

Role of dendritic synapse location in the control of action potential output

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How effective are synaptic inputs made at different dendritic sites in the control of action potential output? Recent technical advances have allowed direct observation of the amplitude and time course of excitatory synaptic inputs generated at defined dendritic sites. These findings indicate that contrasting mechanisms exist to enhance the impact of dendritic excitatory inputs to pyramidal neurons of the neocortex and hippocampus. Furthermore, multiple sites of synaptic integration have been revealed, suggesting that proximal and distal inputs are likely to be integrated in different ways. Taken together, these data emphasize the cell- and input-specific strategies used by neurons to enhance the impact of dendritic inputs on action potential generation.

Most CNS neurons possess intricately branched dendritic arbors that extend hundreds of micrometers from the cell body. These remarkable structures are richly decorated with tens of thousands of excitatory and inhibitory synapses. As first proposed by Ramón y Cajal, the primary function of the dendritic tree is to collect and funnel information received at individual synapses to the soma and axon, which represent the main output pathway of neurons. The spatial distribution of synapses across the dendritic tree poses a problem, however, as synapses formed at increasing distance from the soma are progressively isolated from the site of action potential generation in the axon [1] (usually located near the soma, but see Refs [2,3]). A question that has puzzled neuroscientists for decades is how effective are synapses located at different dendritic sites in controlling action potential output?

Answers began to emerge in the 1950s and 1960s through pioneering experimental and theoretical studies. The integration of experimentally determined passive neuronal properties, obtained from somatic intracellular recordings [4–6], with neuronal models based on cable theory [5,7–10] highlighted the substantial electrical filtering properties of dendrites (due to their membrane and cytoplasmic resistance and capacitance). These seminal studies predicted that the amplitude of synaptic potentials would attenuate and the time course would slow after spread from dendritic site of generation to the soma

and axon [7,10] (Fig. 1a). Unless mechanisms are in place to compensate for this attenuation, synaptic potentials generated at progressively distal dendritic sites would be expected to have a diminishing influence on action potential output.

These theoretical studies provided a framework with which experimentalists could investigate the somatic impact of excitatory postsynaptic potentials (EPSPs) generated at dendritic sites. The theoretically derived relationship between somatic EPSP rise time and duration, and synapse location in the dendritic tree was used to assign the site of EPSPs recorded from the soma of motoneurons *in vivo* to points within the dendritic arbor [7,11–13]. Surprisingly, these experiments revealed that the somatic amplitude of EPSPs was independent of EPSP time course and therefore presumed dendritic site of generation [13] – a finding that could only be reconciled with passive cable theory if the amplitude of EPSPs was augmented in a distance-dependent manner by an increase in the underlying synaptic current or by an interaction with voltage-activated ion channels, or both. Jack and colleagues [14,15] used quantal analysis to explore the possibility that site-independence of somatic EPSP amplitude was generated by a distance-dependent increase in the amplitude of unitary (quantal) events generated at individual release sites. When measured from the soma, quantal size was found to be independent of the presumed dendritic site of EPSP generation (see also Ref. [16] for analysis of CA1 pyramidal neurons), suggesting a distance-dependent increase in the number of postsynaptic neurotransmitter receptors activated at individual release sites.

Although intriguing, these studies relied heavily upon model assumptions to assign synapse location to points within the dendritic arbor (but see Ref. [17]). To test if dendritic synapses are stronger, direct verification of the site of EPSP generation was required. Development of imaging techniques capable of resolving dendrites in brain slice preparations [18], coupled with direct electrical recording from dendrites using patch-clamp techniques [19], have recently allowed experimentalists to directly examine the axo–somatic impact of dendritic synapses.

Are distal synapses stronger?

In two classes of cortical pyramidal neurons, multi-site patch-clamp recordings from the soma and apical dendrites

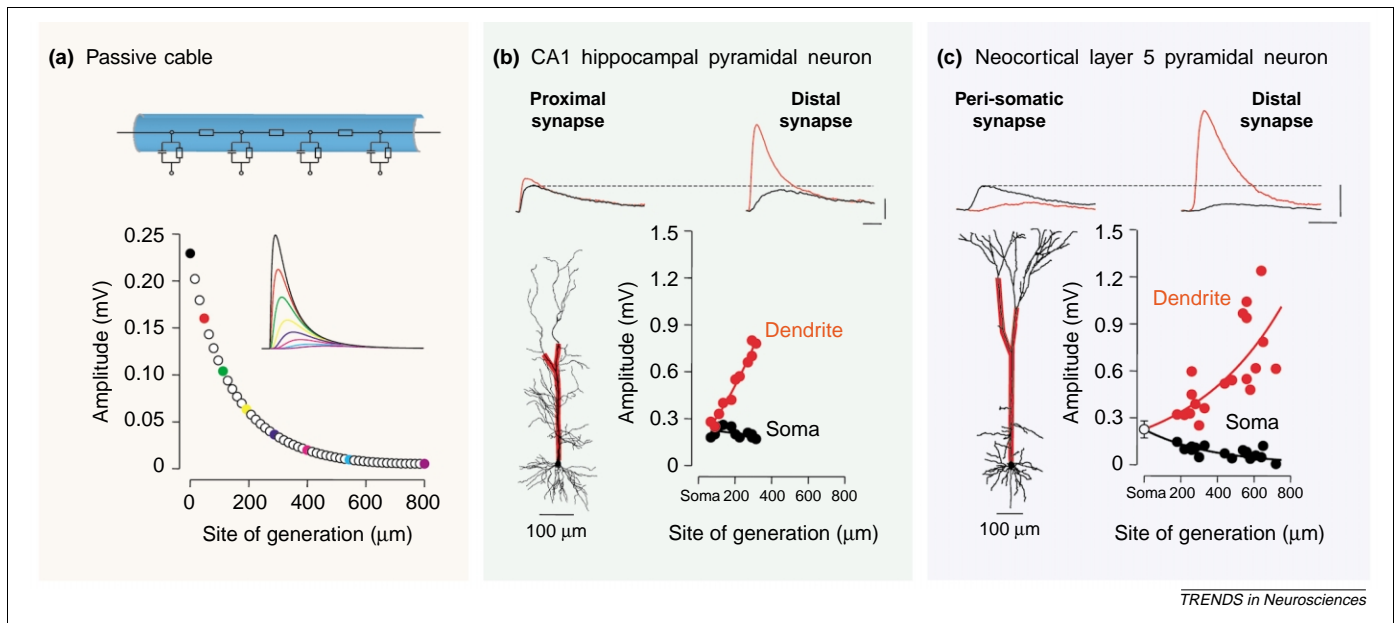


Fig. 1. Attenuation of synaptic potentials. (a) Attenuation of excitatory postsynaptic potentials (EPSPs) along a uniformly passive cable. EPSPs were generated at progressively distal sites from the recording site ($0 \mu\text{m}$). The line graphs show recorded EPSPs generated at the color-coded sites. (b) Site-independence of somatic EPSP amplitude in CA1 pyramidal neurons. Traces illustrate simultaneously recorded somatic (black) and dendrite (red) EPSPs generated at proximal ($70 \mu\text{m}$) and distal dendritic ($300 \mu\text{m}$) sites. Scale bars, 3 ms (horizontal) and 0.2 mV (vertical). Note the similar amplitude of somatic EPSPs. Graph indicates the relationship between local dendritic EPSP amplitude (red) and somatic EPSP amplitude (black), and the site of EPSP generation in rat CA1 pyramidal neurons. Adapted, with permission, from Ref. [20], © (2000) Nature Publishing Group (<http://www.nature.com/>). Typical CA1 pyramidal morphology is shown to the left of the graph; the highlighted region represents the recorded dendritic area. (c) Site-dependence of somatic EPSP amplitude in neocortical layer 5 pyramidal neurons. Traces illustrate simultaneously recorded somatic (black) and dendritic (red) EPSPs generated at perisomatic and distal dendritic ($560 \mu\text{m}$) sites. Scale bars, 5 ms (horizontal) and 0.3 mV (vertical). Graph indicates the relationship between local dendritic EPSP amplitude (red) and somatic EPSP amplitude (black), and the site of EPSP generation in rat layer 5 pyramidal neurons. Reproduced, with permission, from Ref. [21], © (2002) American Association for the Advancement of Science. Typical morphology is shown to the left of the graph; the highlighted region represents the recorded dendritic area.

have been used to examine the somatic impact of EPSPs generated at known dendritic sites [20,21]. Contrasting findings have emerged: in CA1 hippocampal pyramidal neurons the average somatic amplitude of EPSPs is independent of the apical dendritic site of generation [20] (Fig. 1b), whereas in layer 5 neocortical pyramidal neurons the average somatic amplitude of EPSPs is dependent upon synapse location in the apical dendritic tree [21] (Fig. 1c). In the following sections we discuss the possible mechanisms that underlie this striking difference in the behavior of two canonical neuronal types and the implications for the control of action potential output.

The spread of EPSPs from dendritic site of generation to the soma and axon is constrained by dendritic morphology and electrotonic structure [22], with recent theoretical studies demonstrating that neuronal morphology crucially determines the site-dependence of somatic EPSP amplitude [23]. In some neuronal types, relatively little site-dependence of somatic EPSP amplitude is predicted [23–25], in part because of the impact of neuronal morphology on the amplitude of EPSPs at the site of generation. In both neocortical layer 5 and CA1 hippocampal pyramidal neurons, the local amplitude of EPSPs measured close to the site of generation was found to increase with distance from the soma [20,21] (Fig. 1b,c). Such an increase is predicted from neuronal morphology, owing to the smaller physical diameter of distal dendrites coupled with their electrical isolation from the expanse of the soma (Box 1). To examine the influence of neuronal

morphology directly, artificial synaptic currents with uniform amplitude and kinetics were delivered to known dendritic sites via dendritic recording electrodes [20,21]. When generated at increasingly distal sites, the local dendritic amplitude of artificial EPSPs increased in CA1 pyramidal neurons, but to a lesser degree than for real EPSPs, whereas somatic amplitude decreased in a site-dependent manner [20] (Fig. 2a). In neocortical layer 5 pyramidal neurons, however, the site-dependent increase in local artificial EPSP amplitude, and accompanying decrease in somatic amplitude, closely mirrored the relationship found for real EPSPs [21] (Fig. 2b). These results indicate that site-independence of somatic EPSP amplitude in CA1 pyramidal neurons cannot be explained by neuronal morphology and must, therefore, arise from a progressive increase in synaptic current at distal apical dendritic synapses – a view verified by dendritic voltage-clamp experiments [20]. Conversely, data on layer 5 pyramidal neurons indicate that the synaptic current underlying EPSPs is similar at different apical dendritic sites [21].

What cellular mechanisms are responsible for the increased synaptic current at distal synapses in CA1 pyramidal neurons? One way to generate increased current at distal synapses is to pack more neurotransmitter receptors into distal dendritic synapses. To address this possibility, the number and properties of neurotransmitter receptors can be assessed by rapidly applying glutamate to dendritic membrane patches [26]. Such experiments revealed a twofold increase in the

Box 1. Influence of effective time constant on EPSPs

The time course of synaptic currents mediated by AMPA receptors is extremely rapid [86]. The amplitudes of excitatory postsynaptic potentials (EPSPs) are, therefore, determined primarily by local input capacitance and are largely independent of neuronal membrane resistance [87–90]. The dependence of EPSP amplitude on local input capacitance is illustrated in a simple single-compartment neuronal model with uniform input resistance (Fig. 1a). Lower values of membrane capacitance lead to EPSPs of larger amplitude and briefer duration (Fig. 1a,b), constraining the temporal summation of EPSPs (Fig. 1a, inset) [89]. Simulations predict that the local input capacitance of neurons is non-uniform, decreasing at distal dendritic sites because of the influence of dendritic geometry and neuronal electrotonic structure [89,90]. This is reflected as a speeding of the local effective membrane time constant at dendritic sites [89,90]. In layer 5 neocortical pyramidal neurons, experimentally determined effective time constants at distal apical dendritic sites are approximately four times faster than at the soma (Fig. 1c,d) because of the influence of both dendritic geometry and a distance-dependent increase in the density of I_H channels [91–93]. I_H also acts to make apparent input resistance largely independent of recording location [94] (Fig. 1d, inset). In cortical pyramidal neurons, therefore, a distance-dependent increase in the local amplitude of EPSPs [95] arises primarily from a decrease in effective local input capacitance at apical dendritic sites.

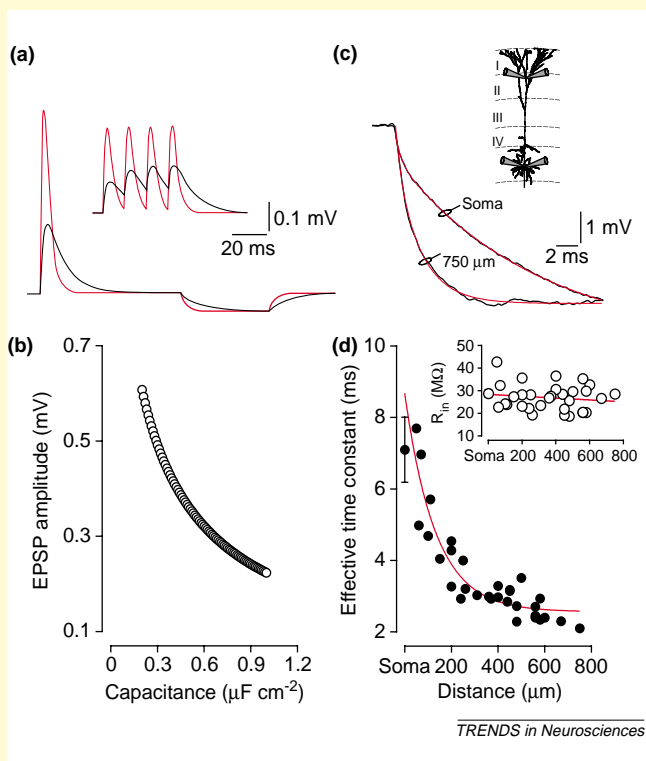


Fig. 1. Dependence of excitatory postsynaptic potential (EPSP) amplitude on local capacitance. (a) Simulation of the effects of changes in membrane capacitance on EPSP amplitude and duration. EPSPs were generated with a point conductance source ($\tau_{\text{rise}} = 0.2$ ms; $\tau_{\text{decay}} = 2$ ms). Specific membrane capacitance was altered from $0.2 \mu\text{F cm}^{-2}$ (red trace) to $1 \mu\text{F cm}^{-2}$ (black trace) in an isopotential compartment with input resistance (R_{in}) of 30 M Ω modeled using NEURON [96]. (b) Pooled simulation results describe the relationship between membrane capacitance and EPSP amplitude. (c) Effective time constant in layer 5 pyramidal neurons at somatic and apical dendritic sites. Current injection (-200 pA step) and voltage recording were made with independent, closely spaced ($< 10 \mu\text{m}$ apart) pipettes. Voltage responses were fit with a double exponential (red line). (d) Distance-dependent variation of the effective time constant in layer 5 pyramidal neurons. Data points represent amplitude weighted mean time constants. The red line represents a double exponential fit to the data. The inset shows the site-independence of apparent R_{in} ; the red line is a linear regression.

number of AMPA-type glutamate receptors, with similar single channel properties, at distal apical dendritic sites in CA1 pyramidal neurons [27]. The use of excised patches does not, however, allow discrimination between sub-synaptic and extra-synaptic receptor populations. An alternative approach is two-photon uncaging of glutamate to individual dendritic spines [28]. Using this technique, recent findings suggest that the number of functional AMPA-type glutamate receptors on spines of a similar size is greater at distal apical dendritic sites of CA1 pyramidal neurons [29]. These data reveal that individual distal apical dendritic synapses are stronger in CA1 pyramidal neurons because of an increased average density of AMPA-type receptors.

Pathway specificity

Functionally distinct streams of information are conveyed by synaptic inputs that terminate at different dendritic sites in cortical pyramidal neurons [30,31]. In CA1 pyramidal neurons, experimental investigation of somatic EPSP amplitude normalization has been restricted to the main apical dendrite, where excitatory synaptic inputs arise primarily from CA3 pyramidal neurons in the Schaffer collateral pathway [30] (Fig. 1b). Can these findings be generalized to other synaptic inputs to CA1 pyramidal neurons? Conversely, are there pathway specific inputs to neocortical layer 5 pyramidal neurons that exhibit somatic EPSP amplitude normalization? EPSPs generated at the most distal apical dendritic sites in CA1 and layer 5 neocortical pyramidal neurons are predicted to undergo severe dendro-somatic attenuation (Fig. 2c). In the face of such attenuation, a precipitous increase in synaptic current delivered at distal synapses would be required to produce somatic EPSP amplitude normalization (S.R. Williams, unpublished; T.J. Mickus, N.L. Golding and N. Spruston, unpublished). As a consequence, the local amplitude of EPSPs at distal dendritic sites will approach voltage saturation, particularly during activation of multiple inputs [32]. These data suggest that normalization of the somatic amplitude of EPSPs by synaptic mechanisms is unlikely to be expressed for distal apical dendritic inputs to either layer 5 or CA1 pyramidal neurons. At more proximal dendritic sites, however, independence of somatic EPSP amplitude and synapse location might occur for specific inputs – as is the case for the Schaffer collateral input to hippocampal CA1 pyramidal neurons. A specific pathway employing site-dependent synaptic scaling mechanisms in neocortical layer 5 pyramidal neurons has yet to be described, despite analysis of a defined excitatory pathway from layer 2–3 pyramidal neurons [21].

EPSP time course

The charge generated by dendritic synapses attenuates to a lesser degree than EPSP amplitude [22]. The voltage consequences of this is the generation of axo-somatic EPSPs with prolonged time course – a feature that in principle should facilitate temporal summation [9] and increase the somatic impact of distal synaptic inputs. However, experiments indicate that the duration of EPSPs at the soma of hippocampal CA1 and neocortical layer 5

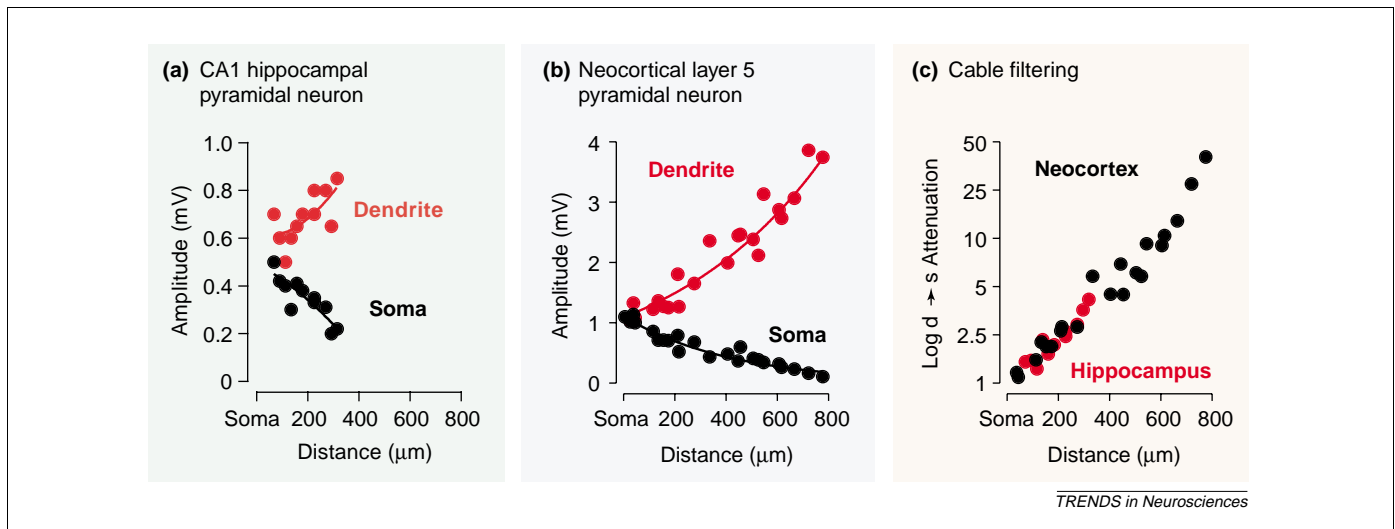


Fig. 2. Effect of morphology on local and propagated excitatory postsynaptic potential (EPSP) amplitude. (a) Site-dependent modification of simulated EPSPs in CA1 hippocampal pyramidal neurons. Amplitude of simulated EPSPs at their site of generation (dendrite; red) and at the soma (black). Note that the increase in local simulated EPSP amplitude is less than observed for real EPSPs (Fig. 1b). Adapted, with permission, from Ref. [20], © (2000) Nature Publishing Group (<http://www.nature.com/>). (b) In neocortical layer 5 pyramidal neurons, the relationship between local dendritic (red) and somatic (black) simulated EPSP amplitude mirrors that found for real EPSPs (Fig. 1c). Reproduced, with permission, from Ref. [21], © (2002) American Association for the Advancement of Science. (c) The degree of dendro–somatic attenuation (log scale) of simulated EPSPs along the apical dendrite is tenfold greater in neocortical layer 5 (black) compared with hippocampal CA1 (red) pyramidal neurons, primarily because of the longer main apical dendrite of layer 5 pyramidal neurons.

pyramidal neurons is independent of the apical dendritic site of generation [33–35]. This arises because the dendrites of these neurons possess high densities of a class of voltage-activated channels known as I_H channels [33–38]. As the density of I_H channels increases with distance from the soma, a distance-dependent sculpting of local and propagated EPSP time course occurs, rendering EPSP time course and temporal summation at the soma relatively independent of synapse location [33–35]. Normalization of somatic EPSP time course by I_H comes at a cost, however, as the activation of I_H increases dendro–somatic attenuation of EPSPs and thus the dependence of somatic EPSP amplitude on synapse location [34,35].

Normalization *in vitro* and *in vivo*

Taken together, the results from *in vitro* experiments demonstrate that the functional impact of isolated small amplitude EPSPs generated at apical dendritic sites in CA1 hippocampal and neocortical layer 5 pyramidal neurons is likely to be different [20,21]. In CA1 hippocampal neurons, both the somatic amplitude and time course of Schaffer collateral EPSPs are site-independent, suggesting an equality of impact on action potential output [39]. Note that this conclusion neglects the influence of axo–somatic EPSP rise time on the probability and timing of action potential firing [40]. By contrast, in layer 5 neocortical pyramidal neurons, the somatic impact of apical dendritic EPSPs is constrained: the site-dependence of somatic EPSP amplitude, but site-independence of somatic EPSP time course, suggests that the probability of action potential generation will be determined directly by synapse location within the apical dendritic tree.

In vivo, however, synaptic events do not occur in isolation. Intracellular recordings from both anaesthetized and unanaesthetized animals have demonstrated a diversity in the rate of ongoing synaptic activity and action potential firing in neocortical and CA1 hippocampal

pyramidal neurons [41–47]. Experimental and computational studies have demonstrated that changing levels of ongoing synaptic activity lead to distributed modifications of membrane resistance that sculpt the degree of dendro–somatic filtering of EPSPs [32,47–51]. This action of ongoing synaptic activity will modify the relationship between the somatic amplitude of EPSPs and dendritic site of EPSP generation, potentially disturbing the fine balance between the strength of apical dendritic synapses and their impact at the soma and axon in CA1 hippocampal pyramidal neurons [32]. Similarly, if the dendritic membrane potential of pyramidal neurons *in vivo* is depolarized relative to *in vitro* conditions [41,45], normalization of somatic EPSP time course by interaction with I_H channels will be disrupted. The somatic impact of dendritic EPSPs *in vivo* is therefore likely to be dynamically determined by the level of ongoing synaptic activity. Detailed information on the frequency and spatial patterning of synaptic activity under *in vivo* conditions will be required to access the physiological relevance of mechanisms uncovered by *in vitro* experiments.

Amplification by dendritic voltage-activated channels

In several neuronal types, EPSPs, which are subthreshold for the generation of axonal action potentials, have been shown to activate dendritic Na^+ and Ca^{2+} channels [52–58]. The recruitment of voltage-activated ion channels by EPSPs provides an additional and complimentary mechanism that, in principle, could augment the somatic amplitude of dendritically generated synaptic potentials in a distance-dependent manner. Modeling studies have demonstrated that amplification of dendritic EPSPs by voltage-activated channels dramatically decreases the degree of site-dependent variability of somatic EPSP amplitude [59–61]. To illustrate this, consider the case of dendritic Na^+ channels. Electrophysiological mapping studies have demonstrated that Na^+ channel density is

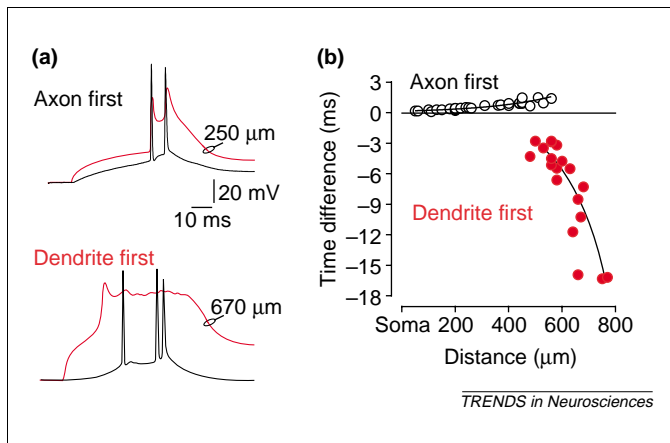


Fig. 3. Properties of dendritic spike generation. (a) Simultaneous somatic (black) and dendritic (red) recordings demonstrating dendritic spike initiation before axonal action potentials during distal (bottom), but not proximal (top), dendritic current injection in layer 5 pyramidal neurons. (b) Pooled data of the time difference between somatic and dendritic spikes during current injection at different sites. At proximal sites, axonal action potentials occur first and back-propagate to the dendritic recording site (open circles), whereas at distal dendritic sites dendritic spikes precede axonal action potentials (red circles).

uniform along the main apical dendrite of neocortical layer 5 and hippocampal CA1 pyramidal neurons [62–64]. The impact of distal dendritic EPSPs could therefore be enhanced by a distance-dependent recruitment of dendritic Na^+ channels as a consequence of the site-dependent increase in local dendritic EPSP amplitude formed by neuronal morphology (Box 1). Intriguingly, such amplification mechanisms might emerge only under *in vivo* conditions, as tonic membrane depolarization is required for small amplitude dendritic EPSPs to recruit Na^+ and Ca^{2+} channels efficiently [60]. Consistent with this idea, experimental recreation of patterns of excitatory synaptic activity likely to occur *in vivo* suggest that interaction of EPSPs with dendritic Na^+ channels can enhance the impact of apical dendritic inputs on action potential output in layer 5 neocortical pyramidal neurons *in vitro* [65].

Amplification of distal dendritic EPSPs by recruitment of dendritic voltage-activated channels has also been found to lead to the generation of dendritic spikes [21,58,66–71]

(Fig. 3). Dendritic spike generation has profound consequences for synaptic integration, as the forward propagation of these events to the soma and axon directly influences the initiation of axonal action potentials, often leading to action potential burst firing *in vitro* [21,58,66–71] and *in vivo* [72] (Figs 3,4). The recruitment of dendritic spikes, therefore, represents an effective amplification mechanism – enhancing the impact of distal dendritic EPSPs on action potential output. Indeed, the generation of dendritic spikes can render distal excitatory inputs more efficient triggers of axonal action potentials than identical somatic inputs [21,70] (Fig. 4).

Sites of synaptic integration

The site-dependent generation of dendritic spikes has been suggested to form a framework for compartmentalized integration in pyramidal neurons [21,70] (Fig. 3). Excitatory inputs at proximal apical dendritic sites do not, under *in vitro* conditions, give rise to local dendritic spikes; synaptic integration at these sites is therefore focused at the level of the soma and axon (Fig. 3b), and proceeds over the relatively long effective axo–somatic time constant (Box 1). At distal dendritic sites, however, the faster effective membrane time constant (see Box 1), coupled with the non-linear nature of dendritic spike generation, forms a distal integration compartment with a significantly briefer integration time window [21] (Fig. 4). The time window for synaptic integration at both axonal and dendritic sites will be further sculpted by inhibitory synaptic inputs, suggesting that the temporal precision of synaptic integration is dynamically regulated [73,74].

Compartmentalization of synaptic integration has further consequences, as the output signal of one compartment can interact with synaptic integration in other compartments. For example, axonal action potentials have been shown to back-propagate into the apical and basal dendritic arbor of pyramidal neurons, and could act to reset synaptic integration throughout the dendritic tree [75]. In both hippocampal CA1 and layer 5 pyramidal neurons, however, single back-propagating action potentials typically fail to invade the most distal dendritic

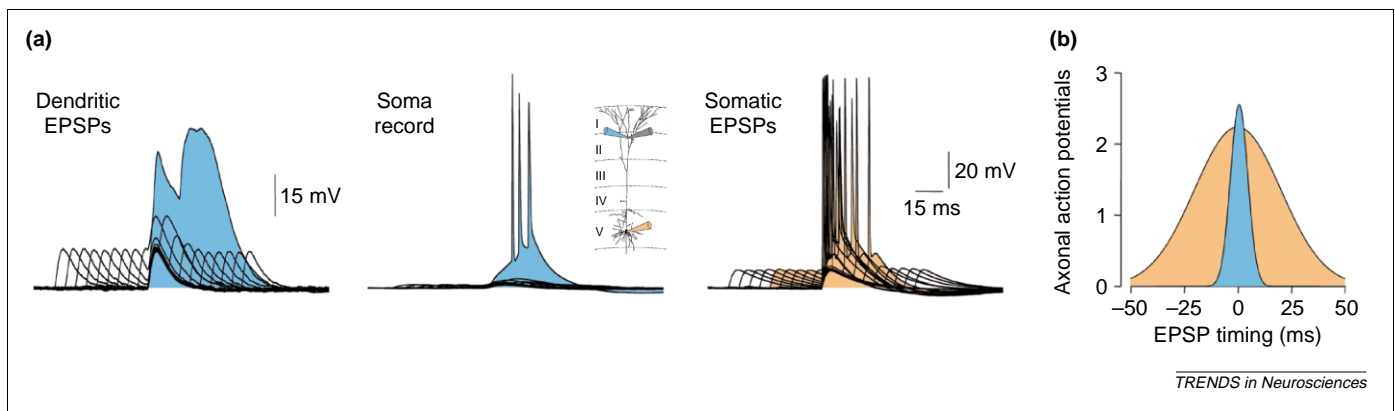


Fig. 4. Time window for synaptic integration depends on synapse location. (a) Narrow time window for integration of distal dendritic excitatory postsynaptic potentials (EPSPs) in layer 5 pyramidal neurons. Pairs of simulated EPSPs separated in time by 0–45 ms generated at distal dendritic sites (620 μm from the soma). When activated simultaneously, dendritic simulated EPSPs elicit a dendritic spike (left traces, highlighted in blue) that propagates to the axon to initiate a burst of action potentials (middle traces, soma record). The injection of identical simulated excitatory currents at the soma (right) results in a broader time window for integration (orange). (b) Gaussian fits to pooled data that demonstrate the average time window for synaptic integration at distal dendritic (blue) and somatic (orange) sites. Reproduced, with permission, from Ref. [21], © (2002) American Association for the Advancement of Science.

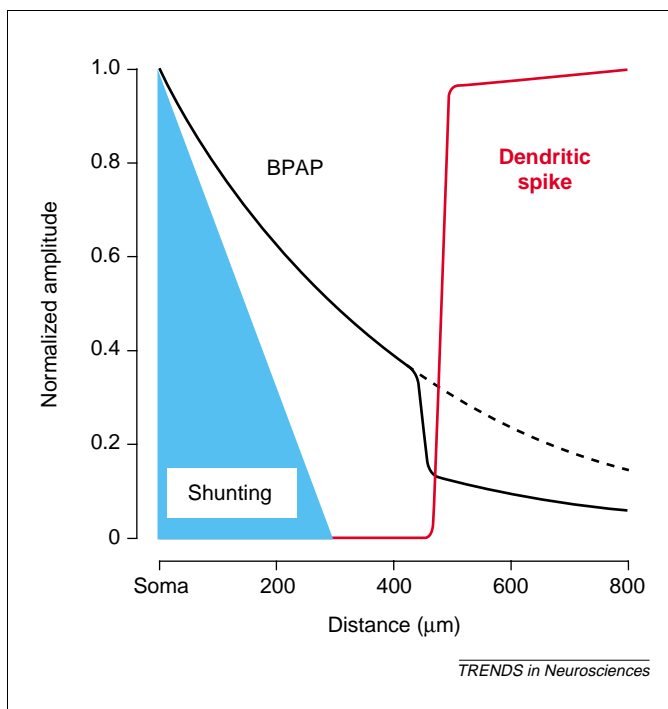


Fig. 5. Interaction between integration compartments. The relationship between normalized single back-propagating action potential (BPAP) and local dendritic spike amplitude and apical dendritic location. At sites $> 500 \mu\text{m}$ from the soma, BPAPs typically fail (black line), whereas dendritic spike initiation is most robust (red line). The blue region represents the dendritic area over which axonal action potentials are capable of resetting synaptic integration by shunting the membrane resistance. See Refs [70,76,79,80].

regions [70,76–79], where dendritic spike initiation is most robust (Fig. 5). Furthermore, the resetting of synaptic integration by the abrupt and massive increase in membrane conductance associated with axonal action potentials is only ‘felt’ at proximal dendritic sites [80] – a feature that would allow synaptic integration at distal dendritic sites to proceed unabated (Fig. 5). Back-propagating action potentials, despite their reduced amplitude, dramatically augment dendritic spike generation [81], whereas appropriately timed dendritic EPSPs amplify back-propagating action potentials [76,82]. These data indicate that integration compartments are not isolated, but interact dynamically, with the activation of one compartment influencing the gain in other compartments. Together with other studies [83,84], these findings indicate the computational power of neurons is augmented by the emergence of multiple sites for synaptic integration within the dendritic arbor, which allows the parallel processing of spatially segregated synaptic inputs to be executed.

Concluding remarks

Recent technical advances have allowed direct observation of the factors that control the amplitude and time course of dendritic synaptic potentials *in vitro*. In support of early work on spinal motoneurons *in vivo* [13], findings in CA1 hippocampal pyramidal neurons suggest that for individual inputs the somatic amplitude of EPSPs is independent of synapse location, owing to a site-dependent scaling of dendritic synaptic current [20]. By contrast, in neocortical layer 5 pyramidal neurons, dendritic synaptic current is

approximately uniform, leading to distance-dependence of somatic EPSP amplitude [21]. These *in vitro* studies have, however, examined only a small fraction of all the excitatory synaptic inputs to pyramidal neurons, as analysis with current recording techniques is restricted to large-diameter dendritic processes such as the main apical dendrite (Fig. 1), which in CA1 hippocampal pyramidal neurons receive only 10% of the total number of excitatory synapses [85]. New techniques will be required to determine the axo–somatic impact of EPSPs generated at smaller diameter basal, oblique and tuft dendritic sites. Furthermore, future experiments need to investigate the functional impact of dendritic inputs under active network conditions, where the integration mode and degree of compartmentalization of synaptic integration will be dynamically regulated.

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