foundation, the Danish Medical Research Council, and the Danish Medical Association’s Research Fund.

REFERENCES


