The decade of the dendritic NMDA spike

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Review

The Decade of the Dendritic NMDA Spike

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In the field of cortical cellular physiology, much effort has been invested in understanding thick apical dendrites of pyramidal neurons and the regenerative sodium and calcium spikes that take place in the apical trunk. Here we focus on thin dendrites of pyramidal cells (basal, oblique, and tuft dendrites), and we discuss one relatively novel form of an electrical signal ("NMDA spike") that is specific for these branches. Basal, oblique, and apical tuft dendrites receive a high density of glutamatergic synaptic contacts. Synchronous activation of 10–50 neighboring glutamatergic synapses triggers a local dendritic regenerative potential, NMDA spike/plateau, which is characterized by significant local amplitude (40–50 mV) and an extraordinary duration (up to several hundred milliseconds). The NMDA plateau potential, when it is initiated in an apical tuft dendrite, is able to maintain a good portion of that tuft in a sustained depolarized state. However, if NMDA-dominated plateau potentials originate in proximal segments of basal dendrites, they regularly bring the neuronal cell body into a sustained depolarized state, which resembles a cortical Up state. At each dendritic initiation site (basal, oblique, and tuft) an NMDA spike creates favorable conditions for causal interactions of active synaptic inputs, including the spatial or temporal binding of information, as well as processes of short-term and long-term synaptic modifications (e.g., long-term potentiation or long-term depression). Because of their strong amplitudes and durations, local dendritic NMDA spikes make up the cellular substrate for multisite independent subunit computations that enrich the computational power and repertoire of cortical pyramidal cells. We propose that NMDA spikes are likely to play significant roles in cortical information processing in awake animals (spatiotemporal binding, working memory) and during slow-wave sleep (neuronal Up states, consolidation of memories).

Key words: synaptic integration; plateau potential; summation; regeneration; Up state; neocortex; basal; oblique; glutamate

The previous decade, 2000–2009, started with a paper describing N-methyl-D-aspartate (NMDA) spikes in basal dendrites of cortical layer 5 pyramidal neurons (Schiller et al., 2000) and ended with a paper describing NMDA spikes in the apical tuft dendrites of the same neuron type (Larkum et al., 2009). The study conducted by Schiller et al. (2000) has pioneered this area of research in two fundamental ways. First, it has provided direct experimental evidence that an isolated NMDA conductance can support regenerative membrane potential (spike) in a dendritic branch of a living central nervous system (CNS) neuron. Second, it has expanded the focus of dendritic physiology from the apical dendrite to other branches of cortical pyramidal neurons (e.g., basal, oblique, and tuft), here termed "nonapical" dendrites.

For didactic purposes, one can divide the last 20 years of cortical dendritic physiology into two nicely rounded calendar decades (Table I). In the first decade, 1990–1999, experimenters systematically explored the physiological properties of the apical dendrite in pyramidal neurons. They found that apical dendrites express voltage-gated sodium, voltage-gated potassium, and voltage-gated calcium channels, which allowed apical dendrites to propagate action potentials (AP) actively back into the dendritic tree (Stuart and Sakmann, 1994; Magee and Johnston, 1995; Spruston et al., 1995; Waters et al., 2005) and to participate in the process known as "spike-timing-dependent synaptic plasticity" (STDP; for review see Lisman and Spruston, 2005; Sjostrom et al., 2008). Aside from this role in AP back-propagation, upon adequate stimulation the active apical membrane conductances are also involved in producing regenerative membrane potentials, also known as "dendritic spikes" (Table I, local regenerative potentials; Herreras, 1990; Kim and Connors, 1993; Schiller et al., 1997; Kamondi et al., 1998). Among the spikes that initiate in the apical

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TABLE I. Two Decades of Dendritic Spikes in Cortical Pyramidal Neurons

	1990–1999 Decade of the thick apical dendrite	2000–2009 Decade of thin branches
Dendrite class	Apical trunk	Basal Oblique Tuft
Local regenerative potential	Calcium spike	Sodium spikelet NMDA spike Plateau potential

dendrite, the two most impressive entities were local spikes that failed to invade the soma (Golding et al., 2002) and calcium spikes that could be triggered either by coincident arrival of back-propagating AP and a distal excitatory postsynaptic potential in brain slice preparations (Larkum et al., 1999) or by whisker deflection in living animals (Helmchen et al., 1999).

Local (dendrite-restricted) spikes that fail to invade the cell body brought a lot of excitement in the field, because they were able to mediate long-term potentiation of synaptic inputs in the absence of neuronal action potential firing (Golding et al., 2002). Before 2002, one could argue that local dendritic spikes were just side effects of the lateral diffusion of voltage-gated channels from the soma into the apical trunk, a trifling epiphenomenon, with no specific physiological relevance. The 2002 paper by Golding et al. provided a solid factual demonstration of the utility of a purely dendritic regenerative event and the critical role such an event might play in cellular neurobiology (see also Remy and Sprusston, 2007).

Calcium action potentials in the dendritic initiation zone near the main apical bifurcation, described by Larkum et al. (1999; Table I, calcium spike; Fig. 1B2), constitute a mechanism by which the most distal synaptic inputs in neocortical pyramidal cells (tuft inputs) could impact the neuronal output (axonal action potential initiation zone). Besides a powerful boost for layer 1 and layer 2 synaptic inputs, the dendritic calcium action potentials also serve as reliable coincidence detectors. Recall that, in layer 5 pyramidal neurons, these spikes initiate near the primary bifurcation of the apical trunk (Fig. 1B2, initiation site) in response to synchronous strong input into both deep and superficial cortical layers (Larkum et al., 1999, 2001).

It can be safely said that this 10-year-long (1990–1999), and quite prolific, experimental quest on the apical dendrite function was propelled by two technical achievements that took place in the early 1990s: 1) the infrared differential interference contrast (IR-DIC) visualization of the apical trunk (infrared video microscopy; Dodt, 1993) and 2) the dendritic patch-electrode recordings (Stuart and Sakmann, 1994). Ten years ago, these two methods worked well on thick apical dendrites but not so well in thin, submicrometer-diameter dendritic branches. The thin branches (basal, oblique, and tuft dendrites) were poorly visible in a standard IR-DIC setup, which rendered their visually guided patching quite difficult and impractical for systematic analysis. This may explain a relatively low yield in the number of studies addressing the membrane physiology of nonapical dendrites in that period. Only occasionally, a small section of an elaborate paper would explore the physiology of a thin dendrite as a side project (Regehr and Tank, 1992; Yuste et al., 1994; Schiller et al., 1995; Cossart et al., 2000).

Schiller et al. (2000) turned the searchlight upon small-diameter branches by introducing one novel experimental approach, suitable for the analysis of the thin-dendrite function, and by showing that some exciting physiological phenomena reside not in the apical trunk but rather in nonapical branches, in this case, basal dendrites of cortical pyramidal neurons. The novel experimental approach was not based on the improvement in recording of dendritic physiological signals per se but rather on the improvement in the dendritic stimulation technique. Fueled by advances in laser scanning technology and confocal microscopy, a new stimulation technique emerged that allowed a precise delivery of glutamate ions onto one thin dendrite of choice. This technique, also known as ''glutamate uncaging'' (Callaway and Katz, 1993; Pettit et al., 1997; Wei et al., 2001), provided researchers with the ability to control precisely four critical parameters of glutamatergic stimulation: 1) a specific location (in any given segment along the thin dendritic branch), 2) an exact area of the membrane receiving the stimulus in the shape of a glutamate cloud of variable diameter (several micrometers usually), 3) stimulus intensity (by adjusting the intensity of the laser beam), and 4) stimulus duration (by setting the time for which a laser beam is turned on). Once it has been established that glutamatergic stimuli were restrictively targeting one thin dendritic branch, the somatic whole-cell recordings could then be used to detect membrane potential changes that arise in the targeted thin dendrite and propagate to the cell body. In addition to whole-cell recordings, Schiller et al. (2000) also used dendritic calcium imaging to monitor the glutamate evoked dendritic calcium influx. This trinity of experimental techniques, 1) glutamate stimulation (either by laser uncaging or microiontophoresis), 2) optical imaging (either calcium-sensitive dye or voltage-sensitive dye), and 3) somatic whole-cell recordings, would become the ''Holy Trinity'' of thin-dendrite physiology in the decade to come (Oakley et al., 2001b; Wei et al., 2001; Cai et al., 2004, 2007; Carter and Sabatini, 2004; Milojkovic et al., 2004, 2005a, 2007; Noguchi et al., 2005; Losonczy and Magee, 2006; Sobczyk and Svoboda, 2007; Losonczy et al., 2008; Major et al., 2008; Suzuki et al., 2008; Remy et al., 2009). The availability of experimental methods was not the only propellant for the ensuing interest in thin dendrites. A genuine scientific curiosity was also at play. In the particular case of thin dendrites, understanding their properties is an important step toward understanding the operation of cortical neurons and networks. Basal, oblique, and tuft branches

receive the overwhelming majority of excitatory glutamatergic synaptic inputs impinging on any given cortical pyramidal cell. It has been estimated that as much as 85% of the total number of excitatory glutamatergic drive, which impinges on an individual layer 5 pyramidal neuron, actually arrives on its basal, oblique, and tuft dendrites, whereas just a tiny fraction, less than 15%, is being received by the soma and the apical trunk below main bifurcation (Larkman, 1991). Recall that dendritic spines are putative sites of long-term potentiation and long-term depression (Emptage et al., 1999; Luscher et al., 2000; Matsuzaki et al., 2004; for review see Yuste and Bonhoeffer, 2001; Nimchinsky et al., 2002). Being the principle bearers of dendritic spines in pyramidal neurons, the basal oblique and tuft dendrites are most likely the key elements of cellular mechanisms for learning and memory (Yang et al., 2009). Moreover, if thin dendrites were involved in the processes of cortical computations (synaptic integration) and cortical learning (synaptic plasticity), then it would be prudent to know more about their intrinsic physiological properties. This was, in our opinion, the second catalyst for the wave of thin-dendrite physiology exploration in the past decade (2000–2009).

Arguably, the most exciting feature of the thin-dendrite membrane is its ability to initiate a local regenerative membrane potential (spike), whose major ionic contributor is not a sodium or calcium voltage-gated channel but rather a ligand-gated receptor channel, NMDAr (Schiller et al., 2000; Rhodes, 2006; Major et al., 2008; Larkum et al., 2009). When glutamate-binding sites of an NMDAr channel become occupied with two glutamate ions, then the voltage sensitivity of the NMDAr current exhibits a region of negative slope conductance because of the relief of magnesium block (Mayer et al., 1984; Nowak et al., 1984). In other words, under conditions of abundant glutamate supply, the current–voltage (I-V) relationship of an NMDAr current has a waveform similar to the I-V relationship of the voltage-gated sodium channel; therefore, during strong glutamatergic release, the NMDAr channels fire a regenerative NMDA spike, just like sodium channels upon adequate depolarization fire an action potential. Much earlier research had established that NMDAr current has a region of negative slope conductance, which is a biophysical substrate of the regenerative property (Mayer et al., 1984; Nowak et al., 1984), but in 2000 it

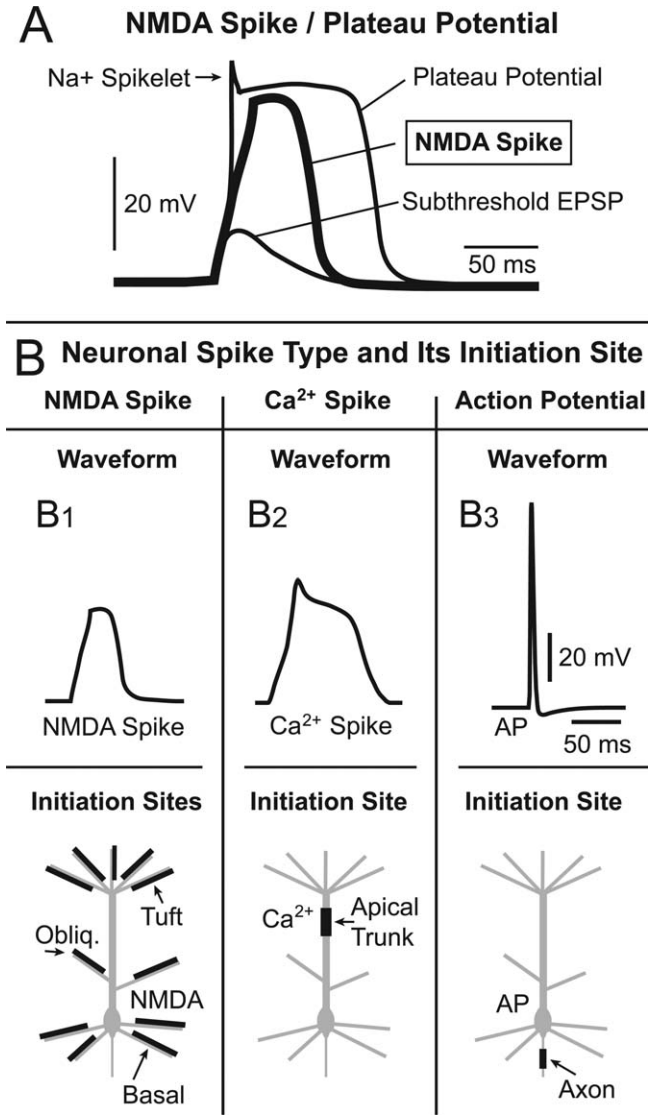

Fig. 1. Each class of neurites (basal, oblique, tuft, apical trunk, and axon) supports a characteristic regenerative potential (spike). **A:** In thin dendrites of pyramidal neurons (basal, oblique, and tuft), weak glutamatergic inputs produce EPSP-like depolarizations (''subthreshold EPSP''). Stronger (suprathreshold) inputs regularly trigger dendritic ''plateau potentials.'' Plateau potentials are characterized by a rapid onset, an initial spikelet (Na^+ spikelet), a plateau phase, and an abrupt collapse at the end of the plateau phase. A glutamate-evoked plateau potential is the product of several dendritic conductances. The major ionic contributor is regenerative NMDA receptor current. Block of sodium and calcium channels with TTX and Cd^{2+}, respectively, reveals a pure ''NMDA spike'' in the dendrite (Schiller et al., 2000). **B:** The waveforms of three regenerative potentials (spikes) are shown side by side on the same scale (B1–B3). The neuronal compartment that serves as the spike initiation site is colored black below each spike waveform (initiation sites). The principle compartments of cortical pyramidal cells are soma, axon, apical trunk, basal, oblique, and tuft dendrites. B1: NMDA spikes last for approximately 50–100 msec, and they can be initiated in the apical tuft, apical oblique, and basal dendrites. B2: Calcium spikes have slightly greater amplitudes and durations than NMDA spikes. Calcium spikes are often found in the calcium spike initiation zone on the apical trunk. B3: The action potential (AP) initiates in the axon initial segment. Once initiated in the axon, the AP propagates back into the dendritic tree (Stuart et al., 1997). The voltage waveforms of a back-propagating AP at dendritic sites are not shown in this figure (see Antic, 2003; Nevian et al., 2007; Zhou et al., 2008; Holthoff et al., 2010). Dendritic-spike initiation sites (B1–B3) are based on Larkum et al. (2009).

was not clear whether CNS neurons could actually support NMDA spikes. At that time, there were three obstacles to solving the ''NMDA spike question.'' 1) It was not clear whether any neuronal compartment possessed an NMDA channel density (conductance density) adequate to support NMDA spike initiation. 2) What type and what intensity of glutamatergic stimulation would be needed to activate those conductances efficiently? 3) What kind of experimental design should one employ to demonstrate the existence of NMDA spikes in real neurons? The first problem was solved by shifting the experimental focus from the apical trunk to smaller diameter branches (basal dendrites), in which surface to volume ratio is high and in which NMDAr-bearing dendritic spines reside in great numbers. The second problem was solved by using the power of an ultraviolet laser beam to raise the local concentration of glutamate to millimolar values. The third problem was solved by combining an exogenous glutamate pulse with bath application of drugs that blocked both voltage-gated sodium and calcium channels [tetrodotoxin (TTX) and Cd^{2+}, respectively]. It is important to note that synaptic stimulation is not possible in the presence of TTX and Cd^{2+}, because sodium and calcium channels are necessary for triggering the synaptic release of glutamate. Schiller et al. (2000) arrived at an excellent experimental design to solve the ''dendritic NMDA spike'' question by combining three aforementioned approaches: 1) glutamatergic stimulation, 2) whole-cell recording, and 3) dendritic calcium imaging. Glutamatergic stimulations were instrumental not only for finding the adequate (threshold) stimulus intensity but also for the graded control of the stimulus intensity between sub- and suprathreshold levels and for coapplication with voltage-channel antagonists (TTX and Cd^{2+}). Whole-cell recordings were critical for precise detection of nonlinearity in the family of membrane potential changes (hallmark of spike generation; see Schiller et al., 2000, their Fig. 1b). Finally, dendritic calcium imaging unequivocally proved that only one segment of one dendritic branch had been receiving the glutamate input (Schiller at al., 2000, their Fig. 1d).

PHYSIOLOGICAL PROPERTIES OF DENDRITIC NMDA SPIKES

Glutamate Threshold

The glutamate concentration needed to induce an NMDA spike can be deduced from glutamate uncaging experiments. A typical concentration of caged glutamate in the bath solution is 1 mM (Schiller et al., 2000). Under these conditions, the maximum concentration of uncaged (free) glutamate in the center of the laser beam (assuming a 100% success rate of UV photolysis) cannot exceed 1 mM. Because glutamate uncaging is a very reliable stimulus for dendritic NMDA spikes (Schiller et al., 2000), we conclude that glutamate concentrations $\leq$1 mM are sufficient to generate this event.

Ionic Composition

Pure NMDA spikes (Fig. 1A, NMDA spike) are initiated in thin dendrites when two major voltage-gated conductances (Na^+ and Ca^{2+}) are blocked with drugs (TTX and Cd^{2+}) and when the concentration of glutamate reaches a certain threshold. In normal physiological saline (no drugs), suprathreshold glutamatergic stimulations generate NMDA spikes mixed with strong activation of dendritic voltage-gated Na^+ and Ca^{2+} channels. The resulting plateau potential (Fig. 1A, plateau potential) is a complex spike comprising several complementary conductances that activate in a relatively strict temporal order. According to model predictions (Schiller et al., 2000), the plateau potential seems to involve a ''spike-chain'' mechanism: the AMPA response evokes a fast local sodium spikelet, which elicits a slower calcium-mediated regenerative response, which in turn initiates the full-blown NMDA spike. These model predictions were based on whole-cell somatic recordings (Schiller et al., 2000). Voltage-sensitive dye recordings performed in basal dendrites that were stimulated either synaptically or by exogenous glutamate application revealed the actual waveform of the plateau potential at dendritic loci (Milojkovic et al., 2004). This dendritic membrane potential transient is characterized by a fast-onset initial spikelet (Fig. 1A, Na^+ spikelet), a prominent plateau phase, and an abrupt collapse at the end of the plateau phase (Fig. 1A, plateau potential). The initial sodium spikelet was not a robust and widespread phenomenon. On the contrary, in the greater majority of basal dendrites, the initial sodium spikelet did not accompany glutamate-evoked plateau potentials (Milojkovic et al., 2005b; Acker and Antic, 2009). Although suprathreshold glutamate stimulations invariably evoked plateau potentials in every basal dendrite tested so far (several hundred), only a fraction (10–25%) of basal branches belonging to neocortical layer 5 pyramidal neurons possess the adequate density of sodium channels to support local sodium regenerative potentials (Milojkovic et al., 2005b; Nevian et al., 2007; Acker and Antic, 2009). Thus the activation of dendritic voltage-gated sodium channels is not the determining factor for the initiation of glutamate-dependent dendritic spikes. Sodium channels assist in spike initiation but are not necessary for it (Schiller et al., 2000; Oakley et al., 2001b; Wei et al., 2001; Milojkovic et al., 2005a, 2007; Rhodes, 2006; Major et al., 2008; Larkum et al., 2009).

Amplitude

Voltage-sensitive dye recordings have determined that the amplitude of a glutamate-evoked dendritic plateau potential during its plateau phase is approximately two-thirds of the amplitude of a back-propagating action potential in the same dendritic site (Milojkovic et al., 2004, their Fig. 4). Previously, computer simulation based on realistic neuronal morphology and multisite voltage-sensitive dye measurements predicted that, in basal dendritic segments 150 μm from the soma, the ampli-

tude of the back-propagating action potential (AP) is at least 60 mV (Antic, 2003). Based on these two pieces of data, Milojkovic et al. (2004) concluded that the amplitude of the glutamate-evoked plateau at 150 μm from the soma was at least 40 mV. Direct patch electrode recordings from basal dendrites showed that the peak-to-peak amplitude of the dendritic glutamate-evoked regenerative event (spike) is in the range between 40 and 50 mV (Nevian et al., 2007). Therefore, in terms of the peak amplitude, the glutamate-evoked NMDA-dependent regenerative potentials are quite comparable and could stand shoulder to shoulder with previously described dendritic calcium spikes (Fig. 1B2, Ca^{2+} spike) and back-propagating sodium APs that sweep through basal, oblique, and apical tuft branches of cortical pyramidal neurons (data not shown; Antic, 2003; Canepari et al., 2007; Nevian et al., 2007; Zhou et al., 2007, 2008; Acker and Antic, 2009; Holthoff et al., 2010).

Duration

The duration of a pure NMDA spike obtained with near-threshold stimulation intensity is on the order of 50–100 msec (Fig. 1B1; Schiller et al., 2000; Polsky et al., 2004; Rhodes, 2006; Major et al., 2008). In normal physiological saline (saline without blockers of dendritic conductances), and upon suprathreshold stimuli, the durations of dendritic glutamate-evoked plateau potentials are somewhat greater than the duration of a pure NMDA spike (Fig. 1A), presumably because of the activation of voltage-gated calcium channels. One interesting aspect of dendritic plateau potentials is that their durations depend on the intensity of glutamatergic stimulation. This is in striking contrast to sodium APs (Fig. 1B3, AP), which are largely insensitive to stimulus properties.

In a typical experiment designed to study properties of NMDA-dependent dendritic spikes, a series of consecutive glutamate pulses of gradually increasing intensities is applied on a dendritic segment (Fig. 2A), and both the dendritic and somatic voltage transients are recorded simultaneously (Fig. 2B). The dendritic voltage imaging performed in the presence of the sodium channel blocker TTX have shown that the local dendritic voltage response to suprathreshold glutamate levels was quickly saturated. The amplitude of the dendritic spike did not increase with further increase in stimulus intensity (Fig. 2B, intensities 1–4). This could be explained by the fact that the maximal amplitude of the NMDA-dependent spike is determined by the glutamate reversal potential, which is about 0 mV (Jonas and Sakmann, 1992). We think that dendritic plateau potentials approach the glutamate reversal potential and thus saturate (Fig. 2B, intensities 1–4).

Although the peak amplitude of the dendritic membrane potential transient remained the same throughout the wide range of suprathreshold stimulus intensities, the duration of the dendritic plateau potential, on the other hand, grew linearly with the stimulus intensity (Fig. 2B, sweeps 1–4). Identical results were obtained in normal physiological saline, in which glutamate-evoked sustained depolarizations are accompanied by AP generation in the cell body (Fig. 2D). Here again, a gradual increase in glutamate stimulation intensity causes a gradual increase in the duration of the somatic slow component measured at half-amplitude (Fig. 2E). This means that, despite amplitude saturation of their voltage response, the thin dendritic branches have not lost the ability to code the intensity of glutamatergic excitatory input. In the suprathreshold range of input intensities (Fig. 2B, intensities 1–4), the coding mechanism is based not on the amplitude of the slow depolarization (Fig. 2E, amp.) but rather on its duration (Fig. 2E; see also Nevian et al., 2007, their Fig. 7B,C). An in vitro study has indicated that, when strong excitatory inputs converge in middle segments of basilar branches, then all aspects of the ensuing dendritic plateau potentials (timing, amplitude, duration) are mirrored in the cell body (Milojkovic et al., 2005a). Consequently, the dendritic input–output function becomes essentially the neuronal input–output profile. A flexible duration of dendritic plateau potentials (Fig. 2B) is the basis for linear correlation between the intensity of glutamatergic stimulation received in the basilar dendrite and the number of somatic action potentials per stimulation event (not shown here but see Milojkovic et al., 2005a, their Fig. 2G).

Propagation of Dendritic NMDA Spikes

Calcium imaging and computational modeling suggested that NMDA spikes are highly localized events that envelop just one small dendritic segment, 10–40 μm in length (Schiller et al., 2000; Rhodes, 2006; Larkum and Nevian, 2008; Major et al., 2008). Simultaneous multisite recordings have determined that glutamate-evoked dendritic plateau potentials propagate from their initiation site (Fig. 3, glut. input) in two directions, distally toward the end of the dendritic branch (Fig. 3, gray arrows) and proximally toward the cell body (Fig. 3, white arrows). The degree of amplitude attenuation is significantly smaller in the direction from the initiation site (distally) toward the dendritic tip (Milojkovic et al., 2007, their Fig. 4A). This is because the sealed end of the basal dendrite has high impedance, and it can be easily charged by a spreading plateau potential (Fig. 3, dend. tip). In contrast, in the orthograde (proximal) direction (Fig. 3, white arrows), the rate of amplitude attenuation is much faster. As a result of an impedance mismatch between the thin basal dendrite and large soma, the plateau potentials are drastically reduced in amplitude as they approach the cell body (Milojkovic et al., 2004, their Fig. 7). Nevertheless, suprathreshold glutamatergic stimulations delivered in the middle and proximal segments of a single basal dendrite (Fig. 3, rectangle) often produced 10–20-mV sustained depolarizations of the cell body (Figs. 2, 3). The timing and duration of the somatic depolarization phase (Fig. 3, Soma) are in strict relationship with the time course of the dendritic plateau potential at the initiation site (Fig. 3, glut. input). Several milliseconds after the onset of a dendritic

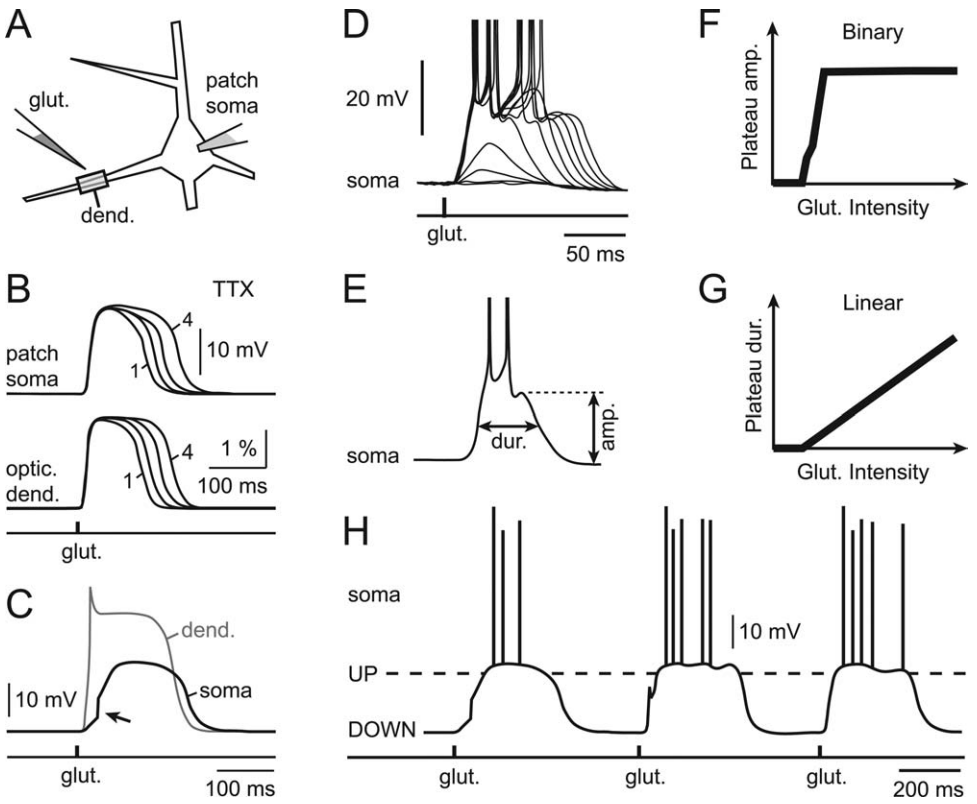

Fig. 2. Strict correlation between dendritic plateau potential and somatic sustained depolarization. **A:** Recording configuration showing glutamate iontophoresis electrode positioned in the middle segment of a basal dendrite. **B:** Voltage waveforms are recorded at the stimulation site optically (dend.) and in the cell body electrically (patch) as indicated in A. Intensity of glutamate current pulse was increased in four equal increments (1–4). In this and the following panels, the timing of glutamate pulse is marked by a vertical tick below the recording trace. In the presence of TTX, the somatic membrane potential waveform closely follows that in the dendrite. The amplitudes of both dendritic and somatic responses are saturated, but their durations increase gradually in consecutive sweeps. There is a positive correlation between the stimulus intensity and duration of the electrical event (Milojkovic et al., 2005a). **C:** In normal physiological saline, the glutamate-evoked dendritic plateau potential is often preceded by a fast sodium spikelet. At this same moment when the spikelet fired in the dendrite, the cell body showed fast inflection (arrow; Milojkovic et al., 2005b; Nevian et al., 2007; Remy et al., 2009). **D:** Somatic voltage waveforms generated by a sequence of incrementally increasing glutamate stimuli delivered on a basal dendrite, as shown in A. **E:** Slow component of the somatic depolarization can be described in terms of amplitude (amp.) and half-width (duration, dur.). The amplitude and duration of the slow component (somatic) are plotted against stimulus intensity in F and G, respectively. **F:** The amplitude of somatic slow depolarization exhibits an all-or-none highly nonlinear behavior (binary), whereas duration exhibits steady growth with stimulus intensity (linear; **G**). **H:** Cortical Up-state-like somatic depolarizations were triggered in acute brain slice by a sequence of three identical glutamate puffs (glut.) delivered on a single basilar branch (Milojkovic et al., 2004).

plateau potential, the somatic membrane shifts into the sustained depolarized state (Fig. 2C). The cell body remains in a depolarized state for the whole duration of the dendritic plateau phase, and it returns to resting immediately after the collapse of the dendritic plateau potential (Fig. 2C; Milojkovic et al., 2005a). In other words, the onset of the somatic plateau depolarization is a consequence of the onset of the dendritic plateau spike, and, by the same token, the breakdown of the somatic depolarized state occurs as a consequence of the collapse of the glutamate-evoked dendritic plateau potential (Fig. 2C). With strong glutamatergic stimulations, one can often detect a sharp inflection on the rising phase of the somatic plateau potential (Fig. 2C, arrow), which is quite prominent in the first derivative of the voltage waveform (Acker and Antic, 2009). It is now firmly established that the early inflection on the somatic waveform is caused by a sodium spikelet firing at the dendritic initiation site (Ariav et al., 2003; Milojkovic et al., 2005b; Nevian et al., 2007; Larkum and Nevian, 2008; Losonczy et al., 2008; Remy et al., 2009).

FUNCTIONAL SIGNIFICANCE OF NMDA SPIKES

Neuronal Up State

During sleep, and sometimes even in the awake state, cortical pyramidal neurons alternate between intervals of strong activity (Up states) and intervals of almost complete

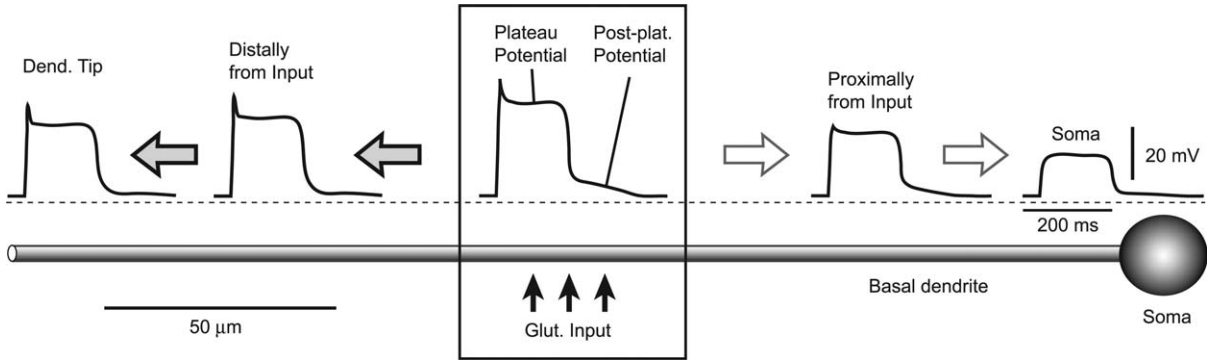

Fig. 3. Bidirectional propagation of glutamate-evoked dendritic plateau potentials. The dendritic plateau potential propagates from its initiation site (glut. input) in two directions, distally toward the end of the basal dendrite (dend. tip) and proximally toward the cell body (soma). In the proximal direction (white arrows), the rate of amplitude decline is much faster than that in the distal direction (gray arrows). Glutamate-evoked dendritic plateau potentials initiated in the midsection of a typical basal dendrite (rectangle) regularly cause 10–20-mV sustained (>100 msec) depolarizations of the cell body (Milojkovic et al., 2004, 2005a). Note that, at the glutamate stimulation site (glut. input), the dendritic plateau potential is followed by a small postplateau depolarization (postplateau potential). Both the plateau and the postplateau potential support calcium influxes, which when combined constitute the glutamate-evoked dendritic ''calcium plateau'' (not shown but see Milojkovic et al., 2007).

silence (Down states; Cowan and Wilson, 1994; Timofeev et al., 2000; Petersen et al., 2003). The Up states are based solely on patterned synaptic (glutamatergic) excitation (Steriade et al., 1993; Cowan and Wilson, 1994; Lampl et al., 1999; Shu et al., 2003). Because Up states spread consistently and rapidly throughout the entire cortex at a typical frequency of ~1 Hz and seem to engage every cortical neuron in the way (Volgushev et al., 2006), they are poised to generate synchronous activity of afferent axon terminals impinging on an individual cell. The density of glutamatergic afferents is highest in middle segments of thin branches (Larkman, 1991; Benavides-Piccione et al., 2002). Therefore, a cortical Up state may trigger a sudden surge in the concentration of extracellular glutamate around thin dendrites of cortical pyramidal neurons. Transient increases in both exogenous and synaptic glutamate in basal and oblique dendrites have been shown to elicit local regenerative dendritic potentials (Schiller et al., 2000; Oakley et al., 2001a; Wei et al., 2001; Polsky et al., 2004; Gordon et al., 2006; Nevian et al., 2007), so dendritic NMDA-dependent spikes and plateau potentials may occur during cortical Up states (discussed by Antic et al., 2007).

In acute brain slice preparations, glutamate-evoked dendritic plateau potentials cause sustained depolarizations of the pyramidal cell somata (Fig. 2B,D). These sustained somatic depolarizations resemble cortical Up states with respect to 1) amplitude of the slow component, 2) duration of the depolarized state, 3) irregular firing of accompanying APs, 4) fast onset, and 5) abrupt collapse at the end of the plateau depolarization (Fig. 2H; Milojkovic et al., 2004, their Fig. 1). This is not to say that NMDA-dependent plateau potentials are causing cortical Up states. Quite the opposite. We are suggesting that cortical Up states, via a massive increase in extracellular glutamate concentration, create favorable conditions for initiation of dendritic plateau potentials. The all-or-none nature of dendritic plateau potentials, combined with neuronal ''restorative'' (repolarizing) conductances (see Wilson, 2008), may explain the constant and uniform voltage waveforms (amplitude and duration) regularly observed in individual cortical pyramidal neurons in vivo during the consecutive cortical Up states (Cowan and Wilson, 1994; Branchereau et al., 1996; Lewis and O'Donnell, 2000; Timofeev et al., 2000; Petersen et al., 2003). So far, there has not been an adequate explanation for the observed uniformity of amplitudes in consecutive cortical Up states. A perfectly balanced excitatory/inhibitory activity is one possibility (Shu et al., 2003; Waters and Helmchen, 2006). Here we propose that saturation of the dendritic voltage response during the NMDA-dependent plateau potential (Fig. 2B–F) may also produce consecutive Up states of uniform amplitudes (Fig. 2H). In summary, through their potential role in cortical Up states, the NMDA-dependent dendritic plateau potentials could be important for arousal of attention, proper cognition, and working memory in awake (Funahashi et al., 1989; Major and Tank, 2004; Durstewitz and Seamans, 2006; Haider and McCormick, 2009), as well as for memory consolidation in asleep, mammals (Stickgold et al., 2000; Sirota et al., 2003; Rasch et al., 2007; for review see Diekelmann and Born, 2010).

Independent Multisite Subcellular Integration

Calcium spikes that initiate in the apical trunk (Fig. 1B2) and sodium APs that initiate in the axon initial segment (Fig. 1B3) both propagate several hundred micrometers to invade relatively large sections of the axodendritic arbor, acting as global broadcasting signals (Stuart et al., 1997). In contrast to calcium spikes or APs, the NMDA spikes in thin dendritic branches (basal, oblique, and tuft) can be truly local and spatially restricted phenomena involving only one sister branch in the entire dendritic tree (Schiller et al., 2000; Oakley et al., 2001b; Wei et al., 2001; Holthoff et al., 2004; Milojkovic et al.,

2004, 2005b; Major et al., 2008; Larkum et al., 2009). By being both localized and regenerative, NMDA spikes could contribute uniquely to processes of synaptic integration and synaptic plasticity (Gordon et al., 2006; for review see Holthoff et al., 2006). Glutamatergic inputs clustered over approximately 20–50 μm of dendritic length can elicit local NMDA spike/plateau potentials in terminal dendrites of cortical pyramidal neurons, inspiring the notion that a single terminal dendrite can function as a decision-making computational subunit (Major et al., 2008). This notion has been explored in biophysically detailed compartmental models, and those numerical studies concluded that active dendrites of a single neuron can perform the multiple independent subunit computations and enrich the computational power and repertoire of cortical pyramidal cells (Archie and Mel, 2000; Poirazi et al., 2003; Gollo et al., 2009). Multiple-subunit computations combined with long durations of the dendritic glutamate-evoked regenerative potentials (Milojkovic et al., 2004, 2005a) amply support the persistent neuronal activity (Goldman et al., 2003; Major and Tank, 2004; Morita, 2008).

Early in the ''decade of the NMDA spike,'' it was proposed that functionally related synaptic contacts are spatially clustered on particular dendritic branches of cortical pyramidal neurons. Namely, in response to everyday life experience, synaptic afferents that carry similar informational content would tend to aggregate in a restricted part of the dendritic tree, presumably on the same dendritic branch (Poirazi and Mel, 2001). Clustering of synaptic inputs in space (and time) improves the chances for reaching the dendritic threshold for firing a regenerative (amplified) response and provides the opportunity for faster and more frequent cooperation among synaptic contacts involved in the same computational task. This intriguing concept, if true, might have profound implications for cortical information processing. Instead of thousands of synaptic inputs, the pyramidal cell requires only a ''correct'' set of <50 active synaptic contacts (Gasparini et al., 2004; Larkum et al., 2009) to trigger a regenerative dendritic response (e.g., NMDA/plateau potential). Inside the dendritic segment that is experiencing a clustered glutamatergic input sufficient to trigger an NMDA spike, there is a massive calcium influx (calcium plateau; Milojkovic et al., 2007; Major et al., 2008; Takahashi and Magee, 2009), which could serve a multitude of calcium-dependent cellular processes, including the short-term and long-term synaptic plasticities (Nimchinsky et al., 2002; Zucker and Regehr, 2002; Holthoff et al., 2006; Lau et al., 2009). Owing to its prolonged plateau phase, the glutamate-evoked dendritic NMDA/plateau potentials may enable dendrites to retain information for hundreds of milliseconds, which potently extends the time window for binding of fragmented information, such as multiple modalities of a sensory stimulus (Nakamura et al., 1992; Wilson et al., 1993). Each individual feature of a perceptual event, regardless of whether the event was based on external (sensory perception) or internal (recall of memory) presentation, is coded by an assembly of cortical neurons. The neural assemblies, defined in terms of time-resolved correlated neural firing patterns, are the basic functional units in cortical information processing (Singer, 2001; Wolters and Raffone, 2008). During the Down state, cortical pyramidal neurons are electrically quiescent, as documented in several species and several cortical areas, including the visual, somatosensory, and prefrontal cortices (Cowan and Wilson, 1994; Lampl et al., 1999; Lewis and O'Donnell, 2000; Timofeev et al., 2000; Petersen et al., 2003; Volgushev et al., 2006). Dendritic NMDA spikes can bring cortical pyramidal neurons to a sustained depolarized state, the Up state (Fig. 2H). A transition from a Down state to an Up state dramatically increases the AP firing probability and therefore provides a basis for synchronization with an active assembly of neurons (group of neurons already in an Up state performing a computational task). Furthermore, the glutamate-evoked plateau depolarization is a special form of a ''high-conductance state,'' which causes the shortening of the membrane time constant, which, in turn, favors finer temporal discrimination of distant synaptic inputs (Bernander et al., 1991). Computer simulations predict that cortical neurons in these high-conductance states can resolve higher frequency inputs and therefore efficiently participate in temporal binding (Shadlen and Movshon, 1999; Shelley et al., 2002; Destexhe et al., 2003). In summary, two features of dendritic glutamate-evoked plateau potentials may serve in the temporal binding processes of the CNS: 1) maintenance of neuronal sustained depolarization, the Up state (Fig. 2C), and 2) shortening of the neuronal membrane time constant.

The impact of individual synapses on the generation of the neuronal output (axonal AP) is weak because of the biophysical constraints imposed by the morphology and membrane properties of the dendritic tree (Gulledge et al., 2005; Spruston, 2008). That is, distal synaptic inputs are severely attenuated as they travel from their site of origin (e.g., terminal tuft branch) through the entire length of the apical dendrite, then through the soma, finally to reach the AP initiation zone in the initial segment of the axon. Spatiotemporal clustering of glutamatergic inputs and the ensuing generation of dendritic spikes can dramatically increase the impact of distal synapses on the AP initiation process and neuronal AP burst firing (Fig. 2D). Neurons equipped with dendrites capable of firing NMDA spikes (active dendrites) can exhibit a greater specificity of spiking responses and perform a greater number of transformations of synaptic input into AP output, which would otherwise require more than one neuron with passive dendrites (discussed by Larkum and Nevian, 2008). Apart from the ''classical'' synaptic integration process (summation of electrical events), the dendritic NMDA spikes may also serve to couple synaptic inputs to intracellular signaling cascades. For example, strong activation of NMDA receptor channels in oblique dendrites synergistically enhances metabotropic glutamate receptor-mediated regenerative

Ca^{2+} release from internal stores (Nakamura et al., 2002). The large amplitude and long duration of the intracellular Ca^{2+} increases resulting from Ca^{2+} release from stores is thought to affect downstream signaling mechanisms in pyramidal neurons (Ross et al., 2005). The benefits of synaptic clustering are thus multiple, and they all seem to depend on the ability of dendrites to generate an NMDA spike.

CONCLUSIONS

Thin dendrites of cortical pyramidal neurons (basal, oblique, and tuft dendrites) are crowded with glutamatergic synaptic contacts. Each glutamatergic contact has its own anatomical substrate in the form of a dendritic spine. Synchronous activation of 10–50 neighboring glutamatergic inputs (spines) triggers a local regenerative potential, NMDA spike/plateau, which is characterized by significant local amplitude (40–50 mV) and duration (up to several hundred milliseconds). Depending on the path distance from the cell body, these glutamate-evoked NMDA-dependent plateau potentials can either bring the cell body into a sustained depolarization (e.g., proximal segments of basal dendrites) or maintain an isolated dendritic segment in a sustained depolarized state (e.g., the distal part of a long basal branch, or an apical tuft dendrite). Regardless of the thin-dendrite subtype (basal, oblique or tuft), at each dendritic initiation site, an NMDA spike creates favorable conditions for causal interactions of active synaptic inputs, including the spatial or temporal binding of information, as well as processes of short-term and long-term synaptic modifications (e.g., LTP or LTD). Local dendritic NMDA spikes are the cellular substrate for multisite independent subunit computations that enrich the computational power and repertoire of cortical pyramidal cells and are likely to play significant roles in cortical information processing in awake animals (spatiotemporal binding, expansion of the dynamic range, working memory) and during sleep (neuronal Up states, consolidation of memories).

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