Action potential initiation and backpropagation in neurons of the mammalian CNS

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Most neurons in the mammalian CNS encode and transmit information via action potentials. Knowledge of where these electrical events are initiated and how they propagate within neurons is therefore fundamental to an understanding of neuronal function. While work from the 1950s suggested that action potentials are initiated in the axon, many subsequent investigations have suggested that action potentials can also be initiated in the dendrites. Recently, experiments using simultaneous patch-pipette recordings from different locations on the same neuron have been used to address this issue directly. These studies show that the site of action potential initiation is in the axon, even when synaptic activation is powerful enough to elicit dendritic electrogenesis. Furthermore, these and other studies also show that following initiation, action potentials actively backpropagate into the dendrites of many neuronal types, providing a retrograde signal of neuronal output to the dendritic tree.

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TO CARRY OUT any cognitive or motor task, be it memory formation or the execution of a movement, action potentials must occur in specific sets of neurons at the right time. To accomplish this, neurons of the CNS continuously evaluate their inputs, arriving in the form of ever-changing combinations of synaptic potentials, to determine if and when an action potential should be initiated. Fundamental to an understanding of this process of synaptic integration is the knowledge of where within a neuron these synaptic inputs sum to initiate a neuron's main output signal – the action potential.

Work in the 1950s suggested that action potential initiation in neurons of the CNS occurs in the axon initial segment (for review, see Ref. 1), the unmyelinated region, which forms the beginning of the axon (Fig. 1). As the axon usually originates from the soma of these neurons, this site provides a natural focal point for summation of synaptic inputs from different locations in the dendritic tree. Over the years, however, many studies have suggested that action potentials can also be initiated within dendrites[2–16]. This idea has gained appeal in recent years following evidence that the dendrites of many neurons in the CNS are electrically active (for review, see Ref. 17). This review summarizes recent findings pertaining to the debate concerning the site of action potential initiation in neurons of the mammalian CNS (Ref. 18), and describes how, once initiated, action potentials propagate within the dendritic tree.

Axonal or dendritic action potential initiation: what is the difference?

Action potentials are regenerative electrical events, usually mediated by voltage-activated Na^+ channels, which are initiated following depolarization of the membrane potential to a threshold level. During the normal functioning of the CNS this threshold is reached after temporal or spatial summation of synaptic inputs made largely on to a neuron's dendritic tree. The ability of a synaptic event to influence action potential initiation (its efficacy) will therefore depend on the location of the activated synapse in relation to the site of action potential initiation, and on how this synaptic event is shaped by the active and passive properties of the dendritic tree. If action potential initiation can occur only in the axon, and the dendritic tree behaves passively, the efficacy of each synaptic input will be related to its electrotonic distance from the axon[19].

Conversely, if action potentials can also be initiated in the dendrites, then local interactions in the dendritic tree (both active and passive) will play a more important role. While such a neuron could have increased computational power, to utilize this would require tight control over the precise timing of activation of synaptic inputs to particular parts of the dendritic tree[20]. In addition, to transfer fully the information contained within a dendritic action potential to other neurons, dendritic action potentials would need to propagate reliably from their site of initiation to the axon – normally the sole output pathway for action potentials in neurons. This would require dendritic voltage-activated Na^+ (or Ca^{2+}) channels at densities sufficient to support both the initiation and propagation of dendritic action potentials to the axon. A consequence of such an arrangement would be that once threshold for an action potential is reached somewhere in the neuron no more integration in the neuron would be possible, as this action potential would propagate everywhere, resetting the membrane potential over the entire dendritic tree. Furthermore, the information contained in action potentials initiated in distal parts of the dendritic tree would sometimes

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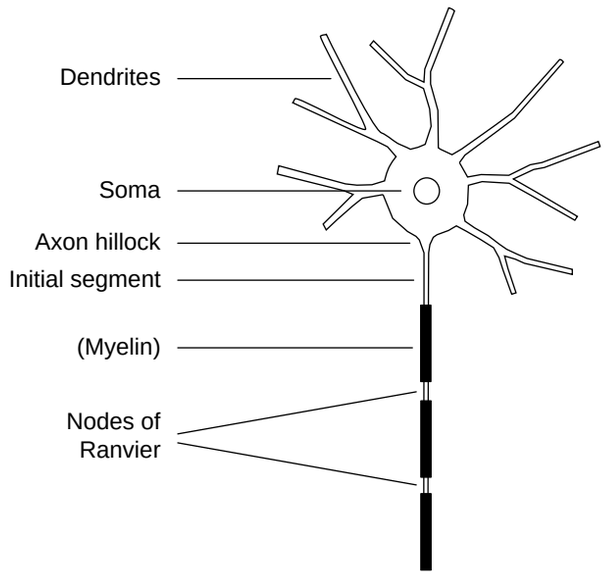

Fig. 1. *Schematic diagram of a neuron indicating possible sites of action potential initiation.*

be lost following collision with action potentials initiated closer to the axon propagating retrogradely into the distal dendrites.

An alternative to these two extreme cases is a neuron with partially active dendrites. In this case, the density of dendritic voltage-activated conductances would be insufficient to support action potential initiation and propagation to the axon, but could still contribute to synaptic integration in complex ways. As in the case with passive dendrites, action potential initiation in such a neuron would occur in the axon after spatial and temporal summation of synaptic input from different parts of the dendritic tree. Regenerative responses could still be initiated in the dendrites of these neurons, but the low density of active dendritic conductances together with unfavorable geometric conditions[21–23] would mean that these events would fail to propagate fully to the axon. However, the presence of dendritic active conductances could still affect synaptic integration, for example, by preferentially amplifying distal synaptic inputs[24,25].

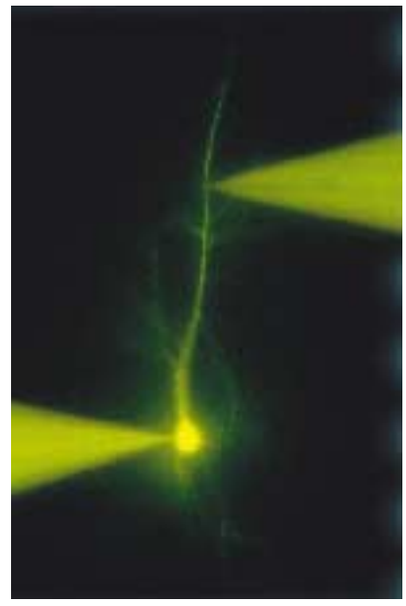

Fig. 2. ***Lucifer yellow fill of a CA1 pyramidal neuron during simultaneous somatic and dendritic recording.*** *The dendritic recording was made 145 μm from the soma.*

Three scenarios of synaptic integration and action potential initiation can therefore be envisioned: (1) passive synaptic integration followed by axonal action potential initiation; (2) active synaptic integration with dendritic action potential initiation; and (3) active synaptic integration with axonal action potential initiation. The pattern of action potential firing of a neuron in response to synaptic input will differ depending on which one of these scenarios holds. Knowledge of where action potentials are initiated and how they spread in neurons is therefore crucial for understanding how neurons transform synaptic input into axonal output.

Evidence for axonal action potential initiation

Experimental evidence provided by intracellular recordings from spinal motoneurons in the 1950s suggested that action potentials are initiated in the axon of CNS neurons[26–28]. Action potentials recorded at the soma of these neurons were found to be composed of at least two components, a smaller, 'initial segment' (IS) spike, followed by a larger 'somato–dendritic' (SD) spike. The IS spike was thought to originate from the axon initial segment as it could be elicited in isolation by antidromic stimulation. As the IS spike always preceded the SD spike, independent of the manner by which action potentials were initiated, it was concluded that action potentials are initiated in the axon. Furthermore, the depolarization required for initiation of the SD spike was two to three times greater than that of the IS spike, indicating that the site with the lowest threshold for action potential initiation was in the axon. Subsequently, similar findings were made in other neurons of the CNS (see Ref. 1).

Other evidence that action potentials are initiated close to the soma of neurons, possibly in the axon, has come from experiments where the dendrites of neurons have been impaled with microelectrodes and the regenerative events recorded compared to those observed at the soma of the same neurons[29–31]. Furthermore, many, but not all, studies using extracellular recording of action potentials have concluded that action potential initiation occurs close to the soma[32–35,99].

Direct experimental evidence that action potentials are initiated in the axon of CNS neurons comes from recent experiments where simultaneous whole-cell patch-pipette recordings have been made from different locations on the same neuron (Fig. 2). These experiments can be used to determine the site of action potential initiation by simply observing at which recording site the action potential occurs first. Simultaneous somatic and dendritic recordings have shown that action potentials in neocortical and hippocampal pyramidal neurons, cerebellar Purkinje neurons, GABA-releasing neurons of the substantia nigra and spinal cord neurons are usually observed to occur first at the soma[36–40] (see also Ref. 100). The fact that glutamate-releasing[37,39] and GABA-releasing[36,38] neurons behave similarly suggests that the site of initiation of the action potential is conserved across both excitatory and inhibitory classes of neurons. Extracellular cell-attached recordings have been used to rule out the possibility that cytoplasmic washout or electrical loading of the dendrite by the dendritic recording pipette affects the site of action potential initiation[39].

Dopamine neurons of the substantia nigra provide an interesting exception, as action potentials were often observed first in the dendrites[38]. Histological examination showed that when this occurred the axon always originated from the dendrite from which the recording had been made. Hence, it was concluded that action potentials were initiated in the axon of these neurons, and observed first at the dendritic recording site as a consequence of the dendritic origin of the axon.

Verification that action potential initiation occurs in the axon has been provided by simultaneous somatic and axonal recordings from neocortical pyramidal and cerebellar Purkinje neurons[36,37]. These studies show that action potentials always occur in the axon before the soma, providing direct evidence that the site of action potential initiation in neurons of the CNS is in the axon. Work on dopamine neurons of the substantia nigra[38], mentioned above, also provides strong evidence for axonal action potential initiation in these neurons, as the recording pipette that detected action potentials first was always the one closest to the axon. An example of recordings comparing the relative timing of the action potential at somatic, dendritic and axonal sites in a neocortical layer-5 pyramidal neuron during action potential initiation by synaptic stimulation is shown in Fig. 3.

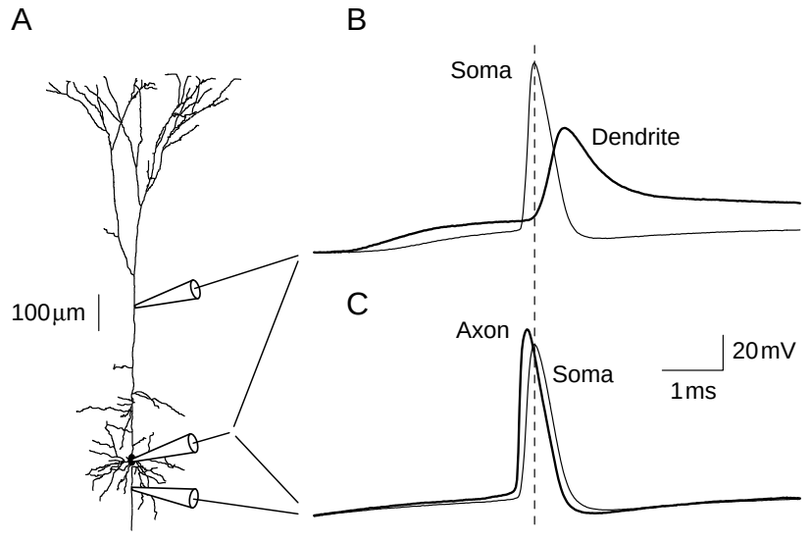

Fig. 3. ***Action potential initiation in a neocortical pyramidal neuron.*** **(A)** *Camera-lucida drawing of neocortical layer-5 pyramidal neuron. Somatic and dendritic* **(B)** *and somatic and axonal* **(C)** *recordings of action potentials elicited by threshold synaptic stimulation in rat neocortical layer-5 pyramidal neurons (4 weeks old, 35°C; G. Stuart and B. Sakmann, unpublished observations). The approximate locations of the recordings is indicated. Dendritic and axonal recordings (thicker traces) were 270 μm and 17 μm from the soma, respectively, and are from different cells. Action potential threshold at the soma was 13 mV* (B) *and 15 mV* (C) *depolarized from a somatic resting membrane potential (RMP) of –62 mV* (B) *and –61 mV* (C)*. The RMP at the dendritic and axonal recording sites were –60 mV and –61 mV, respectively. The dotted line indicates when the peak of the somatic action potential occurred.*

Evidence for dendritic action potential initiation

Although the usual site of action potential initiation appears to be in the axon, the question arises whether action potentials can also be initiated in the dendrites. Some early experimental evidence suggesting that this might be the case came from the finding that at the soma of hippocampal pyramidal neurons small all-or-none spike-like events can often be observed both in isolation and preceding somatic action potentials[4]. These 'fast prepotentials' (FPPs) have also been observed in other neuronal types (for example, visual cortex neurons[15]). While it was originally thought that FPPs represent dendritically initiated action potentials, there is now evidence suggesting that they are caused by action potential activity in neighboring, electrically coupled neurons[41,42] (but see Ref. 16).

More direct evidence that the dendrites of mammalian neurons are electrically excitable has come from recordings from the dendrites of neurons with sharp microelectrodes[6,7,10,29–31,43–45], and more recently with patch-clamp pipettes[36–39,46–49]. Together these studies have shown that not only do the dendrites of mammalian CNS neurons contain voltage-activated channels, but also that they can often support fast, regenerative, action potential-like events mediated by voltage-activated Na^+ channels, or slower, regenerative events mediated by voltage-activated Ca^{2+} channels, often called Ca^{2+} spikes. Before it can be concluded that these events represent dendritic action potential initiation, however, their temporal relationship to somatic and axonal action potentials, and their ability to propagate to the soma and axon need to be established.

Some analyses of extracellular field potentials during synchronized synaptic activation of populations of hippocampal pyramidal and cerebellar Purkinje neurons *in vivo* have led to the conclusion that action potentials can be initiated in the dendrites before the soma[2,3,5,6,9]. The interpretation of these experiments, however, is complicated as the recorded extracellular field depends on the geometric arrangement of the activated cells, their degree of synchronization of activation, the shape and possible inhomogeneity of the extracellular space, and the location of both the recording and reference (ground) electrodes[50,51]. Nevertheless, these studies may represent instances where the high-intensity synaptic activation required for such experiments can lead to initiation of dendritic regenerative events prior to somatic action potentials, suggesting that the site of action potential initiation could shift into the dendrites under some conditions. Using a combination of intra- and extracellular recording, Turner and colleagues[11] provide evidence that this might be the case by showing that intracellularly recorded dendritic action potentials can precede the extracellularly recorded somatic action potential during high-intensity synaptic stimulation (see also Ref. 39). Recent experiments in neocortical pyramidal neurons provide more direct evidence for a possible shift in the site of action potential initiation. Simultaneous somatic and dendritic recordings from layer-5 neocortical pyramidal neurons show that high-intensity stimulation of the distal dendrites can initiate dendritic regenerative responses prior to somatic action potentials, whereas during proximal or threshold synaptic stimulation somatic action potentials usually occur before any dendritic response[52].

In addition, a number of recent Ca^{2+}-imaging studies have shown that synaptic stimulation can elicit dendritic Ca^{2+} signals in isolation from the soma[53–57], suggesting that in many neurons dendritic Ca^{2+} electrogenesis can be initiated independently of somatic or axonal action potentials. Several recent studies using simultaneous recording from the soma and dendrites of the same neuron provide direct evidence for

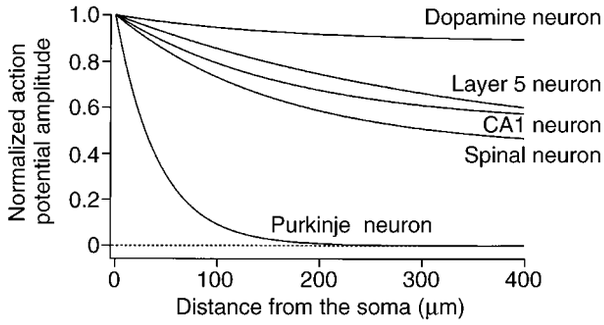

Fig. 4. ***Comparison of dendritic action potential amplitude at different distances from the soma.*** *Dendritic action potential amplitude, normalized to the amplitude of action potentials at the soma, is plotted against the distance from the soma the dendritic recording was made for neocortical layer-5 and hippocampal CA1-pyramidal, spinal cord, cerebellar Purkinje and substantia nigra dopamine neurons. The best single exponential fit to the experimental data in the different neuronal types is shown.* Adapted from Refs 36–40.

this, showing that distal synaptic stimulation can elicit dendritic Ca^{2+} spikes in neocortical pyramidal neurons[58] and cerebellar Purkinje neurons[59], while the soma of the same cells remains subthreshold for action potential initiation. As the regenerative potentials in the dendrites of these neurons fail to propagate to the soma effectively, this suggests that the distal dendrites of these neurons might be able to operate as a separate functional compartment (see also Ref. 54). The failure of these dendritic regenerative events to propagate to the soma and axon presumably occurs due to the low density of dendritic Na^+ and Ca^{2+} channels together with electrically unfavorable impedance mismatches at dendritic branch points and dendritic broadening, encountered as an active event propagates from the dendrites towards the soma[21–23].

How does this distal dendritic electrogenesis relate to the initiation of action potentials? This issue has been addressed directly in triple recordings from the soma, dendrite and axon of neocortical layer-5 pyramidal neurons. These experiments show that fast, Na^+ action potentials are always initiated in the axon before the soma, independent of whether slower, dendritic regenerative responses occur or not[52]. This finding, together with the experiments showing that distal dendritic regenerative events can fail to propagate to the soma and axon effectively, demonstrates that the site of action potential initiation in mammalian CNS neurons occurs in the axon, even when synaptic activation is strong enough to elicit dendritic electrogenesis.

It seems likely that dendritic electrogenesis of the type described above might also have been detected in extracellular studies, where it was concluded that action potential initiation can occur in the dendrites[2,3,5,6,9,11]. The unreliability of propagation to the soma and axon, however, makes these dendritic regenerative events functionally distinct from the action potential that occurs in the axon. As a result, this type of dendritic electrogenesis, while presumably amplifying the synaptic response that initiates it, should be considered an active form of synaptic integration rather than action potential initiation. Of importance will be to determine whether such dendritic electrogenesis also occurs during the normal functioning of the CNS, or whether it is simply a consequence of the synchronized, localized, synaptic activation that occurs following extracellular stimulation[60].

Why are action potentials initiated in the axon?

The fact that action potentials are initiated in the axon demonstrates that this site has the lowest threshold for action potential initiation, as originally suggested from somatic recordings from spinal motoneurons (see above). There are a number of reasons why this might be the case. First, as the diameter of the axon is small the amount of current required to charge the membrane capacitance and drive the membrane potential to threshold will also be small. Second, the density of voltage-activated Na^+ channels might be higher in the axon than in the soma and dendrites. Third, the properties of Na^+ channels in the axon might be different from that in the soma and dendrites.

Both theoretical and experimental evidence suggest that the axon contains a high Na^+-channel density[1,61–65], with recent studies simulating action potential initiation in morphologically realistic neuronal models predicting that the Na^+-channel density in the axon initial segment or the first nodes of Ranvier must be 20–1000 times that in the soma and dendrites[64,65]. In agreement with this idea, it is well known that the Na^+-channel density at nodes of Ranvier is orders of magnitude higher than recent estimates of somatic or dendritic Na^+-channel density (see Ref. 66). Attempts to assess the density of Na^+ channels in the axon hillock and initial segment using patch-clamp recording, however, have found similar densities of Na^+ channels to that at the soma[67] (G. Stuart, unpublished observations). This suggests that action potential initiation might actually occur at the first nodes of Ranvier, rather than at the axon initial segment[26,64,65,67,68].

Propagation of action potentials back into the dendritic tree

Once initiated in the axon, action potentials will propagate into the dendritic tree in a retrograde fashion[50,100,101]. The extent of this action potential backpropagation has been found to vary depending on the type of neuron (Fig. 4). This finding can in part be explained by cell-specific differences in dendritic Na^+-channel density. The boosting effect of dendritic Na^+ channels on backpropagating action potentials is demonstrated most clearly by comparing backpropagation of a somatic action potential under control conditions with that of a simulated action potential waveform (with the same amplitude and shape as a somatic action potential) when voltage-activated Na^+ channels are blocked by tetrodotoxin (TTX)[37] (Fig. 5). These experiments show that the amplitude of a backpropagating action potential waveform is reduced greatly when dendritic Na^+ channels are blocked by TTX in those neurons with a similar density of dendritic and somatic Na^+ channels[37–39], whereas in neurons with a low dendritic Na^+-channel density, such as cerebellar Purkinje neurons, the amplitude of a backpropagating action potential waveform is similar in the absence and presence of TTX (Ref. 36). Experiments like this, and others, show that action potentials propagate actively into the dendrites of neocortical and hippocampal pyramidal, hippocampal granule, substantia nigra and spinal cord neurons[33,34,37–40,69], whereas backpropagation is largely passive in cerebellar Purkinje neurons[29,36].

Factors other than dendritic Na^+-channel density will also influence the extent of action potential backpropagation. For example, the dendritic morphology and branching pattern would be expected to play an important role[21]. Evidence that this is the case comes from the finding that backpropagation of action potentials into the dendrites of hippocampal pyramidal neurons can fail at dendritic branch points[39]. Somatic action potential shape will also be a factor, as the broader an event the less it will attenuate as it propagates into the dendritic tree[70]. With respect to this point, it is worth noting that backpropagation into the dendritic tree is most effective in the dopamine neurons of the substantia nigra, which have the broadest somatic action potentials of all neurons in which action potential backpropagation has been studied (see Fig. 4). The passive electrical properties of the dendritic tree also need to be considered. For example, a decrease in the effective membrane resistance, as might occur during an increase in the level of background synaptic activity, could cause a graded, but moderate reduction in the amplitude of backpropagating action potentials[65]. The distribution and activation of dendritic K^+ conductances will also play a role, as their activation could shunt the dendritic membrane and so decrease the effectiveness of action potential backpropagation. The rate of action potential firing must also be considered, as the extent of action potential backpropagation during a train of action potentials has been shown to be dependent on the frequency of somatic action potential firing, both *in vitro*[39,45,71] and *in vivo*[99] (Fig. 6). This phenomenon, which might occur as a consequence of a reduction in dendritic Na^+ current following cumulative Na^+-channel inactivation[72,73], could have important implications during the normal functioning of the CNS where neurons are usually spontaneously active. Finally, inhibitory neurons that target dendritic sites could suppress backpropagation and associated dendritic Ca^{2+} electrogenesis[74–77,99].

What does a backpropagating action potential do?

Some neurons have backpropagating action potentials, while others do not. This cell-specific difference suggests that active backpropagation of action potentials into the dendritic tree is functionally important in those neurons where it occurs. But what is the point of a backpropagating action potential? First and foremost, backpropagating action potentials will provide a retrograde signal to the dendritic tree indicating the level of neuronal output. This might serve as an associative link between presynaptic excitation and the postsynaptic response of a neuron necessary for some forms of synaptic plasticity[78–82]. For example, some long-term changes in synaptic strength are dependent on the activation of NMDA-receptor channels (for a review, see Ref. 83). Relief of the voltage-dependent Mg^{2+} block of NMDA-receptor channels by backpropagating action potentials could enhance the induction of such changes in synaptic strength by increasing synaptic Ca^{2+} influx through NMDA receptor-activated channels[84,85]. With reference to this point, it is interesting to note that cerebellar Purkinje neurons, which lack backpropagating action potentials, also lack functional NMDA receptors[86].

Another possible retrograde signal mediated by backpropagating action potentials is a transient rise in intracellular dendritic Ca^{2+} following the activation of dendritic voltage-activated Ca^{2+} channels[39,54,60,71,87–89]. This rise in Ca^{2+} correlates linearly with the average rate of somatic action potential firing in neocortical pyramidal neurons[60,90]. Imaging studies also show that backpropagating action potentials effectively invade dendritic spines, where they cause an increase in intracellular Ca^{2+}, presumably due to activation of voltage-activated Ca^{2+} channels in the spines themselves[91]. Apart from the role of Ca^{2+} in the induction of certain forms of synaptic plasticity, a rise in dendritic intracellular Ca^{2+} might also influence synaptic integration by downregulating NMDA receptor-mediated responses[92,93] or by activating dendritic K^+ conductances[94], which could shunt out parts of the dendritic tree. Activation of dendritic K^+ channels would also result in K^+ efflux and a subsequent increase in extracellular K^+ (Ref. 95), which could, in principle, depolarize presynaptic terminals, thereby transiently influencing the probability of transmitter release. Another possibility is that in neurons where dendritic release of transmitter is thought to occur, such as in the olfactory bulb or substantia nigra, a rise in dendritic Ca^{2+} via backpropagating action potentials might play a role in dendritic transmitter release[38,50].

Backpropagating action potentials will also briefly interrupt synaptic integration by resetting the dendritic membrane potential and by clamping excitatory synaptic conductances close to their reversal potential. The coincidence of backpropagating action potentials with incoming synaptic inputs might

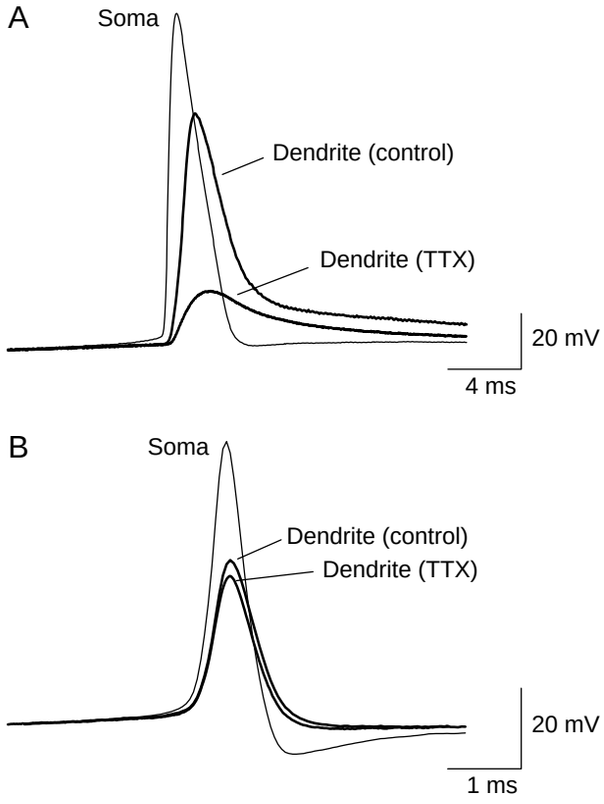

Fig. 5. ***Comparison of active and passive action potential backpropagation.*** *Somatic and dendritic (thicker traces) responses in a hippocampal CA1 pyramidal neuron* **(A)** *and a cerebellar Purkinje neuron* **(B)** *during elicited and simulated action potentials in control conditions and in the presence of tetrodotoxin (TTX). Dendritic recordings were 210 μm (hippocampal neuron) and 50 μm (Purkinje neuron) from the soma. See text for details.* Adapted from Refs 36,39.

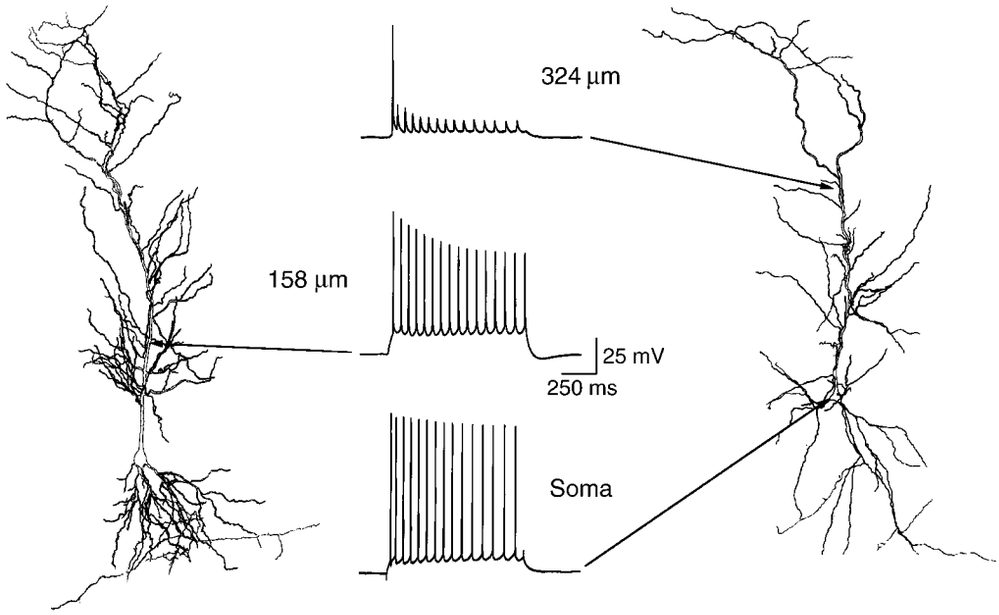

Fig. 6. ***Failure of action potentials to invade the dendrites of CA1 pyramidal neurons during repetitive action potential firing.*** *Trains of action potentials elicited by 1 s, depolarizing current injections to the soma of two neurons are shown. In each case little attenuation of somatic action potentials was observed, while attenuation of action potentials during the train was substantial in both dendritic recordings, with failure of action potential backpropagation in the most distal dendritic recording.* Adapted, with permission, from Ref. 39.

therefore have important implications for the precise timing of subsequent action potential initiation. In neurons without backpropagating action potentials[36], or where backpropagation can fail[39], synaptic integration in some parts of the dendritic tree would be expected to continue without interruption during somatic action potential firing.

Concluding remarks

Together, these studies demonstrate that a fundamental feature of synaptic integration in CNS neurons is that the output signal of neurons, the action potential, is initiated in the axon, even under conditions where synaptic input initiates regenerative responses in the dendrites. As a result, the axon acts as the final site for synaptic integration. An important consequence of this is that it provides the CNS with a single site where inhibition will be most effective. Indeed, many inhibitory neurons make synaptic contacts close to the soma and some make contacts specifically onto the axon initial segment of neurons[76,96]. Thus, the nervous system has concentrated inhibition precisely at the location where it is best suited to inhibit action potential initiation. This arrangement might also have important consequences for the synchronization of action potential firing between groups of neurons[97,98].

Another implication of axonal action potential initiation is that if the dendritic tree behaves largely passively, the efficacy of each synaptic event will depend mainly on its electrical distance from the axon. The symmetry of the dendritic tree of many neurons and the fact that the axon usually emerges from the soma, will mean that synaptic inputs made at similar electrotonic distances from the soma will influence action potential initiation approximately equally, regardless of which branch of the dendritic tree a synapse contacts. An increased quantal size or probability of transmitter release of distal synaptic events, or amplification by voltage-activated channels, could compensate for differences in the efficacy of distal versus proximal synaptic inputs. On the other hand, in neurons where the axon emerges from a dendrite, synapses onto this dendrite would be expected to have a greater influence on action potential initiation[38]. It will be of interest to determine if these synapses are in some way different from those on other dendrites of these neurons.

Finally, despite the fact that the final site of synaptic integration and action potential initiation is in the axon of neurons rather than their dendrites, the activation of voltage-activated channels in the dendritic tree will nevertheless influence the process of synaptic integration in important and complex ways. This is underscored by the observation that the dendrites can initiate regenerative events independent of somatic and axonal action potential firing, and that action potentials backpropagate into the dendritic tree in a complex and cell-specific manner.

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