The Guide to Dendritic Spikes of the Mammalian Cortex In Vitro and In Vivo

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Abstract—Half a century since their discovery by Llinàs and colleagues, dendritic spikes have been observed in various neurons in different brain regions, from the neocortex and cerebellum to the basal ganglia. Dendrites exhibit a terribly diverse but stereotypical repertoire of spikes, sometimes specific to subregions of the dendrite. Despite their prevalence, we only have a glimpse into their role in the behaving animal. This article aims to survey the full range of dendritic spikes found in excitatory and inhibitory neurons, compare them in vivo versus in vitro, and discuss new studies describing dendritic spikes in the human cortex. We focus on neocortical and hippocampal neurons and present a roadmap to identify and understand the broader role of dendritic spikes in single-cell computation.

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INTRODUCTION

The “negative variation” discovered by du Bois-Reymond in the mid-19th century later became known as the action potential (du Bois-Reymond, 1848; Finkelstein, 2000). Since then, the understanding of the action potential (AP) generated at the axon has been refined over many years, culminating in the hands of Hodgkin and Huxley (1952) in the form of a biophysical model. Neuroscientists like Lorente de Nó (Lorente de Nó and Condouris, 1959), Eccles (Eccles et al., 1959), and others (Spencer and Kandel, 1961) hypothesized that dendrites also fire action potentials (hereafter, spikes). They proposed that dendritic spikes may play an essential role in synaptic integration and boost weak distal inputs. Interestingly, these visionary ideas that stressed the importance of dendritic spikes to neural computation started to develop in parallel with the revolutionary invention of the perceptron (Rosenblatt, 1957). The perceptron, in effect, discounted the dendrites as means for collecting inputs from the network, whereas synaptic integration was restricted to the cell body.

Eccles and colleagues (Eccles et al., 1964; 1966) elicited spikes at the distal regions of the Purkinje cell’s dendrites by stimulating the climbing fibers in the anesthetized cat cerebellum. It was hard to conclusively determine the origin of the spikes with the single extracellular electrode used in these experiments. One possibility was that the action potential was initiated at the axon and back-propagated into the dendrites. Due to the waveform of the recorded spikes, Eccles et al. preferred the alternative explanation where the spikes were initiated at the dendrite and consequently propagated towards the soma. Llinàs et al. (1968) provided evidence for the dendritic initiation of the spikes by examining their latency at various depths in the alligator cerebellar cortex. Other studies (e.g., Andersen, 1960; Fujita and Sakata, 1962) examined the latencies in extracellular spikes and suggested that spikes were initiated in the dendrites. However, the work of Llinàs and colleagues eventually led them to record these spikes intracellularly, directly from the dendrites (Llinàs and Nicholson, 1971). Later, they also revealed that these spikes were mediated by calcium channels (Llinàs and Hess, 1976). These pioneering in vivo intracellular dendritic recordings are challenging to perform even today, which explains why only a few in vivo studies use electrodes to record directly from the dendrites. Furthermore, dual recordings with one electrode at the cell body and another at the dendrite are virtually impossible in living animals. Due to this limitation, the experimental basis for understanding the signaling between the dendrite and the axosomatic region has been mainly provided by in vitro studies where dual recordings are feasible. A comprehensive description of the function...
of dendritic spikes during relevant behavioral conditions remains elusive.

Biophysically, dendritic spikes result from a supralinear increase in the membrane potential caused by regenerative inward currents. The different classes of dendritic spikes vary significantly in duration, lasting between about a millisecond and hundreds of milliseconds. Some of them, denoted hereafter as intrinsic spikes, are triggered when the dendritic membrane crosses a voltage threshold determined by voltage-gated ion channels. These include Na⁺ spikes/spikelets, Ca²⁺ spikes, low-threshold spikes (LTS), and Ca²⁺ plateau-potentials (note that back-propagating action potentials, bAPs, will not be discussed here because they are not initiated in the dendrite). Other spikes, denoted hereafter as synaptic spikes, are initiated directly at the synapse and depend on ligand-gated ion channels. Synaptic spikes consist of N-Methyl-D-aspartate (NMDA) spikes, plateau potentials, and NMDA Receptor (NMDAR)-dependent Ca²⁺ spikes. Although we focus on dendritic spikes in the neocortex and hippocampus, it is worth noting that they exist in many other brain regions (Goaillard et al., 2020; for example, plateau potentials were found in the striatum and amygdala (Oikonomou et al., 2014), NMDA spikes in thalamocortical neurons (Augustinaite et al., 2014), calcium spikes in the granule cells of the olfactory bulb (Zelles et al., 2006), sodium spikes at the retinal ganglion cells (Sivyer and Williams, 2013) and LTSs in thalamocortical relay neurons (Andersen and Eccles, 1962). Typically, spikes involve more classes of ion channels than their name suggests. Nevertheless, the spike name is usually a good indication of the main operating channels or initiation mechanism. To date, there is no agreement on nomenclature, and therefore, we addressed the dendritic spikes as they are conventionally called in the relevant literature.

This review aimed to survey all dendritic spikes ever observed in the mammalian neocortex and hippocampus. We categorized them by their initiation mechanism and cell type and then further discussed the differences and similarities reported in vitro versus in vivo and between humans and rodents.

**CA²⁺ SPIKES**

Cortical pyramidal cells of layer 5 (L5PCs) with their long and relatively thick apical trunk have been a preferred target for the early studies of dendritic spikes. The first L5PC dendritic Ca²⁺ spikes were recorded by Houchin (1973) in the rat cortex in vivo in response to forepaw stimulation. Later, Pockberger (1991) showed more systematically in the anesthetized rat that these dendrites fired complex-shaped spikes composed of fast and slow components. The slow depolarizing waveform with an amplitude of about 40–70 mV was presumed to be mediated by Ca²⁺ channels with superimposed fast Na⁺ spikes (Fig. 2B). Indeed, two-photon imaging showed a transient increase in dendritic Ca²⁺ concentration during these spikes (Helmchen et al., 1999). Zhu and Connors (1999) directly recorded electrical dendritic activity in L5PCs of the barrel cortex during whisker deflection. The latter study provided more evidence that dendritic spikes amplify sensory-evoked synaptic inputs. In recent years, the relevance of dendritic Ca²⁺ spikes for sensory perception has been further established; for example, they were found to encode sensory stimulation strength (Murayama et al., 2009) and the threshold of perception (Takahashi et al., 2016; reviewed in Manita et al., 2017). These results made a significant step towards a broader recognition of dendritic spike centrality in neuronal processing in the living, behaving organism.

In the neocortex, PCs of layers 5 and 2/3 have basal and oblique dendrites with an apical tuft extending to layer 1. Despite the similar structure, their dendritic spiking activity is different. In contrast to L5PCs, dendritic regenerative events observed in L2/3PCs (Fig. 2C, D) were not initiated at the dendrite. Instead, Ca²⁺ transients were mostly associated with bAPs (Svoboda et al., 1997; Waters et al., 2003; Waters and Helmchen, 2004) or the coincidence of bAPs and local membrane depolarization (Svoboda et al., 1999). Direct investigation of these dendrites in vitro verified that the dendritic spikes in L2/3PCs were more modest in amplitude and duration. Furthermore, Ca²⁺ spikes in L2/3PCs’ dendrites did not initiate somatic bursting as observed in L5PCs (Larkum et al., 2007; Ledergerber and Larkum, 2012).

Despite the differences in the biochemical environment and electrical activity in the intact brain versus brain slices, dendritic spikes recorded in vivo and in vitro were surprisingly similar (Amitai et al., 1993; Larkum and Zhu, 2002). Consequently, experiments in brain slices that are too difficult to perform in vivo have been indispensable for studies characterizing dendritic spikes. For example, in vitro electrical recordings performed simultaneously at the soma and dendrite in L5PCs (Larkum et al., 2001, 1999) revealed that when a somatic burst firing crosses a critical frequency, it triggers a dendritic Ca²⁺ spike (Fig. 1B, I). Likewise, high-frequency bursts triggered Ca²⁺ spikes in the basal (Kampa and Stuart, 2006; Fig. 1E) and oblique (Castañares et al., 2020) dendrites of L5PCs. L2/3PCs (Larkum et al., 2007) and layer 6 PCs (L6PCs; Ledergerber and Larkum, 2010) also responded to somatic bursts with regenerative Ca²⁺ currents but with smaller amplitudes than in L5PCs. Additionally, current injection directly into the distal apical trunk of L6PCs triggered a small but visible Ca²⁺ spike (Ledergerber and Larkum, 2010). In contrast to neurons in other layers, the contribution of L6PCs dendritic spikes for synaptic integration and computation in vivo is still a mystery (Thomson, 2010).

As in the neocortex, dendrites of PCs in the hippocampus are rich in dendritic regenerative Ca²⁺ events (Schwartzkroin and Slawsky, 1977; Wong et al., 1979). In vivo, spontaneous dendritic bursts containing fast Na⁺ spikes and broader Ca²⁺ spikes were recorded in the apical dendrites of CA1 PCs in rats (Fig. 2E; Kamondi et al., 1998). These dendritic spikes occurred during sharp-wave ripples suggesting that they were facilitated by network activity. Accordingly, evoking these
Fig. 1. The pyramidal neurons of layer 5 are decorated with dendritic spikes. (A) Ca$^{2+}$ spike was triggered in the trunk and recorded at the tuft (dashed line). Ca$^{2+}$ plateau potential (solid line) recorded at the tuft was triggered by pairing current injection in the trunk and the tuft (Xu et al., 2012). These Ca$^{2+}$ spikes were independent of synaptic inputs. (B) Intracellular current injection above (solid line) and below (dashed line) threshold for a Ca$^{2+}$ spike in the mid-distal parts of the apical trunk (Larkum et al., 2001). (C) Na$^{+}$ spikelet (solid line; subthreshold response in dashed line) in the proximal apical trunk triggered by an extracellular electrode in L2/3 (Stuart et al., 1997). (D) Na$^{+}$ spikelet (solid line; subthreshold response in dashed line) in a basal dendritic branch (Nevian et al., 2007) triggered by intracellular current injection. (E) The Ca$^{2+}$ spike enhances the amplitude of the bAP (Kampa and Stuart, 2006) in the distal (solid green line) but not in the proximal (dashed line) basal dendrites. (F) Back-propagating action potential activated Ca$^{2+}$ (BAC) firing: a burst of axosomatic action potentials (solid line) and a dendritic spike (dashed line) triggered by paired current injections in the dendrite and soma (Larkum et al., 1999). (G) Voltage imaging of plateau potentials in the basal dendrites triggered by brief iontophoresis of glutamate near the dendrite (Milojkovic et al., 2007). (H) NMDA spike (solid line; subthreshold response in dashed line) in the basal dendrites (Nevian et al., 2007). (I) Dendritic spike evoked by a somatic burst of APs firing above (solid line) and below (dashed line) a critical frequency (Larkum et al., 1999). (J) NMDA spike (solid line; subthreshold response in dashed line) in the apical dendrite (Larkum et al., 2009). (K) Plateau potentials (solid line; subthreshold response in dashed line) evoked by glutamate uncaging (Larkum et al., 2009). These spikes were independent of voltage-gated Ca$^{2+}$ channels. Bottom: Experimental schematic key for A–K. The position of the pipette indicates the recording/stimulating site. The vertical scale bar applies to all traces but E and G. The horizontal scale bar applies to all traces but G.
spikes in vitro at the distal dendrites of CA1 PCs triggered bursts of APs at the soma (Benardo et al., 1982; Wong and Stewart, 1992; Golding et al., 1999). Recently, Mago et al. (2021) showed in acute slice preparations that CA3 but not CA1 PCs fire different types of dendritic Ca\(^{2+}\) spikes. One was a fast spike that spread into a subtree of the dendrite and triggered only single APs at the soma. This spike was reminiscent of the Ca\(^{2+}\) spike found in human layer 2/3 neurons (see section: Dendritic spikes in humans). The other spike (called “afterdepolarization”) was slower, had smaller amplitude, and resulted from the coincidence of bAP and dendritic depolarization. In contrast to the fast spike, the afterdepolarization spread into the entire dendrite and produced a burst of somatic action potentials.

Calcium imaging in behaving animals revealed that in some cases, dendritic spikes were confined to the apical dendrite (Voigts and Harnett, 2020) whereas, in other cases, they were correlated with somatic activity (Peters et al., 2017; Beaulieu-Laroche et al., 2019; Francioni et al., 2019; Kerlin et al., 2019). Suzuki and Larkum (2020) reported that general anesthesia decoupled the soma from the apical dendrite in the somatosensory cortex and, consequently, dramatically reduced the impact of Ca\(^{2+}\) spikes on the cell body. The somato-dendritic coupling is not fixed but can be learned, as demonstrated by Doron et al. (2020) in L5PCs of the primary somatosensory cortex. Specifically, Doron et al. rewarded rodents that detected electrical stimuli delivered directly to the soma with saccharin water. They found that learning to associate the artificial stimulus and the reward strengthened synaptic inputs to the distal dendrites, enhanced the dendritic Ca\(^{2+}\) spikes, and resulted in an increase in somatic burst firing. This study confirmed a mechanism previously suggested to operate in these cells (Larkum et al., 1999; Larkum, 2013); namely, that coupling of feed-
back (i.e., inputs arriving at the distal dendrites) and feed forward (i.e., inputs arriving at the proximal dendrites) information triggers Ca\(^{2+}\) spikes and somatic bursts (BAC firing; Fig. 1F; Larkum et al., 1999; Takahashi and Magee, 2009). BAC firing may underlay a frequently observed coupling of events at the soma and the dendrites in the behaving animals (Francioni and Harnett, 2021). Interestingly, BAC firing is not unique to L5PCs but was also shown in vivo in hippocampal pyramidal cells (Bittner et al., 2015).

Xu and colleagues (2012) recorded a longer-lasting Ca\(^{2+}\) plateau potential (as compared with the dendritic Ca\(^{2+}\) spike; Fig. 2A) in L5PCs of the barrel cortex in vivo. The Ca\(^{2+}\) plateau potentials were evoked by correlated sensory and motor inputs that converged onto different subregions of the same apical dendrite. Xu et al. (2012) recreated the plateau potentials in vitro in the absence of synaptic inputs by pairing a dendritic spike at the apical trunk with depolarization at the tuft (Fig. 1A). Despite their relatively long duration (~200 ms), these plateau potentials were different from the synaptic plateau potential (Fig. 1G, K) that depends on the activation of NMDA receptors (Major et al., 2008; Antic et al., 2010).

**NA\(^{+}\) SPIKES/SPIKELETS**

“Fast prepotentials” (Spencer and Kandel, 1961), dendritic Na\(^{+}\) spikes or spikelets (used here interchangeably), are brief dendritic spikes comparable to somatic APs in duration but smaller in amplitude, that have been shown to play a role in dendritic integration, synaptic plasticity (Golding et al., 2002; Kim et al., 2018) and intrinsic plasticity of dendritic excitability (Hoffman and Johnston, 1999; Frick and Johnston, 2005; Sjöström et al., 2003). Due to their steep rising phase, dendritic spikelets in the basal dendrites “sharpened” the synaptic potentials and improved the output spikes’ precision in hippocampal CA1 neurons (Ariav et al., 2003). In the apical dendrites of the same neurons, Na\(^{+}\) spikelets caused depolarizations of variable amplitude that propagated to the soma rather unreliably (Golding and Spruston, 1998). The effect of local changes in dendritic membrane potential on the spike amplitude and propagation may explain the apparent unreliability (Gasparini, 2004). Specifically, supralinear summation of synaptic inputs in a particular branch or bAPs in the entire dendrite inactivated the Na\(^{+}\) channels and dampened the dendritic spike for a short time window of milliseconds to seconds. In contrast, input summation in the linear range did not have the same effect. (Mickus et al., 1999; Remy et al., 2009). Additionally, pairing supralinear inputs and a burst of bAPs resulted in long-term potentiation at the branch firing these spikes (Losonczy et al., 2008). Together, these studies demonstrate a complex short and long term modulation of Na\(^{+}\) spikes by multiple biophysical factors throughout the different dendritic subdomains of CA1 neurons, i.e., the apical (Golding and Spruston, 1998; Mickus et al., 1999) basal (Remy et al., 2009) and oblique (Losonczy and Magee, 2006) regions.

As in CA1, neurons in other subregions of the hippocampus, namely, CA2 (Sun et al., 2014), CA3 (Kim et al., 2012), and the dentate gyrus (Kim et al., 2018) fire dendritic Na\(^{+}\) spikes with different degrees of excitability. The dendrites of the dentate gyrus granule cells appear less excitable than other hippocampal PCs, which is possibly the reason for their characteristic sparse firing in vivo (Piatti et al., 2013; Pofahl et al., 2021). Triggering a dendritic spike required current injection into the dendrite or high-frequency activation of the perforant path synapses (Kim et al., 2018), whereas more subtle inputs such as uncaging glutamate onto a single branch was insufficient (Krueppl et al., 2011). Under similar conditions, uncaging glutamate onto single branches of CA1 PCs readily evoked dendritic Na\(^{+}\) spikes (Krueppl et al., 2011). Compared to CA1 PCs, Na\(^{+}\) channels density was high in the distal dendrites of CA3 PCs (Kim et al., 2012). Additionally, the Na\(^{+}\)-to-K\(^{+}\) conductance ratio was also high in these neurons (Kim et al., 2012). Consequently, dendritic spike probability in CA3 PCs was higher than in CA1 PCs.

The CA2 tuft dendrite comprises long branches that fan out from a short main apical trunk. Sun et al. (2014) investigated the effect of dendritic morphology on the coupling between the distal dendritic input and the axonal output. They found that CA2 PCs’ dendritic geometry facilitates the forward propagation of Na\(^{+}\) spikes from distal regions to the soma and axon (see also Vetter et al., 2001). Consequently, synaptic inputs from the entorhinal cortex onto CA2 PCs triggered spikes in multiple tuft branches that summated at the short trunk very close to the soma and effectively enhanced the axosomatic output (Sun et al., 2014).

**In vitro** spikelets could be evoked in pyramidal cells in all cortical layers but layer 4 (excluding the immature electrically coupled layer 4 neurons; Valiullina et al., 2016), in L2/3PCs at the apical dendrites (Larkum et al., 2007), in L5PCs at the basal (Nevian et al., 2007) and the apical dendrites (Stuart et al., 1997; Fig. 1C, D), and L6PCs apical dendrites (Ledergerber and Larkum, 2010). In agreement with these results, Crochet et al. (2004) recorded from the somata of PCs in the cat cortex in vivo and found spikelets in all cortical layers but layer 4. Interestingly, Kalmbach et al. (2017) found that previous inputs to the apical trunk of L5PCs in the prefrontal cortex were decisive in determining whether subsequent Na\(^{+}\) spikes triggered axosomatic APs.

Several studies demonstrated recently that dendritic Na\(^{+}\) spikes are an integral part of neural activity in awake, behaving animals. In the visual cortex, dendritic spikelets enhanced the orientation tuning of L2/3PCs in lightly anesthetized and awake mice (Smith et al., 2013; see also Goetz et al., 2021; Fig. 2J). Because spikelets are ubiquitous, particularly in principal cells, it is not always straightforward to distinguish between spikelets initiated in the dendrite and those originating from axonal APs or ephaptic coupling (Chorev and Brecht, 2012; Michalikova et al., 2019). Smith and colleagues verified that these spikes originated in the dendrites rather than back-propagated from the soma with simultaneous in vivo dendritic recording and imaging of the cell body.
(Smith et al., 2013; Fig. 2J). Moore and colleagues developed a unique technique for quasi-intracellular recording using tetrodes, which enabled them to record the dendritic potential for hours in freely behaving mice (Moore et al., 2017; Fig. 2K). The dendritic spike rate they recorded in the posterior parietal cortex was modulated by the animal movement direction (in an egocentric frame of reference) but not by movement anticipation (cf. Whitlock et al., 2012). The direct observations into dendritic electrical activity, as done in the few studies mentioned above, mark a beginning of a better understanding of how dendrites transform input into output in vivo.

NMDA SPIKES AND NMDAR–DEPENDENT PLATEAU POTENTIALS

In contrast to intrinsic Ca\(^{2+}\) and Na\(^{+}\) dendritic spikes that depend on voltage-gated ion channels and can be readily evoked by membrane depolarization (e.g., direct current injections), synaptic spikes are mediated by NMDA receptors (NMDARs) and require both the presence of neurotransmitter and local membrane depolarization (Antic et al., 2010; Major et al., 2013). One of these receptors’ unique characteristics is the nonlinear dependence of the current on the membrane voltage (MacDonald and Wojtowicz, 1982). The nonlinear behavior is mediated by Mg\(^{2+}\) block (Mayer et al., 1984), which was quantitatively characterized by Jahr and Stevens (1990a, 1990b). The consequences of the mysterious properties of NMDAR were finally revealed by Schiller et al. (2000), showing that activating synapses in L5 cortical PCs can trigger local synaptic spikes with Ca\(^{2+}\) transients in the corresponding branch (Fig. 1H, J). Initiation of the spikes required cooperativity of spatially clustered inputs (Larkum and Nevian, 2008; Iacaruso et al., 2017; Kumar et al., 2018; Kerlin et al., 2019) since typically, the potential caused by a single synapse is insufficient to cross the local threshold for removing the Mg\(^{2+}\)-mediated receptor block. Yang et al. (2014) described how the spatial organization of the synaptic inputs affected the spiking of hippocampal CA1 dendrites (see also Wei et al., 2001). Yang and colleagues triggered NMDA spikes by activating clustered inputs on single branches at any dendritic subregion. However, inputs distributed across multiple branches could trigger dendritic spikes only when delivered to the apical tuft. These spikes were mediated by voltage-gated Ca\(^{2+}\) channels.

In the neocortex, excitatory neurons in all layers fire NMDA spikes. In the somatosensory cortex L2/3 PCs, NMDA spikes occurred during sensory processing (Fig. 2I; Palmer et al., 2014) and increased the firing at the soma. Long-term potentiation due to whisker stimulation in L2/3 PCs synapses (Gambino et al., 2014) required NMDAR-dependent plateau potentials (Fig. 2H) but not somatic APs. An increase in the frequency of the plateau potentials was associated with the plasticity of somatosensory maps (Pagès et al., 2021). These plateau potentials were similar to the NMDAR-dependent dendritic plateau potential observed in vitro (Fig. 1G, K; Milojkovic et al., 2007; Major et al., 2008; Larkum et al., 2009; Antic et al., 2010). In layer 4 of the barrel cortex, NMDA spikes enhanced the tuning of spiny stellate cell to the angle of whisker deflection (Lavzin et al., 2012; Fig. 2G). The excitatory neurons in layer 4 express the NMDAR subunit NR2C/D, which is less affected by the Mg\(^{2+}\) block than the NR2A/B subunits typical to other cortical layers (Fleidervish et al., 1998; Binshok et al., 2006). This particular composition of subunits lowered the threshold for NMDA spikes and sustained their activity at the resting membrane potential (Fleidervish et al., 1998; Traub et al., 2020).

A number of studies looked at the properties of NMDA spikes in the different dendritic subdomains of L5 PCs in vitro (Larkum et al., 2009; Antic et al., 2010; Major et al., 2013). Surprisingly, in vivo characterization of these spikes is yet to be achieved. Nevertheless, NMDARs were implicated with the initiation of Ca\(^{2+}\) spikes during motor task learning (Cichon and Gan, 2015). The authors of the latter study reported that different tasks evoked NMDAR-dependent Ca\(^{2+}\) spikes on different dendritic branches. Typically, when the dendrite is bombarded with synaptic inputs in vivo, NMDA spikes are initiated at multiple locations (Lavzin et al., 2012; Grienberger et al., 2014; Palmer et al., 2014). Consequently, the mapping of dendritic spikes onto specific branches or a combination of branches as observed in L5 PCs has interesting consequences for learning and memory in dendritic structures (Mel, 1992; Rhodes, 2008). NMDA spikes are also present in layer 6 PCs (Ledergerber and Larkum, 2010), but no studies have characterized them in vivo.

In the hippocampus, NMDAR dependent plateau potentials amplified coincidental inputs arriving from the entorhinal cortex and CA3 onto CA1 PCs (Tsay et al., 2007; Takahashi and Magee, 2009). Studying CA1 PCs in vivo, Grienberger and colleagues (2014) showed large multi-branch Ca\(^{2+}\) transients in the basal and proximal apical dendrite (Fig. 2F) that depended on both NMDA receptors and voltage-gated Ca\(^{2+}\) channels. These events correspond to the spontaneous firing of somatic complex action potentials bursts (i.e., prolonged somatic bursts firing riding on a large depolarizing envelope; Kandel and Spencer, 1961) and were able to modify and form new place fields (Bittner et al., 2015). These results are in agreement with in vitro studies showing that NMDA spikes are necessary for long term potentiation (e.g., Brandalise et al., 2016; Kumar et al., 2021; see also Lodge et al., 2019).

NMDA spikes can vary in amplitude and kinetics, thus leading to diversity of input integration properties even in the same dendrite (Makara and Magee, 2013). The presence of NMDARs in excitatory neurons does not necessarily lead to the firing of NMDA spikes. This was demonstrated in the granule cells of the dentate gyrus, where NMDARs were able, at most, to linearize synaptic integration (Kruepvel et al., 2011). The underlying mechanisms for the NMDA receptor activity are fundamental to synaptic integration. Our understanding of these mechanisms and their function has dramatically improved in the last two decades (Augusto and Gambino, 2019). However, the behavior of NMDARs during high conductance state in vivo (Destexhe et al., 2003) has only been studied.
through modeling (Rhodes, 2006; Major et al., 2013; Doron et al., 2017) and awaits experimental validation.

**SPINE SPIKES**

Since the idea of excitable spines was proposed (Diamond and Yasargil, 1969; Diamond et al., 1969; Jack et al., 1975) it has inspired theoretical and modeling studies (Jack et al., 1975; Miller et al., 1985; Perkel and Perkel, 1985; Segev and Rall, 1988). These studies have viewed the spine as a small electrical compartment endowed with voltage-gated fast Na⁺ (or possibly Ca²⁺) channels capable of firing spikes when the local voltage threshold was crossed (Koch and Zador, 1993). Despite the lack of experimental evidence at the time, these theoretical spikes were intriguing since they could have far-reaching implications for boosting the synaptic efficacy, plasticity, local impact of inhibition, and even cooperativity between nearby synapses.

From a theoretical perspective, dendritic spines are favorable sites for the initiation of intrinsic spikes. The small bulbous head of the spine has high input resistance such that only a small number of channels are needed to generate a spike. If the spine stem is sufficiently narrow (Tennesen et al., 2014) it can create the necessary electrical isolation from the dendritic branch and confines the spike to the spine head (Kwon et al., 2017). Given the right circumstances (e.g., spine density and stem width), a spine spike can activate nearby spines and propagate throughout the dendrite via a chain reaction (Baer and Rinzel, 1991).

Attempts to find spine Na⁺ spikes with voltage and Na⁺ imaging (Palmer and Stuart, 2009; Popovic et al., 2015) and electrical recordings in spines (Jayant et al., 2016) were unsuccessful. Na⁺ ions predominantly entered the spines through AMPA receptors rather than via voltage-gated Na⁺ channels (Miyazaki and Ross, 2017). In cases where Na⁺ channels were expressed on the spine membrane, they did not evoke a spike, but instead, they increased the amplitude of the excitatory potentials (Araya et al., 2007; Bloodgood and Sabatini, 2007) and linearized their summation (which otherwise would sum sublinearly; Araya et al., 2006). These studies indicated that cortical dendrites do not fire Na⁺ spikes at the level of a single spine. Even so, the spine spike envisioned by early theoretical work is comparable to the NMDA spike as both are evoked at the level of the synapse. The distinction predominantly arises from the fact that the NMDAR is both a ligand and voltage-gated channel, and therefore, it requires presynaptic activity. Further, NMDA spike is typically not evoked by individual synapses as the spine spikes were described, but rather by clusters of synapses aided by extrasynaptic NMDAR (Chalifoux and Carter, 2011) expressed on the dendritic branches.

Despite the discrepancies between NMDA spikes and spine spikes, it is clear that the theoretical insights turned out to be very useful in guiding the subsequent experimental work (Segev and Rall, 1998). Indeed, the predictions of the synaptic spike’s role in input amplification (Noguchi et al., 2005; Harnett et al., 2012), inhibition (Chiu et al., 2013; Marlin and Carter, 2014; Doron et al., 2017), plasticity, and cooperativity were confirmed experimentally.

**DENDRITIC SPIKES IN INTERNEURONS**

GABAergic interneurons (INs) in the neocortex and hippocampus consist of about 10–20% of the total cortical neuronal population, but they are far more diverse than principal cells (Markram et al., 2004; Klausberger and Somogyi, 2008; Tremblay et al., 2016). Their thin dendrites make them an ultimate challenge for dendritic patch-clamp experiments that only a handful of laboratories have successfully overcome. Accordingly, dendritic integration in the INs of the neocortex and hippocampus is less understood than in principal neurons (Hu et al., 2014; Hu and Vervaeke, 2018). Using Ca²⁺ imaging as an alternative to dendritic patch clamp can be misleading; the various Ca²⁺ signals in the dendrites (Goldberg and Yuste, 2005; Topolnik and Camiré, 2019) do not always correlate with voltage signals (Tran-Van-Minh et al., 2016; Camiré et al., 2018; Sancho and Bloodgood, 2018) and therefore, nonlinearities in the Ca²⁺ transients might not reflect dendritic spikes. For example, in cortical INs, the summation of EPSPs remained linear or sub-linear even when the synaptic stimulation evoked supralinear calcium signals (Hu and Vervaeke, 2018; Sancho and Bloodgood, 2018). The handful of studies that managed to perform dual somato-dendritic recordings in cortical and hippocampal interneurons (Martina, 2000; Kaiser et al., 2001; Hu et al., 2010; Nörenberg et al., 2010; Vervaeke et al., 2012; Connelly et al., 2015; Szoboszlay et al., 2016) have not reported intrinsic spikes initiated in the dendrites (excluding the AP initiation in the axon-bearing dendrites described in Martina, 2000). Therefore, it was somewhat surprising that Katona et al. (2011) demonstrated that hippocampal INs of CA1 fire dendritic NMDA spikes (Fig. 3B). Specifically, glutamate uncaging onto clusters of synapses in dendrite-targeting stratum radiatum INs resulted in supralinear integration at the soma and a corresponding calcium transient at the dendrites. NMDARs were responsible for most regenerative currents, whereas voltage-gated sodium or calcium channels had little to no effect on these spikes.

So far, the dendrites of parvalbumin-expressing (PV) neurons have been described as passive cables. bAPs hardly invade into their distal dendrite (Aponte et al., 2008; Camire and Topolnik, 2014; Casale et al., 2015; Evstratova et al., 2011; Goldberg et al., 2003a) due to the high expression of K⁺ channels in the dendrites (Hu et al., 2010). Therefore, when Chiovini et al. (2010) found that Ca²⁺ transients during sharp-wave ripples (SWR) were mildly attenuated in PV INs’ apical dendrite, they hypothesized that dendritic regenerative behavior might be at play during particular network states (i.e., SWR).

Following this lead, Chiovini et al. (2014) activated a cluster of synapses on a small apical dendritic segment (~20 μm) of stratum pyramidale PV INs and discovered that EPSPs summed supralinearly (Fig. 3A). Unlike in excitatory neurons, NMDARs had a minor contribution
to the EPSP’s amplitude relative to Ca\(^{2+}\)-permeable and nonpermeable AMPARs (Booker and Wyllie, 2021; Camire and Topolnik, 2014; Chiovini et al., 2014; Goldberg et al., 2003b; Topolnik and Camiré, 2019). The dendritic spike induced supralinear calcium signals through subsequent activation of L-type Ca\(^{2+}\) channels. Additionally, fast membrane oscillations in the SWR frequencies (Fig. 3A) were superimposed with the dendritic spike. These oscillations depended on voltage-gated Na\(^+\) channels and controlled the phase of the axosomatic AP within the SWR.

Studying the same population of interneurons, Cornford et al. (2019) recorded a supralinear summation of EPSPs following glutamate uncaging in the basal but not the apical dendrites. In contrast to the findings of Chiovini et al. (2014), this supralinear integration depended on the NMDARs which was consistent with the higher ratio of NMDARs/AMPARs in basal versus apical dendrites (Le Roux et al., 2013). The differences between the two studies may be related to the high efficiency of the caged glutamate compound (DNI-glutamate) used by the two studies may be related to the high efficiency of the caged glutamate compound (DNI-glutamate) used by Chiovini et al. (2014) which possibly emulated the intense dendritic activity present during SWR.

The synaptic spikes discovered in different populations of CA1 INs (Katona et al., 2011; Chiovini et al., 2014; Cornford et al., 2019) are typically weak compared to PCs. This weaker excitability in some INs was proposed to underlie their broad tuning (Hu and Vervaeke, 2018) as compared with the sharply tuned principal cells (Sohya et al., 2007; Kerlin et al., 2010; Ma et al., 2010; Hofer et al., 2011; Lavzin et al., 2012; Smith et al., 2013). Nevertheless, the diversity of interneurons, their heterogeneous population of glutamate receptors (Nyiri et al., 2003; Wang and Gao, 2009; Matta et al., 2013; Akgöl and McBain, 2016; Sancho and Bloodgood, 2018; Booker and Wyllie, 2021), their electrical synapses (Galarreta and Hestrin, 2001; Vervaeke et al., 2012; Trenholm et al., 2014; Rudolph et al., 2015), and modes of activity (Goldberg et al., 2004; Chiovini et al., 2010) may provide the basis for challenging the conventional portrayal of the INs’ dendrites as mostly passive elements (Tzilivaki et al., 2019). At present, in vivo dendritic integration in INs is poorly understood (Chen et al., 2013; Ding et al., 2017; Francavilla et al., 2019).

### LOW-THRESHOLD SPIKE

In the cortex, low-threshold spiking cells are considered as a subclass of INs, distinct from the fast-spiking INs (Kawaguchi, 1993; Kawaguchi and Kubota, 1997; Bacci et al., 2003). The low–threshold spike (LTS; Fig. 3C) is a slow and broad depolarization (> 100 ms; Goldberg et al., 2004) that results in an axosomatic burst of APs (Thomson, 1988). It is mediated by T-type Ca\(^{2+}\) channels and does not require synaptic NMDARs or Na\(^+\) channels (Goldberg et al., 2004). In contrast to other spikes, LTS can be triggered following a hyperpolarizing current due to a strong repolarization overshoot (“rebound”). The LTS has been described in many types of neurons and several brain regions such as the cerebellar inferior olivary nucleus (Llinás and Yarom, 1981), thalamus (Connelly et al., 2015), and other subcortical regions (Burghas and Aghajanian, 1987; Nakanishi et al., 1987; Kawaguchi, 1993). Although T-type Ca\(^{2+}\) channels are expressed at the soma and throughout the dendritic tree (Goldberg et al., 2004), LTSs are triggered only when the threshold is crossed at the soma (demonstrated in thalamic neurons; Connelly et al., 2015). This results in a unique mechanism that ensures an all-or-none global dendritic spike (Fig. 3C).

### DENDRITIC SPIKES IN HUMANS

Recently, the activity of a population of cortical dendrites was presumably recorded using intracranial laminar electrodes in epileptic patients (Leszczynski et al., 2020). Despite such recent advances in human brain electrophysiology and imaging (Dumoulin et al., 2018; Lawrence et al., 2017), resolving single dendritic recordings in vivo is still impossible in humans. This imposes a notable limitation on our ability to study dendrites in the intact human brain. The studies discussed in this review demonstrate that, more often than not, there has been a striking similarity between in vivo and in vitro experimental results. Therefore, in vitro experiments using surgically removed human brain tissue from patients (Kramvis...
et al., 2018) dominate our understanding of dendritic computation in humans. Direct recording of dendritic spikes in human cortical tissue was achieved only recently. These recordings (Fig. 4B–C) were mostly performed in brain tissue resected from temporal lobe epileptic patients. Consequently, several interesting dissimilarities between humans and rodents were revealed. From a morphological standpoint, the dendrites of cortical L2/3PCs in humans are up to two- or threefold longer than in rodents (Fig. 4A; Deitche et al., 2017). Even more important than their physical length (~1–2 mm), dendrites of L2/3PCs (Gidon et al., 2020) and L5PCs (Beaulieu-Laroche et al., 2018) are electrotonically long. Namely, voltage attenuation is so massive that synaptic inputs at the distal apical tufts had negligible to no impact on the neuron’s output. Furthermore, in the living brain, the dendrites are bombarded with synaptic inputs and thus, become electrically leakier, which may lead to even steeper voltage attenuation (Borg-Graham et al., 1998; London and Segev, 2001; Destexhe et al., 2003).

Backpropagating APs (Stuart and Sakmann, 1994), which are regarded as a signaling mechanism for Hebbian plasticity (Markram et al., 1997), are also attenuated at the distal dendrites (Beaulieu-Laroche et al., 2018; Gidon et al., 2020). The limited reach of the bAP in the long dendrites of human neurons means that Hebbian learning would be restricted to a small “Hebbian bubble” consisting mainly of the proximal dendritic regions (Thome et al., 2014). Learning outside of the Hebbian bubble (Goldberg et al., 2002; Gidon and Segev, 2009) would depend on local dendritic plasticity rules (Holthoff et al., 2004; Remy and Spruston, 2007). Therefore, the question remaining is whether distal human synapses are effectively disconnected from the neuronal output? Thicker dendritic branches, such as found in CA1 pyramidal neurons of the human hippocampus compared to mice (Benavides-Piccione et al., 2020), could make neurons electrically more compact and, to some degree, alleviate the problem. Addi-

Fig. 4. Dendritic spikes of human and rat neocortex. (A1) Human and rat brains approximately to the same scale (modified from Univ. Wisconsin-Madison brain collection, brainmuseum.org) (A2) Rat deep layer 3 PCs (somatosensory cortex). (A3) Human deep layer 3 PC (temporal cortex). (B1) Dendritic spikes (putative Ca²⁺ spike) in rat somatosensory cortex. (Larkum et al., 2007). (B2) Dendritic Ca²⁺ spikes (or dCaAPs) in layer 2/3 in the human temporal cortex (Gidon et al., 2020). (C) Ca²⁺ spike in layer 5 apical dendrite in rat (C1; Beaulieu-Laroche et al., 2018) and human (C2; Kalmbach et al., 2021; C3; Beaulieu-Laroche et al., 2018) temporal cortex. Step current was injected into the apical dendrites for B1,2 and C1–3. Scale bar for B2 and C1–3 as in B1 (D1) NMDA spike in human layer 2/3 PC basal dendrite (Testa-silva et al., 2021) triggered by glutamate iontophoresis. (D2) EPSPs’ amplitude at the soma against the iontophoretic current. (E1) NMDA spike in layer 5 PC basal dendrite of a rat triggered by glutamate uncaging (Schiller et al., 2000; scale bar as in D1) (E2) EPSP amplitude as a function of the laser intensity.
tionally, boosting the impact of distal synaptic inputs with dendritic spikes seems to be a natural solution for this problem (for review, see Poirazi and Papoutsis, 2020). Kalmbach et al. (2021) found a formidable Ca\(^{2+}\) spike (amplitude of \(~60\) mV) that lasted hundreds of milliseconds in the apical dendrites of human cortical L5PCs (Fig. 4C). For the same region and neuronal class, however, Beaulieu-Laroche et al. (2021, 2019) observed much weaker dendritic spikes, even when compared to rodents (Fig. 4C), with only a minor influence on the output. Further work is needed to clarify the discrepancies between these two studies.

In human L2/3PCs, Gidon et al. (2020) observed fast (half width of \(~4\) ms) dendritic calcium spikes (dendritic calcium action potentials or dCaAPs; Fig. 4B). These spikes did not cause somatic bursts; instead, a single dendritic spike could trigger at most a single axosomatic spike, in some cases with a delay of \(~50\) ms, which added a temporal component to the boosting effect. The decrease of dCaAPs’ amplitude with the stimulus intensity (Gidon et al., 2020) resulted in a non-monotonic activation function that can serve as a biological mechanism for solving the “exclusive-OR problem” (Minsky, 1969) in single cells. Solving the exclusive-OR (XOR) operation requires a multi-layer network (Werbos, 1975) and is considered a challenge for biological neurons (Zador et al., 1992; Fromherz and Gaede, 1993; Costa and Sjöström, 2011; Cazé et al., 2013; Tran-Van-Minh et al., 2015).

Recently, Magó et al. (2021) found that dendrites of hippocampal CA3 PCs in vitro fire fast Ca\(^{2+}\) spikes with similar waveform and behavior as the dCaAPs. These findings may indicate that dendritic spikes with non-monotonic activation functions are widespread across different species and brain regions.

In addition to the dendritic intrinsic spiking, human L2/3PCs also express NMDA receptors (Scherzer et al., 1998) and fire synaptic NMDA spikes (Eyal et al., 2018; Testa-Silva et al., 2021; Fig. 4D). Testa-Silva and colleagues (2021) probed the synaptic excitability of these cells’ basal dendrites with both glutamate iontophoresis and extracellular electrical stimulations. Only a small subset of these stimulations triggered NMDA spikes in the human cells (Fig. 4D), whereas most attempts in the homolog mice cells readily evoked NMDA spikes (Testa-Silva et al., 2021; Fig. 4E). It is still unclear whether, generally, the dendrites of human pyramidal neurons are more decorated with spikes than their counterparts in rodents or other species. Future studies are needed to answer this question and clarify the relevance of the answer at the network level.

DENDRITIC SPIKES’ PROPERTIES DEPEND ON THE CORTICAL AREA

The properties of dendritic spikes can vary considerably among cell types, within a brain area and from one brain area to another. Thick-tufted L5PCs’ dendrites exhibited modest Ca\(^{2+}\) electrogenesis in the prefrontal cortex and the anterior cingulate cortex (Marti Mengual et al., 2020; Santello and Nevian, 2015) compared to the somatosensory cortex (Gulledge and Stuart, 2003; Kalmbach et al., 2017; Seamsans et al., 1997) whereas dendritic Na\(^+\) spikes were more consistent among these regions. By modeling their experimental results, Marti Mengual et al. (2020) showed that boosting distal inputs was unnecessary in the anterior cingulate cortex L5PCs because the dendrites were both physically and electrophysiologically shorter than in the corresponding somatosensory cortex L5PCs.

Fletcher and Williams (2019) found that dendrites exhibit a gradient in their spiking properties even within the same brain region. Specifically, the size of thick-tufted L5PC dendrites gradually increased between the caudal and rostral regions of the primary visual cortex. Rostral PCs with their long dendrites fired high amplitude Ca\(^{2+}\) spikes, whereas the shorter caudal PC’s dendrites did not (Fig. 5A, B). Variations in the dendritic electrophysiological properties were also observed in hippocampal CA1 PCs across the ventrodorsal axis. These electrophysiological properties were correlated with a gradient in morphology (Malik et al., 2016; Fig. 5C, D) and gene expression (Cembrowski et al., 2016).

CONCLUSION AND FURTHER QUESTIONS

We aimed to deliver a comprehensive and up-to-date summary of all known dendritic spikes recorded in the mammalian cortex and surveyed Na\(^+\) spikes/spikelets, Ca\(^{2+}\) spikes, low–threshold spikes, Ca\(^{2+}\) plateau-potentials, NMDA spikes, plateau potentials, and NMDA Receptor (NMDAR)-dependent Ca\(^{2+}\) spikes. An accurate picture of dendritic integration and computation must comprise the exquisite details of the different dendritic spikes described here and interactions between them (Larkum et al., 2009; Görski et al., 2018).

Ca\(^{2+}\) imaging, specifically in the behaving animal, had a central role in advancing the field of dendritic computation to where it is today. Paradoxically, because Ca\(^{2+}\) transients are a proxy to the membrane potential, Ca\(^{2+}\) imaging obscures the precise sub- and supra-threshold dendritic activity accessible only to electrical recordings (Stuyt et al., 2021). The direct electrical recordings of dendritic spikes from behaving animals (Fig. 2) are essential for understanding the neurons as an input–output device (Hay et al., 2016), but they are challenging and not widespread. A solution to this problem may emerge from advances in the development of voltage indicators. Notably, the new generation of genetically encoded and chemogenetic hybrid voltage indicators (Abdel fattah et al., 2019; Adam et al., 2019; Piatkevich et al., 2019; Villette et al., 2019) allow recordings from the fine-dendritic branches in vivo (for review, see Knöpfel and
Song, 2019). Voltage imaging has promising prospects for the future (e.g., Roome and Kuhn, 2020, 2018) despite its minor contribution to the study of dendritic spikes so far (Kulkarni and Miller, 2017).

The diversity of cortical neurons is remarkable (e.g., Bakken et al., 2021; Barz et al., 2021; Helton et al., 2019; Kim et al., 2015; Oswald et al., 2013). Markram et al. (2015) estimated at least 207 subtypes in the rodent somatosensory cortex. As in the case of other cellular properties, it is not unlikely that dendritic spikes with different properties are associated with specific neuron subtypes. For example, classically, the excitatory neurons of L5 are subdivided (at least) into two types: the intratelecephalic (IT) slender tufted neurons and the thick tufted pyramidal tract (PT) neurons (Harris and Shepherd, 2015). PT and IT neurons are sensitive to different spatial and temporal input patterns impinging on their dendrites (Dembrow et al., 2015). Takahashi et al. (2020) enhanced perception of a weak (near-threshold) whisker stimuli in mice by optogenetically evoking dendritic Ca$^{2+}$ currents in PT neurons of the mouse barrel cortex. They could not obtain a similar enhancement with IT neurons. Somatic bursts triggered by the dendritic Ca$^{2+}$ spikes (Larkum et al., 1999; Williams and Stuart, 1999) are possibly the reason for the enhanced mice perception. In support of these results, De Kock et al. (2021) showed that when a mouse whisker touches an object, PT neurons but not IT neurons significantly increase bursts firing at the soma. Furthermore, Doron et al. (2020) showed that after learning, burst firing is more salient than regular firing in single presumed PT neurons. The extent to which the properties of dendritic spikes are cell subtype-specific, as in the case of PT and IT neurons, particularly given the diversity of neuronal classes and dendritic spikes, raises an interesting question regarding the universality of computation they perform. Namely, are dendritic spikes typically tailored to satisfy a particular computation in each cell subtype (Oesch et al., 2005; cf. Sivyer and Williams, 2013) or designed to achieve a general-purpose computation in many of the cell subtypes (e.g., Branco et al., 2010)? This question also concerns dendritic spikes in different brain regions or even different species. Namely, do homologous dendritic spikes in a given neuron subtype in different brain areas (e.g., Ca$^{2+}$ spike in PT neurons of the visual cortex and the somatosensory cortex) or even in different species (e.g., NMDA spikes in the auditory cortex of mice and humans) perform a similar computation? Is there a universal set of computations performed by dendritic spikes everywhere they operate? The absence of sufficient data to tackle this question is evident; dendritic spikes in mammals have been recorded (almost) exclusively in rodents and only recently in humans (Beaulieu-Laroche et al., 2018; Gidon et al., 2020; Kalmbach et al., 2021). Further comparative studies that emphasize the variability in the properties of dendritic spikes across neuronal populations (as done for other, more accessible, cellular properties), brain regions, and different species (Beaulieu-Laroche et al., 2021) beyond rodents and humans are essential to assess the “universality” question.

Even with an incomplete understanding of dendritic integration, it is clear that firing a variety of spikes in multiple dendritic branches enhances the neurons’ computational power (Poirazi and Papoutsi, 2020). Integration and computation performed in dendrites can be mimicked by deep artificial neural networks (ANNs; Beniaguev et al., 2021) and, to some degree, even by single point neurons (Li et al., 2019). Additionally, plasticity (Losonczy et al., 2008) and modulation (Hoffman and
Johnston, 1999) of the dendritic and synaptic spikes themselves are another layer of complexity, which may compel new theoretical concepts (Sardi et al., 2018, 2020). It is unclear why evolution prefers computationally (and thus biologically) complex neurons to simple elements such as those used in artificial neural networks (ANNs, see also Cuntz et al., 2021). To paraphrase a familiar question (Häusser and Mel, 2003), “dendritic spikes: bug or feature?” In other words, is the complexity of single neurons, their dendrites, and the collection of spikes summarized in this review the outcome of resolving biological/evolutionary constraints or a strategy to gain computational power?

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