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Progress in Biophysics and Molecular Biology 87 (2005) 145–170

Progress in Biophysics & Molecular Biology

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Review

# Backpropagating action potentials in neurones: measurement, mechanisms and potential functions

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Available online 11 September 2004

**Abstract**

Here we review some properties and functions of backpropagating action potentials in the dendrites of mammalian CNS neurones. We focus on three main aspects: firstly the current techniques available for measuring backpropagating action potentials, secondly the morphological parameters and voltage gated ion channels that determine action potential backpropagation and thirdly the potential functions of backpropagating action potentials in real neuronal networks.
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doi:10.1016/j.pbiomolbio.2004.06.009

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## 1. Measurement of action potential backpropagation

### 1.1. Electrophysiology

From as early as the 1950s, data from extra- and intracellular recordings in a variety of mammalian preparations suggested that dendrites contained active conductances (extracellular: Cragg and Hamlyn, 1955; Fatt, 1957a, b; Andersen, 1960; Fujita and Sakata, 1962; Andersen and Lomo, 1966; Llinas et al., 1968, 1969; Rall and Shepherd, 1968; Wong and Prince, 1978; Llinas and Sugimori, 1979; Miyakawa and Kato, 1986; Turner et al., 1989; Herreras, 1990; intracellular: Spencer and Kandel, 1961; Fujita, 1968; Llinas and Hess, 1976; Wong et al., 1979; Llinas and Sugimori, 1980; Turner et al., 1991; Kim and Connors, 1993). However, it was the combination of patch pipette recording and infra-red differential interference contrast (IR-DIC) optics in acute brain slices that led to a rapid expansion of the field. IR-DIC optics enables visualisation of dendrites in brain slices, greatly facilitating direct measurement of action potentials (APs) in dendrites by enabling the experimenter to accurately place the tip of a patch pipette onto a dendrite under visual guidance (Stuart et al., 1993; Stuart and Sakmann, 1994) and thus map the membrane potential profile along dendrites.

Dendritic recording is still the most direct approach available to measure dendritic initiation and propagation of APs. Dendritic recordings may be obtained using either sharp microelectrode impalement (Llinas and Sugimori, 1980) or the whole-cell variant of the patch-clamp technique (Hamill et al., 1981; Stuart et al., 1993). Using multiple recordings from the same cell, one can determine whether AP spread into the dendrite is active or passive (Fig. 1A). If spread is passive, involving no regenerative dendritic conductances, AP amplitude will decrease markedly with distance into the dendrite. The space constant will depend on dendritic morphology, membrane conductance and axial resistance, but depolarisation will usually be strongly attenuated, possibly within just a few tens of micrometers. At the other end of the spectrum is non-decremental backpropagation in which AP amplitude is maintained over long distances, like propagation along an axon. Dendritic properties most commonly rest between these two extremes, supporting decremental backpropagation in which APs travel long distances through the dendritic arbour, but during propagation their amplitudes decrease (Fig. 1B) and their halfwidths increase.

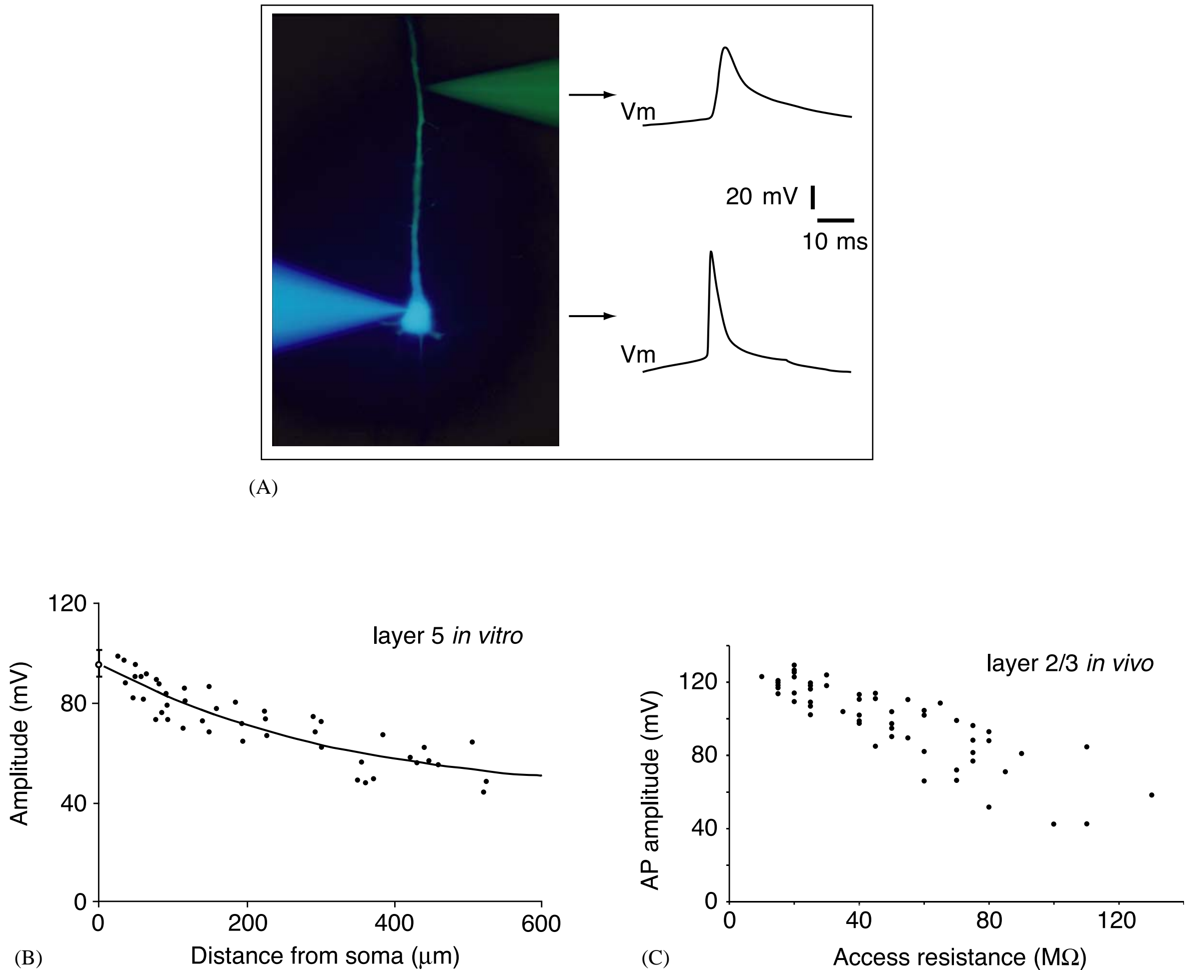



Fig. 1. Dual whole-cell recording of AP backpropagation. (A) Fluorescence image showing dual recording configuration in L5 pyramidal neurone (left) and corresponding somatic and dendritic traces during somatic current injection (right). (B) Plot of AP amplitude with distance from soma for L5 neurones. Panels A and B were adapted from Stuart and Sakmann (1994). (C) Effect of access resistance on apparent AP amplitude (unpublished data, J.W. and Fritjof Helmchen). Peak AP amplitudes were measured from resting membrane potential in somatic recordings from L2/3 neurones in vivo. Recordings were made with an Axoclamp-2B amplifier, uncoated thick-walled borosilicate glass, bridge balance and partial capacitance compensation.

Passive spread and decremental backpropagation are sometimes confused since both result in a decrease in amplitude with distance from the soma. However, they can readily be distinguished pharmacologically since active propagation relies on dendritic sodium channels. Blockade of dendritic sodium channels with tetrodotoxin will therefore attenuate actively backpropagating, but not passively spreading, APs.

At present, dendritic recordings (Sakmann and Stuart, 1995) provide the most reliable, quantitative measurements of dendritic propagation, but have a few disadvantages. First, the

additional capacitance load on the dendrite resulting from the capacitance of the pipette can alter the AP waveform. This cannot be corrected with capacitance compensation or offline analysis, but the effect of whole-cell recording can be estimated, for example, in cell-attached recordings (Spruston et al., 1995; Stuart et al., 1997a). Furthermore, the access resistance and capacitance of the pipette act as an RC filter, decreasing the amplitude and increasing the halfwidth of the AP. In practice, access resistances are typically higher for dendritic than somatic recordings and are often higher in recordings from fine distal dendrites than from proximal structures. As a result, dendritic AP amplitudes and halfwidths are prone to under- and overestimation, respectively, and this problem is likely to be more acute in distal recordings. This will tend to result in underestimation of the extent of backpropagation.

Fortunately the effects of access resistance are relatively forgiving. In our experiments, we have found that the effects of access resistance are modest compared to the real attenuation during decremental backpropagation (compare Fig. 1B and C). However, we should emphasize that the data shown in Fig. 1C are valid for our recording conditions and the effects of access resistance may be more or less pronounced under other conditions. Important factors may include the type of glass used, the effectiveness of capacitance compensation and the choice of amplifier. The latter is a particularly important consideration since the current-clamp mode of many patch-clamp amplifiers is too slow to accurately record AP characteristics (Magistretti et al., 1996).

A more intractable problem is that the recording may perturb dendritic properties, thereby altering propagation. For instance, substantial inactivation of A-type current can occur if a dendrite is depolarised by just a few millivolts since the $V_{1/2}$ for inactivation of A-type current can be near resting membrane potential (Bekkers, 2000a, b; Hoffman et al., 1997; Korngreen and Sakmann, 2000; Wang et al., 1996). A-type current is expressed at high densities in many dendrites where it contributes to repolarisation (Bekkers, 2000a; Christie and Westbrook, 2003; Goldberg et al., 2003; Hoffman et al., 1997; Korngreen and Sakmann, 2000). Hence if recording were to result in even a small depolarisation of the dendrite, inhibition of A-type potassium current could strongly enhance propagation.

Sharp electrode impalement and patch pipette recording can each perturb dendritic function, but in different ways. In the case of patch recordings the major potential source of perturbation is dialysis of the cytoplasm. Dialysis can affect channel activation and inactivation by altering the intracellular milieu (see Horn and Marty, 1988), but we are not aware of any example where an effect of patch recording on dendritic propagation has been experimentally demonstrated. Although sharp electrodes produce less dialysis, impalement gives rise to a substantial leak conductance, which permits exchange of intracellular and extracellular ions. In addition, potassium loading may occur since the pipette typically contains a high concentration of a potassium salt. However, perhaps the most significant concern with sharp electrode impalement is shunting. The leak conductance locally reduces dendritic input resistance, reducing the extent to which depolarising current in adjacent regions of the dendrite charges the membrane around the recording site. Hence leak at the recording site may suppress propagation. Together the ionic leak and change in input resistance induced by sharp electrode impalement could substantially inhibit propagation, particularly if conductances in the dendrite are delicately balanced, such as in hippocampal pyramidal and mitral cell dendrites where A-type current is largely responsible for repolarisation.

Whether using sharp or patch electrodes, in order to cleanly distinguish between dendritic AP initiation and backpropagation of an axo-somatically initiated AP into the dendritic tree, a somatic recording is required in addition to the dendritic recording. Hence one ideally obtains a dual recording, where recordings are simultaneously obtained from the soma and the dendrite of a neurone using two pipettes (Fig. 1A). Obviously, dual recordings are greatly facilitated by visualisation of the neurone of interest, hence the value of IR-DIC techniques. Unfortunately, the need to visualise the dendrite has limited the application of dendritic recording techniques since there are many situations where the dendrite is not readily visualised.

This is a particularly common problem with small-diameter dendrites, which may be impossible to follow over long distances with IR-DIC optics. In these situations, we have found that filling the neurone with a soluble fluorescent indicator can greatly facilitate dendritic recording (Schiller et al., 1995; Waters et al., 2003). Labelling allows the experimenter to trace the dendrite using fluorescence microscopy. Although not the entire dendrite may be visible with IR-DIC optics, short sections of dendrite frequently are and these may be identified by reference to the fluorescence image. Hence this combination of fluorescence tracing and IR-DIC visualisation permits dendritic recording in some situations where IR-DIC alone is insufficient.

Another situation where visualisation of the dendrite is limited is in the intact brain. To generate contrast, IR-DIC relies on the interaction of light with brain tissue during transit through the sample. Transmitted light that has passed through the tissue must be collected and this is obviously not possible in vivo. Hence recording pipettes have not yet been targeted to visualised dendrites in vivo. This situation may change as new optical imaging techniques are developed, perhaps based on fluorescence imaging (Margrie et al., 2003), scattering of reflected light or optical coherence tomography (Boppart et al., 1996). To date electrophysiological recordings of AP backpropagation in vivo have been limited to single-electrode recordings obtained 'blind' (Borg-Graham et al., 1996; Buzsáki et al., 1996; Charpak et al., 2001; Debarbieux et al., 2003; Kamondi et al., 1998; Margrie et al., 2002; Svoboda et al., 1999; Zhu and Connors, 1999). Until dual recordings are feasible in vivo, reliable interpretation of in vivo data will require direct comparison with dual recordings from similar neurones in brain slices (Waters et al., 2003).

It is also worth noting that the tips of sharp microelectrodes are typically too small to be visible under IR-DIC optics. This and the flexibility of these pipettes means that even where the dendrite of interest is visible in brain slice preparations, obtaining dual recordings with sharp microelectrodes is particularly challenging.

### *1.2. Fluorescence imaging*

Fluorescence imaging techniques are an excellent complement to direct recordings. The neurone of interest must be labelled and this is typically achieved by loading functional indicator into the cell through a somatic recording pipette. The fact that dendritic recording is not required means that local perturbation of dendritic function is less likely with imaging techniques than with dendritic recordings, although the addition of exogenous dye could potentially alter propagation on a more global scale. Furthermore, whereas a dendritic recording only provides information from a single dendritic location, with imaging techniques backpropagation can be measured in many locations within a single neurone (see for example: Antic, 2003; Schiller et al., 1995; Waters et al., 2003). Finally, imaging is often possible where dual recording techniques are not feasible.

Hence imaging techniques have been more widely used than direct recordings to study the basal and distal apical dendrites of pyramidal cells and interneurone dendrites (Antic, 2003; Goldberg et al., 2003; Kaiser et al., 2001; Martina et al., 2000).

The most direct way of imaging depolarisation is with a fast voltage-sensitive dye (VSD). VSDs are rarely used, probably because they offer a fairly poor signal-to-noise ratio, typically exhibit pronounced phototoxicity and may be toxic even in the absence of illumination (Antic et al, 1999). In addition, VSDs are membrane-associate dyes. As a result, they diffuse only slowly along dendrites. After loading through a somatic pipette, it may be tens of minutes before the dye reaches sufficient concentration to image distal processes. These factors have limited their use to proximal dendrites and to only a few tens to hundreds of milliseconds of imaging per neurone (Antic et al., 1999; Antic, 2003; Zochowski et al., 2000).

Furthermore, calibration of the VSD fluorescence in terms of membrane potential is difficult (Antic et al., 1999). To stain a single neurone in an acute slice, VSDs are typically introduced through a patch pipette (although, see for example Borst et al., 1997). They diffuse into the neurone and stain membranes, including both the plasma membrane and intracellular organelles. Obviously the membrane potential (of the plasma membrane) is reported only by those dye molecules inserted into the plasma membrane. The stained organelles contribute unwanted additional staining. The percentage change in fluorescence per millivolt of depolarisation will depend on relative amounts of dye in plasma membrane and intracellular organelles. In order to calibrate the VSD signal, one therefore needs a membrane potential recording. Hence one can readily calibrate VSD signals at the soma. In dendrites, the percentage of dye partitioned into organelles is likely to be different since there may be fewer organelles per unit area of plasma membrane. As a result, one cannot reliably use calibration data obtained from the soma and the amplitude of depolarisation in the dendritic will be unclear. It is worth noting that the kinetics of the fluorescence change are not sensitive to background staining and should faithfully reproduce the time course of an AP in the dendrite.

Despite these limitations, VSD imaging has provided valuable information on dendritic AP initiation and propagation in basal and oblique dendrites of pyramidal neurones (Fig. 2), where the small dendritic diameters make direct recordings particularly troublesome (Antic, 2003). Furthermore, fast VSDs in combination with advanced imaging hardware offer a rapid readout of membrane potential, sufficient to accurately describe AP waveforms and their propagation along dendrites. This is the only technique other than multi-site intracellular recording to offer this information. Hence the use of VSDs may become more widespread in the future, particularly if less toxic, more photostable dyes become available.

Calcium indicators (Fig. 3) have been more widely used to image dendritic AP initiation and propagation. Unfortunately, calcium indicators suffer two major disadvantages when compared to direct recordings and voltage sensitive dyes: they lack the temporal resolution of electrophysiological and VSD techniques and they provide only an indirect measure of depolarisation.

The temporal resolution reported in calcium imaging experiments is usually related to the image acquisition hardware. With confocal and 2-photon microscopes, this is the linescan speed of the mirror galvanometer, which will typically gather data points at 2 ms intervals. In 2 ms, an AP will travel between 500 μm and 1 mm through a dendritic tree (Bischofberger and Jonas, 1997; Stuart and Sakmann, 1994). Some camera systems permit faster acquisition, but in reality the binding of

calcium to the fluorescent indicator is the factor limiting the temporal resolution of calcium imaging experiments. Following an AP, equilibration of free and indicator-bound calcium may continue over several milliseconds or even tens of milliseconds (Markram et al., 1998c; Sabatini and Regehr, 1988). Hence calcium imaging is not an appropriate technique to determine the location of initiation or speed of propagation of an AP.

Calcium influx is a secondary consequence of depolarisation and depends on the presence of voltage-sensitive, calcium-permeable channels. Changes in calcium channel density or subtype along the length of a dendrite may influence calcium influx, regardless of any change in AP amplitude or halfwidth. Such subtype changes have been observed in hippocampal pyramidal neurones (Johnston et al., 1996; Magee and Johnston, 1995a). In addition, release from intracellular stores, calcium entry through ionotropic receptors and changes in surface area to volume ratio (for instance in a tapering dendrite) may further complicate interpretation. Hence calibration of calcium signals in terms of depolarisation may be essentially impossible. This problem can be particularly severe in distal dendrites, where the lack of a calcium signal could indicate (i) that a backpropagating AP does not reach this far into the dendritic tree, (ii) that it does but the amplitude is too small to reach calcium channel threshold, (iii) that there are no calcium channels in this region of the dendrite or (iv) that the signal-to-noise ratio is too poor in

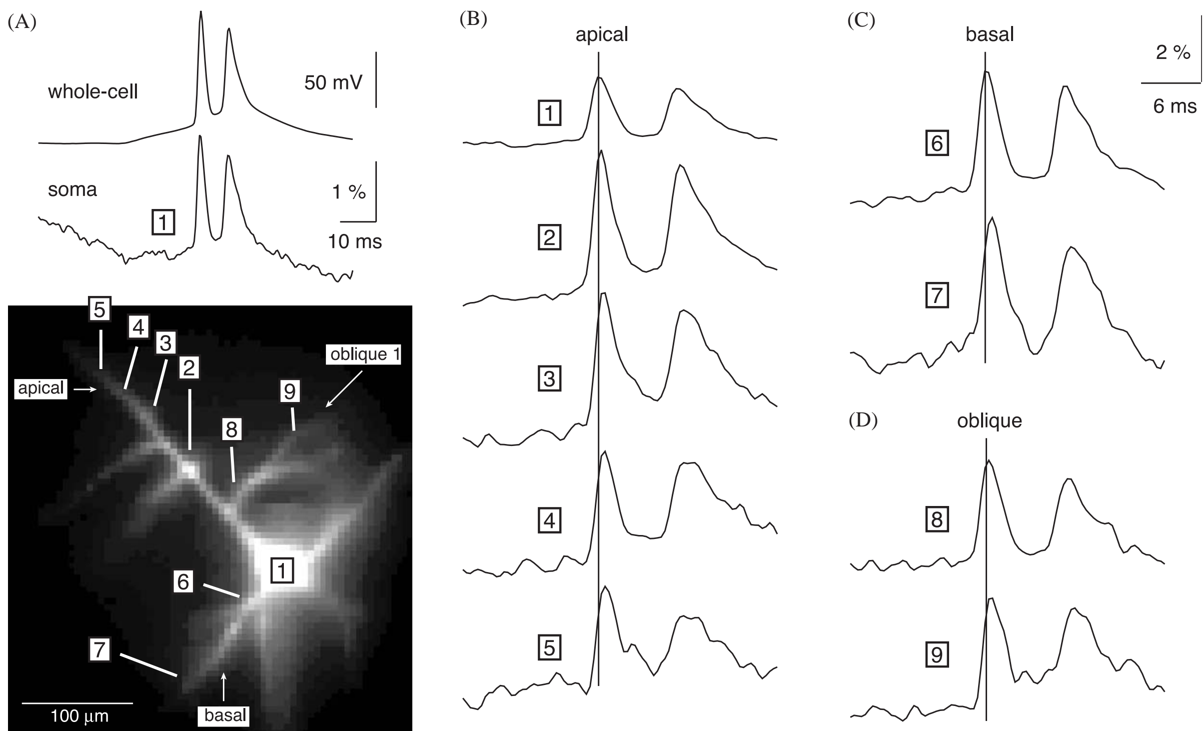



Fig. 2. VSD imaging of backpropagation in L5 neocortical pyramidal neurone. **A** Somatic whole-cell recording and corresponding VSD signal from soma. Image of neurone is shown below. B, C and D Optical signals from apical (B), basal (C) and oblique (D) dendrites showing change in amplitude and timecourse with backpropagation. Adapted with permission from Antic (2003).

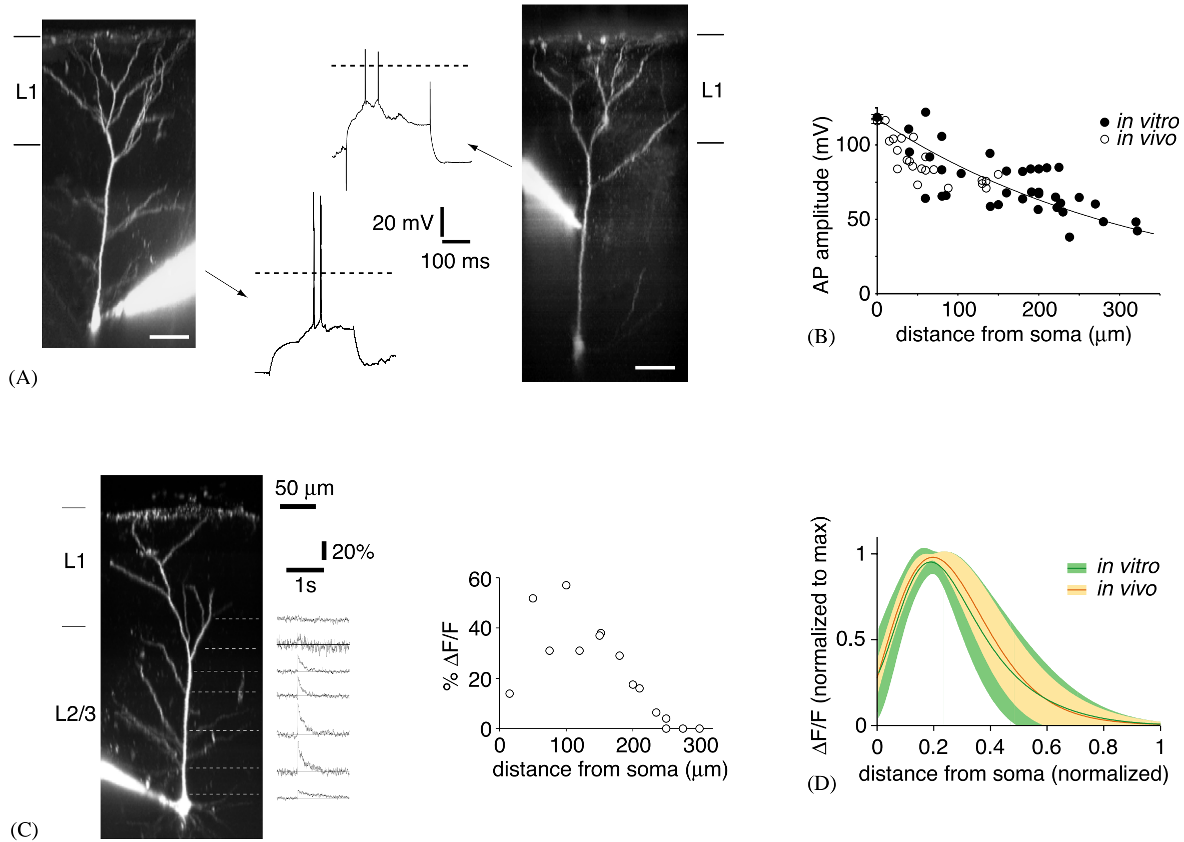



Fig. 3. Backpropagation in L2/3 pyramidal neurones in vitro and in vivo. (A) Somatic and dendritic AP recordings in vivo. Images are side projections of stacks of 2-photon fluorescence images. (B) Amplitudes of single APs evoked by current injection in vitro (filled symbols) and in vivo (open symbols) as a function of distance from the soma. Each point represents a single dendritic recording, with one recording per neurone. (C) *Left:* Examples of $Ca^{2+}$ transients in apical dendrite in vivo, each evoked by a single somatic AP. *Right*: Spatial profile of peak $Ca^{2+}$ transients. (D) Normalized $Ca^{2+}$ profiles for in vitro and in vivo recordings. Shaded areas represent ± one standard deviation from the mean. Adapted from Waters et al. (2003).

such a small structure and a calcium transient is therefore present but undetected. Fortunately, it is often possible to eliminate the latter two possible explanations by studying calcium transients following a burst of several APs. Furthermore, although it is not possible to calibrate calcium signals in terms of depolarisation, one can often demonstrate that a calcium signal results from active AP backpropagation if the calcium signal is attenuated when dendritic sodium channels are blocked using TTX.

Additional complications occur where one wishes to compare different parts of a dendritic arbour since one would ideally require an equal concentration of indicator at all measurement sites. If the dye concentration is lower in more distal sites, calcium transients may appear larger distally because of the reduced exogenous calcium buffering. This may lead to an underestimate of AP attenuation along the dendrite. Unfortunately an equal concentration of indicator throughout

the dendritic tree is rarely achieved in extensive, complex dendritic trees, but the indicator should at least have reached a steady-state concentration if measurements are to remain stable through time. This may require a prolonged recording, perhaps an hour or more, since diffusion of indicator over these distances is slow. An alternative is 'bolus loading,' in which the perisomatic region is loaded with a high concentration of indicator during a brief somatic recording. The pipette is then removed and the dye is allowed to diffuse into the dendritic tree before imaging. Where this is not possible and the dye is distributed as a steady-state concentration gradient along the dendrite, the time integral of the calcium transient may be a more appropriate measure of calcium influx than the amplitude of the calcium transient since the integral is independent of buffer concentration (Helmchen et al., 1996; Rozsa et al., 2004).

Despite these disadvantages, calcium imaging is widely used to monitor backpropagation. Present day calcium indicators have the key advantage that their toxicity is minimal so they are likely to have little effect on dendritic function. The one obvious exception might be where calcium-sensitive conductances, such as calcium-activated potassium channels, play a role in suppressing AP initiation or in repolarisation (Reyes, 2001; Sah, 1996). In these situations dialysis with an exogenous calcium buffer, such as a calcium indicator, could obviously alter AP initiation and/or propagation. This may be especially pronounced after AP trains as calcium-activated potassium conductances are particularly active in such situations.

Another advantage of modern calcium indicators is their excellent signal-to-noise ratio. Hence it is often possible to record calcium signals throughout the dendritic tree even several hundred micrometers from the recording pipette. This is also possible in vivo, where the collection of emitted fluorescence is much less efficient than in brain slice preparations (Helmchen et al., 1999; Helmchen and Waters, 2002; Svoboda et al., 1997, 1999; Waters et al., 2003). This signal-to-noise ratio is partially attributable to the excellent calcium indicators available, but is also related to the large changes in intracellular calcium concentration that occur following an AP. The intracellular calcium concentration can change by one to two orders of magnitude, from a resting intracellular concentration of approximately 50 nM to a peak concentration in the micromolar range. In contrast, the relative concentrations of other intracellular ions change by much smaller amounts. Hence although fluorescent indicators for sodium ions would offer a more direct measure of backpropagation (avoiding one of the main disadvantages of calcium indicators) the relatively small sodium concentration changes that occur lead to small fluorescence changes. Several APs are therefore typically required to generate a measurable signal with sodium indicators (Rose and Konnerth, 2001).

## 2. Backpropagation in different classes of neurons

These techniques have been applied to the study of AP backpropagation in a variety of mammalian neuronal types (Fig. 4; for reviews see also Häusser et al., 2000; Stuart et al., 1997b). The first cells where single dendritic recordings were obtained, cerebellar Purkinje cells, show only weak, almost passive backpropagation (Llinas and Sugimori, 1980; Stuart and Häusser, 1994). At the other extreme are the dendrites of dopaminergic substantia nigra neurones (Häusser et al., 1995), mitral cell apical dendrites (Bischofberger and Jonas, 1997; Chen et al., 1997) and hippocampal interneurones (Martina et al., 2000). Here APs propagate almost unattenuated

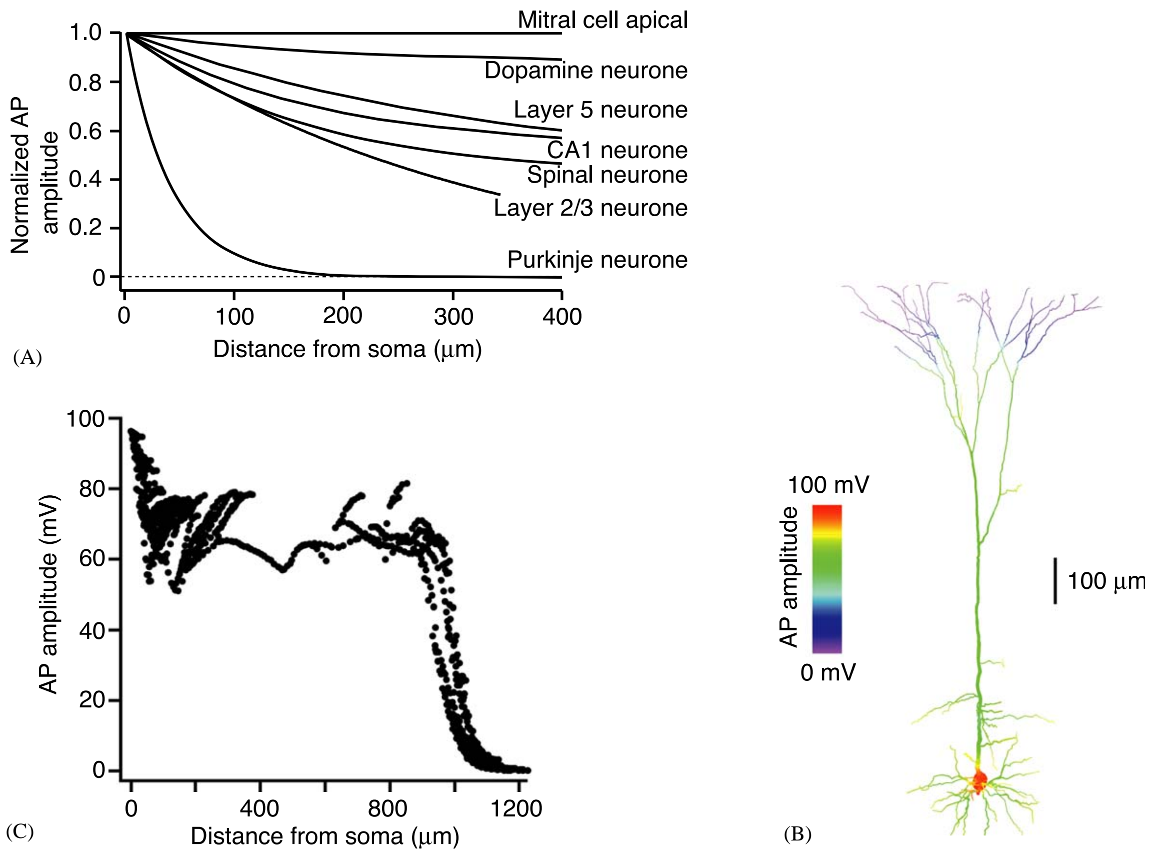



Fig. 4. Summary of backpropagation in different cell types. (A) Dendritic AP amplitude normalized to the somatic AP amplitude and plotted as a function of the distance from the soma. Based on recordings from apical dendrites of mitral cells, CA1 pyramidal cells, L5 pyramidal cells, L2/3 pyramidal cells, spinal cord motoneurones, cerebellar Purkinje cells and dopaminergic substantia nigra neurones. Adapted from (Stuart et al., 1997b; Bischofberger and Jonas, 1997; Chen et al., 1997; Waters et al., 2003). (B) Simulated backpropagation in a reconstructed L5 pyramidal neurone. Pseudocolour representation of peak dendritic AP amplitude. (C) Scatter plots of dendritic AP amplitude vs. distance. Note the amplitude increase upon propagation into side branches. Adapted with permission from Vetter et al. (2001).

through the entire dendrite, or at least those parts of the dendritic tree that are accessible to direct recording techniques. Many dendrites lie between these extremes, supporting decremental propagation. These include the apical dendrites of L5 pyramidal cells (Kim and Connors, 1993; Stuart et al., 1993, 1997a; Stuart and Sakmann, 1994; Williams and Stuart, 2000b), hippocampal CA1 pyramidal cells (Andreasen and Lambert, 1995; Magee and Johnston, 1995b; Spruston et al., 1995), motorneurones (Larkum et al., 1996) and thalamocortical neurones (Williams and Stuart, 2000a). In addition, combined whole-cell recording and calcium imaging techniques have provided evidence for backpropagation in neocortical interneurones (Kaiser et al., 2001), granule cells in the olfactory bulb (Egger et al., 2003), striatal spiny projection neurones (Kerr and Plenz, 2002) and spiny stellate neurones in L4 of the neocortex (Nevian and Sakmann, 2004).

## 3. Backpropagation in different parts of dendritic arbors

The extent of propagation may also differ between dendrites within an individual cell (Figs. 4B and C). In most cell types studied to date only one dendrite has been examined in detail. In the case of pyramidal cells this is the thick apical dendrite. Basal and oblique dendrites of pyramidal cells have only been studied with imaging techniques (Fig. 2; Antic, 2003; Frick et al., 2003; Schiller et al., 1995, 2000). Active backpropagation clearly occurs in these dendrites, but a more detailed, quantitative picture of the properties of these dendrites has yet to emerge.

The only mammalian cells in which backpropagation has been measured in direct recordings from both the thick apical and the thin lateral/basal dendrites are mitral cells of the main olfactory bulb (Bischofberger and Jonas, 1997; Chen et al., 1997; Christie and Westbrook, 2003; Debarbieux et al., 2003; Lowe, 2002; Margrie et al., 2001; Xiong and Chen, 2002). Backpropagation of APs into the apical dendrite is active and non-decremental (Bischofberger and Jonas, 1997; Chen et al., 1997; Christie and Westbrook, 2003; Margrie et al., 2001). Backpropagation into the lateral dendrites is more controversial, with three reports showing decremental backpropagation in the proximal 200 μm (Christie and Westbrook, 2003; Lowe, 2002; Margrie et al., 2001) and one showing non-decremental backpropagation over the proximal 500–600 μm (Xiong and Chen, 2002). The only available in vivo data also suggest non-decremental or weakly decremental backpropagation (Debarbieux et al., 2003), although the influence of network activity remains unclear. More distal regions of the lateral dendrite are too small to be amenable to direct recordings, but have been studied with calcium imaging techniques. Three groups reported distal signals both with single and multiple backpropagating APs (Christie and Westbrook, 2003; Debarbieux et al., 2003; Xiong and Chen, 2002), whereas one (Margrie et al., 2001) found that only four or more APs result in a measurable increase in calcium concentration in distal lateral dendrites. Calcium imaging in lateral dendrites is particularly problematic because they are both pre- and postsynaptic structures. Thus calcium could also enter through glutamate receptors activated by spillover or by excitatory granule cells (Didier et al., 2001).

The reasons for these conflicting results are unclear, but there are a number of methodological differences, including the nature and extent of the dendritic recordings (sharp or patch pipettes and the maximum distance of recordings from the soma), the affinities of the calcium indicators used (influencing the signal to noise ratio and dendritic buffer capacity) and experimental temperature. Given the experimental difficulties of these techniques, including possible perturbation by dendritic recordings and the indirect nature of calcium measurements, it is hardly surprising that there are inconsistencies in the conclusions reached by different groups. A difficulty that is particularly pronounced in mitral cells is that the resting membrane potential is in the middle of the inactivation curve for A-type potassium channels. A small perturbation in dendritic membrane potential could therefore profoundly affect propagation (Christie and Westbrook, 2003). Considering all of the available data, our interpretation is that backpropagation is decremental in the proximal lateral dendrite, but that APs invade the distal dendrite with sufficient amplitude to evoke distal calcium influx. A more quantitative assessment of backpropagation in the distal dendrite will have to await further investigation.

## 4. Backpropagation in vivo

How relevant is backpropagation in vivo? It has been argued that the ongoing synaptic input in an in vivo situation essentially precludes backpropagation (Steriade, 2001a, b). This idea might be consistent with slice studies showing inhibition of backpropagation by GABAergic input (Lowe, 2002; Tsubokawa and Ross, 1996; Xiong and Chen, 2002). In light of this effect of GABA, one might well imagine that the high levels of spontaneous activity that occur during activated states in vivo would lead to strong inhibition of backpropagation. Indeed, some early studies concluded that backpropagation was passive in neocortical layer 2/3 pyramidal neurones in vivo (Svoboda et al., 1997, 1999). Other reports, including a more recent study in which backpropagation in layer 2/3 neurones was examined both in vitro and in vivo, have shown the reverse: that active backpropagation occurs despite background synaptic activity in vivo (Fig. 3; Buzsáki and Kandel, 1998; Buzsáki et al., 1996; Helmchen et al., 1999; Quirk et al., 2001; Waters et al., 2003; Waters and Helmchen, 2004). Again these differences might be attributable to differences in experimental conditions such as cell types examined or the recording techniques employed.

## 5. What determines the extent of backpropagation?

To understand the observed differences in backpropagation between different cell types or between different dendrites of the same cell one has to ask what mechanisms govern backpropagation. Obviously a deeper understanding of these mechanisms will also help to clarify apparent inconsistencies between different experimental approaches.

With the pioneering work of Rall (Rall, 1957, 1959, 1960), the role of dendrites as integrative elements was slowly acknowledged (for a recent review see Häusser and Mel, 2003). Although there was little or no experimental data to guide the early modellers, Rall's ideas were explored further by Jack et al. (1975), concentrating particularly on how electrical signals might be shaped by the structure of the dendrite and the interplay of passive and active membrane conductances. More recently, the tendency has been to focus on heterogeneities in the densities of dendritic ion channels (Magee et al., 1998). Nonetheless, morphology can profoundly affect propagation. This is true even in axons, where propagation is very strongly influenced by active conductances, but Rall and colleagues showed by numerical calculations that active propagation is nonetheless highly sensitive to morphology (Goldstein and Rall, 1974; Manor et al., 1991; Parnas and Segev, 1979; Ramon et al., 1975). Hence both the pattern of expression of active conductances and the morphology of the dendritic tree can influence backpropagation.

### *5.1. Active dendritic conductances*

Channel densities have been mapped and the influence of pharmacological blockade of ion channels on backpropagation has been studied in a variety of cell types (Migliore and Shepherd, 2002; Reyes, 2001). In the majority of neurones investigated, propagation depends on dendritic sodium channels and may also involve calcium channels. Single-channel recordings reveal that sodium channels are present at high densities in the apical dendrites of mitral cells, virtually absent from Purkinje cell dendrites and present at intermediate densities in pyramidal cells,

consistent with the different extent of backpropagation in these cell types. Although electron micrographs show clustering of sodium channels in pyramidal cell dendrites (in the fish, Turner et al., 1994), functional inhomogeneities along dendrites have not been revealed with electrophysiological means (Bischofberger and Jonas, 1997; Magee and Johnston, 1995a; Martina et al., 2000; Stuart and Sakmann, 1994; Williams and Stuart, 2000a).

Similar results have been obtained for calcium channels although the large number of different subtypes makes general statements more difficult. A change in calcium channel subtype along the apical dendrite has been observed in hippocampal pyramidal neurones (Magee and Johnston, 1995a). There is also indirect electrophysiological evidence for a dendritic "hotspot" in calcium channel density in layer 5 neocortical pyramidal neurones (Helmchen et al., 1999; Schaefer et al., 2003b; Schiller et al., 1997; Yuste et al., 1994).

The third ion channel type studied extensively are potassium channels. In both CA1 (Hoffman et al., 1997) and neocortical L5 pyramidal neurones (Bekkers, 2000a; Korngreen and Sakmann, 2000), A-type channels were shown to be present in the apical dendrites. In CA1 pyramidal cells, A-type channels occur at a high density, which increases markedly with distance from the soma (Figs. 5A and B). Pharmacological blockade of these channels promotes backpropagation, demonstrating their importance in limiting dendritic AP propagation (Figs. 5C and D). A-type channels also modulate backpropagation in L5 pyramidal neurones, but no change in channel density has been seen along the apical dendrite, in contrast with hippocampal pyramidal neurones. Furthermore, the density of slowly inactivating potassium currents shows a slight decrease with distance from the soma and this may enhance the excitability of distal sites (Bekkers, 2000a; Korngreen and Sakmann, 2000).

Unfortunately, currently available recording techniques allow only a semi-quantitative description of dendritic channel kinetics and densities. Intracellular dendritic recordings suffer from insufficient space clamp, a severe problem that is impossible to overcome, although off-line compensation may offer a partial solution (Schaefer et al., 2003a). Cell-attached or inside-out patch recordings are considered the most accurate way to determine channel kinetics. However, they require exact determination of the size of the dendritic patch, which is difficult not least because seal formation may stretch the membrane, altering the apparent surface area. Furthermore, recording may severely perturb channel properties, for instance by altering channel kinetics, steady-state inactivation or voltage dependence (Clark et al., 1997; Fenwick et al., 1982). Finally, hundreds of patches would be required to determine channel densities for an individual cell and thus to investigate the variability in channel distribution that might underlie variability in propagation. This precludes an analysis of cell-to-cell variability of channel distribution based on cell-attached recordings.

### 5.2. *Effects of neuronal morphology on backpropagation*

Axonal propagation can fail where a branch point or tapering of the axon results in propagation from a region of higher to lower input impedance (Goldstein and Rall, 1974). In dendrites the reverse situation may be the case, sustaining backpropagating APs further into the dendritic tree. It is not possible to study the effects of morphology quantitatively in physiological experiments since they cannot be distinguished from the influence of ion channel distribution. For example, in mitral cells, where both the thick apical and the thin lateral dendrites have been

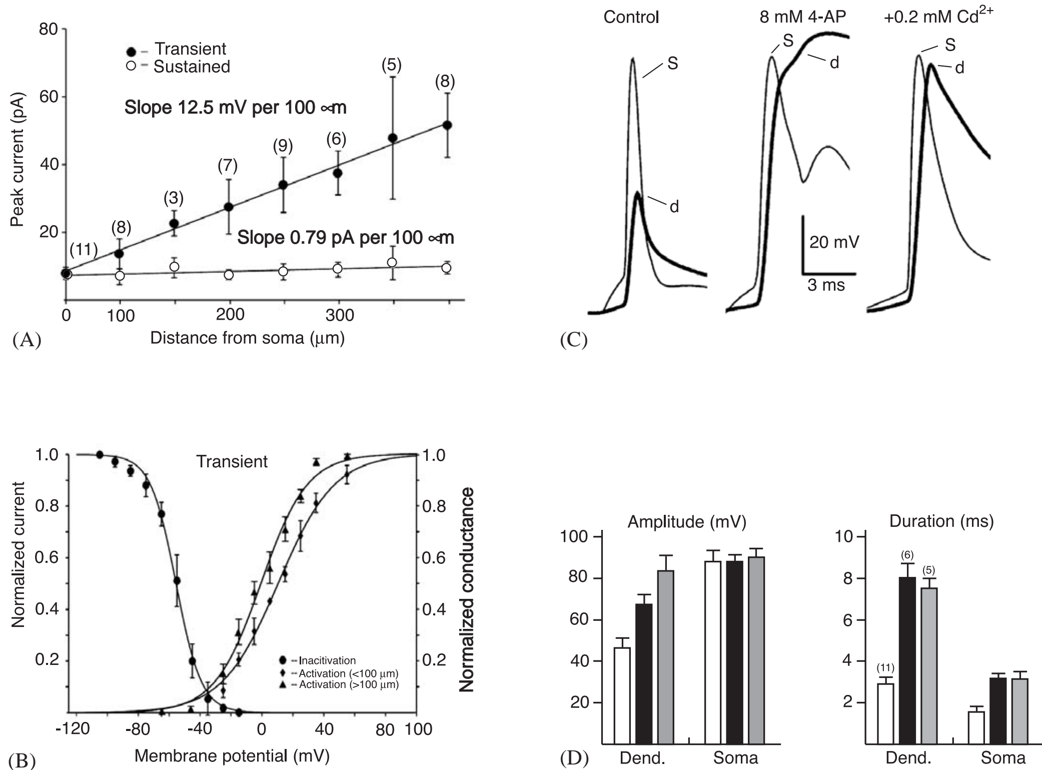



Fig. 5. A-type potassium channels regulate backpropagation in CA1 pyramidal neurones. (A) Cell attached patches reveal an increase in transient potassium currents with distance from the soma. (B) Activation and inactivation curves for somatic and proximal dendritic (<100 μm, diamonds) and distal dendritic (triangles) transient potassium channels. (C) Under control conditions, the somatic AP (s) is severely attenuated upon propagation into the dendrite (d, 250 μm). Blocking potassium currents with 4-AP resulted in a dramatic increase of the dendritic AP and additionally the generation of a slower plateau potential, that was sensitive to cadmium. (D) Summary plot for control (white bars), 3 mM 4-AP (black bars) and 8 mM 4-AP (grey bars). Adapted with permission from Hoffman et al. (1997).

studied electrophysiologically, the differences in backpropagation (see above) are consistent with a large contribution of dendritic morphology. However, a high density of sodium channels has also been reported for the apical dendrite (Bischofberger and Jonas, 1997). Hence the relative contributions of morphology and channel distributions to this difference are unclear. Separation of the effects is possible in compartmental simulations with reconstructed neurones of known dendritic geometry. Early simulations investigated how dendrites influence the axo-somatic AP pattern, demonstrating that dendritic arborization alone can turn a regularly spiking into a bursting or fast spiking neurone (Mainen and Sejnowski, 1996; Pinsky and Rinzel, 1994). However, differences in sodium, calcium and potassium channel densities can also explain differences in propagation (Golding et al., 2001; Magee et al., 1998; Mainen et al., 1995; Pinsky and Rinzel, 1994; Rapp et al., 1996; Stuart et al., 1997b; Vetter et al., 2001).

More recent studies indicate that the experimentally observed differences in propagation between different types of neurones could, in principle, be attributable solely to differences in

morphology (Vetter et al., 2001). The same channel distributions and kinetics result in non-decremental propagation in morphologically accurate models of dopaminergic substantia nigra neurones, in decremental propagation in pyramidal neurones and in failure of propagation in cerebellar Purkinje cells (Häusser et al., 1995; Stuart and Häusser, 1994; Stuart and Sakmann, 1994). As for different neurone types the channel expression is so vastly different, it is hard to decide experimentally how strongly dendritic geometry influences AP backpropagation. By focussing on variation within one cell type, thick tufted neocortical L5B pyramids, it has been shown that small differences in the branching pattern along the apical dendrite control the coupling between the axonal and dendritic AP initiation zones (Larkum et al., 1999b; Schaefer et al., 2003b). Predictions made from detailed compartmental models of pyramidal cells were tested by measuring this coupling and the dendritic branching pattern in a cohort of L5 pyramids. This study confirmed that the variation introduced by differences in dendritic arborization is not necessarily overruled by putative differences in ion channel expression (Fig. 6; Schaefer et al., 2003b).

### *5.3. Modulation of backpropagation by synaptic input*

Dendritic geometry and the distribution of ion channels together set a baseline for backpropagation. AP backpropagation can also be modulated on a more dynamic timescale by synaptic input and by neuromodulators (McCormick, 1992; McCormick et al., 1993; Williams and Stuart, 2003).

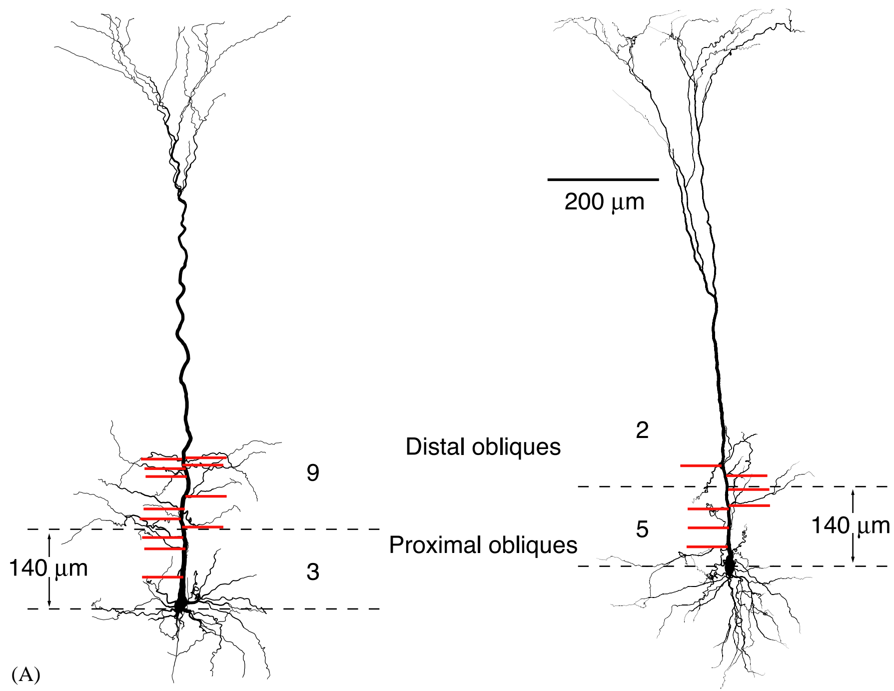
Interactions between synaptic input and backpropagating APs have been studied both for excitatory and inhibitory input. Appropriately timed excitatory input in the distal dendrite amplifies backpropagating APs and may lead to dendritic spiking and/or burst firing (Larkum et al., 1999a, b; Larkum and Zhu, 2002; Magee and Johnston, 1997; Schaefer et al., 2003b; Stuart and Häusser, 2001). The large conductance induced by the backpropagating APs in turn shunts the synaptic input (Häusser et al., 2001). In contrast, inhibitory input may suppress backpropagation (Tsubokawa and Ross, 1996; Xiong and Chen, 2002; Lowe, 2002). Many neuromodulators also influence backpropagation, for instance, via muscarinic or adrenergic receptors (McCormick, 1992; McCormick et al., 1993). The effects of neuromodulators may be more complex but will often lead to a net enhancement of backpropagation. For example, in hippocampal CA1 pyramidal neurones muscarinic agonists enhance the backpropagation by inhibiting potassium channels, which has a progressively stronger effect on the backpropagation of later APs during a brief train (Tsubokawa and Ross, 1997; Hoffman and Johnston, 1999).

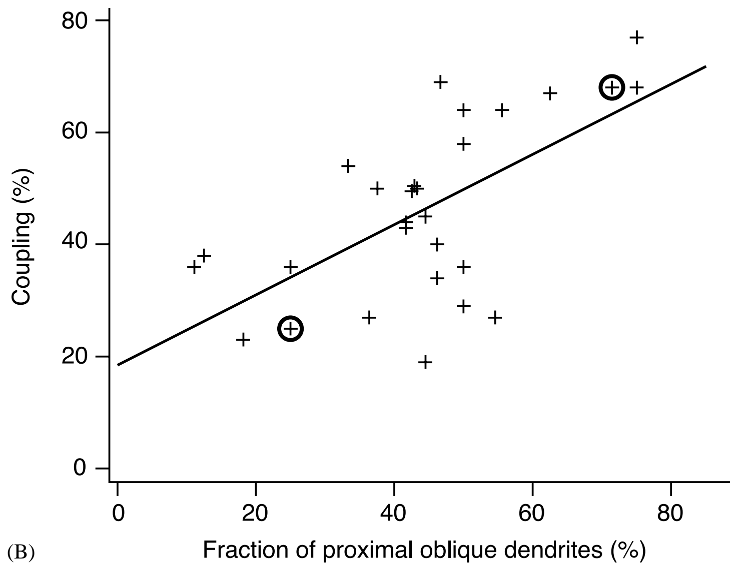
## 6. Potential functions of backpropagating APs

Several functions have been attributed to backpropagating APs. We focus here on four possible functions that involve either an interaction between a backpropagating AP and synaptic input or secondary effects of the backpropagating AP mediated by dendritic calcium influx through voltage-gated calcium channels.

### *6.1. Short-term changes in synaptic efficacy*

Backpropagating APs can lower the threshold for the induction of dendritic regenerative potentials and thus influence a neurone's AP firing pattern. In some types of neurones the


200 μm
Distal obliques
Proximal obliques
9
3
2
5
140 μm
140 μm
(A)


Coupling (%)
Fraction of proximal oblique dendrites (%)
0
20
40
60
80
(B)

initiation of dendritic APs is accompanied by several somatic APs (Larkum et al., 1999b; Schiller et al., 1997). Here the interaction of a backpropagating AP, generated by basal dendritic input and near-coincident excitatory synaptic input to the apical tuft, generates a short burst of APs (Larkum et al., 1999b, 2001; Schaefer et al., 2003b; Williams and Stuart, 1999). The basal/oblique and the apical tuft dendritic trees of pyramidal cells in the somatosensory cortex receive ascending thalamic input from different nuclei, corresponding to specific sensory (lemniscal) and more diffuse (paralemniscal) pathways, respectively. The paralemniscal projections to the tufts are thus candidates for mediating coincidence-dependent increased sensory excitation of those pyramidal neurones in the neocortex that have their tufts located in L1 and which receive (lemniscal) sensory input via their basal dendrites.

Like single APs, a burst of APs is conveyed via the axonal arbor towards the cell's target neurones. At axonal boutons, short-term facilitation of release can render the transmission of AP bursts more effective than the transmission of single APs (Lisman, 1997; Williams and Stuart, 1999). At boutons with short-term depression, this effect will be less pronounced (Markram et al., 1998a, b; Reyes et al., 1998; Thomson, 2003). Individual pyramidal neurones are connected to different classes of postsynaptic cells via synapses that are either facilitating of depressing depending on the target cell type (e.g. Reyes et al., 1998; Rozov et al., 2001). Thus, by inducing axo-somatic AP burst firing, backpropagating APs in neocortical pyramidal neurones can change, on the short term, the "effective" wiring of pyramidal neurones to their different target cells.

### 6.2. Long-term changes in synaptic efficacy

A backpropagating AP could also represent a global signal to the dendritic arbor that reports output activity to sites of synaptic input and induces localised long-term changes in efficacy of excitatory synapses. The induction of such changes depends on correlated pre- and postsynaptic AP activity during a relatively narrow time window on the order of about 100 ms (for review, see Linden, 1999). Depending on the precise order of occurrence of the axonal AP in the presynaptic neurone and the backpropagating AP in the dendrites of a postsynaptic cell, synaptic efficacy may either increase or decrease after repeated epochs of such correlated activity (Bell et al., 1997; Magee and Johnston, 1997; Markram et al., 1997; Bi and Poo, 1998; Debanne et al., 1998; Egger et al., 1999; Feldman, 2000; Froemke and Dan, 2002; Li et al., 2004). Changes in synaptic efficacy induced by repeated epochs of near coincident pre- and postsynaptic APs have been termed spike time dependent plasticity (STDP). The long-term changes in synaptic efficacy are

Fig. 6. Backpropagation-mediated coupling (Larkum et al., 1999a, b; Schaefer et al., 2003b) controlled by dendritic morphology. (A) Neurolucida reconstruction of two L5 pyramidal neurones with low coupling (left, 25%) and high coupling (right, 67%) in the experiment. For details of the measurement see Schaefer et al. (2003b). The position of oblique dendrites is indicated by red bars and the number of proximal ($<140\,\mu m$ away from the soma) and distal ($>140\,\mu m$) branchings are indicated. (B) For 28 pyramids coupling was measured and the fraction of proximal oblique dendrites was determined. Coupling increases with increasing fraction of proximal oblique dendrites ($r=0.63$, $p<0.0005$) indicating that the influence of morphology is not overruled by variations in channel densities and distribution. Adapted from Schaefer et al. (2003b).

often dependent on increased dendritic calcium influx through NMDA receptors, suggesting that backpropagating APs are part of a mechanism that controls the plasticity of synapses through metabolic cascades that are driven by a brief rise in intracellular calcium concentration (for reviews, see Lisman et al., 2002; Sjöström and Nelson, 2002).

The mechanisms by which STDP increases synaptic efficacy involve increased calcium influx via NMDARs. In favour of this view a local, spine-restricted supralinear increase in calcium concentration evoked by coincident EPSPs and backpropagating APs has been demonstrated in hippocampal CA1-pyramidal neurones (Yuste and Denk, 1995), cortical L5 pyramidal neurones (Köster and Sakmann, 1998), spiny stellate neurones in cortical L4 (Nevian and Sakmann, 2004) and bitufted interneurones in cortical L2/3 (Kaiser et al., 2004). In spines of L4 stellate cells the time course of the supralinear summation of calcium signals, evoked by near coincident EPSP and backpropagating APs matches the deactivation time course of NMDAR channels (Nevian and Sakmann, 2004).

The mechanisms by which synaptic efficacy is *reduced* are possibly more diverse. The release of retrogradely acting factors from dendrites that reduce presynaptic glutamate release has been suggested (Egger et al., 1999; Sjöström et al., 2003). The release of such retrogradely acting factors is governed by different calcium-dependent metabolic cascades in different neuronal pathways. Notably, however, the same timing of pre- and postsynaptic APs can have opposite effects in different preparations (e.g. Bell et al., 1997; Markram et al., 1997) and even in different synaptic pathways of the neocortex (Egger et al., 1999).

How global is the backpropagating AP? Due to the fact that backpropagating APs are attenuated to a varying degree in different classes of neurones, such as pyramidal, stellate and bitufted cells, the contribution of backpropagating APs to STDP might, not surprisingly, vary even in the same class of neurones, depending on the exact location and distribution of the synaptic contacts onto their dendritic arbors. This is true especially for pyramidal cells with their basal and apical dendritic arbors, which can have very different geometries. Furthermore the extent of backpropagation increases with the number and frequency of APs (Larkum et al., 1999a) and the extent of backpropagation is greatly dependent on subthreshold excitatory input (Waters et al., 2003).

### 6.3. Local synaptic feedback

Another potential function of AP backpropagation relies upon a transient increase in dendritic calcium concentration that then triggers the release of fast acting transmitters from dendrites. In the olfactory bulb the principal neurones, mitral cells, and the dominant interneurone class, granule cells, form an intricate network of dendro-dendritic synapses (Isaacson, 2001; Isaacson and Strowbridge, 1998; Jahr and Nicoll, 1980; Margrie et al., 2001; Price and Powell, 1970; Rall and Shepherd, 1968; Shepherd and Greer, 1998; Urban and Sakmann, 2002; Schoppa and Urban, 2003). Dendritic GABA release from granule cells, dendritic glutamate release from mitral cells onto granule cells and mitral cell self-excitation are influenced by the extent of backpropagation (Isaacson, 1999; Margrie et al., 2001; Salin et al., 2001; Christie and Westbrook, 2003; Egger et al., 2003; Lowe, 2002; Xiong and Chen, 2002). Only those granule cells that contact the lateral dendrites of mitral cells in regions where such calcium influx is high enough to evoke transmitter release can induce lateral inhibition. In the olfactory bulb lateral inhibition is often described as a

potential cellular correlate of contrast enhancement (Margrie and Schaefer, 2003; Shepherd and Greer, 1998; Urban, 2002; Yokoi et al., 1995). Hence backpropagating APs may regulate the precision of odour discrimination.

Similarly, backpropagation in some neocortical interneurones (Kaiser et al., 2001, 2004) may evoke dendritic release of GABA onto axonal boutons of pyramidal cells (Zilberter et al., 1999) and backpropagating APs in pyramidal neurones may control the release of glutamate or cannabinoid from the dendrite (Zilberter, 2000; Sjöström et al., 2003; Kreitzer and Regehr, 2002; Trettel and Levine, 2003). These two local feedback loops could regulate the AP activity of both the interneurons and the pyramidal cells to maintain stable patterns of APs in local cortical circuits.

### 6.4. *Stabilisation of nascent synapses*

Backpropagation of APs could, in principle, also be required for stabilizing early synaptic contacts in neuronal circuits during the postnatal, experience-dependent development of the CNS. Excitatory synapses are formed mostly on dendrites and thus signaling between axonal growth cones of the projection neurones and the dendrites of the recipient neurones is likely to involve signals emitted by electrically active dendrites via calcium dependent processes.

During early postnatal stages, neurones often exhibit higher levels of spontaneous APs than in the adult. It is tempting to speculate that backpropagating APs not only contribute to synchronising a developing network via dendro-dendritic gap junctions (Peinado et al., 1993; Peinado, 2001) but might also evoke dendritic release of trophic factors which could serve as attractors for axonal growth cones or as a signal for axon collateralisation (Poo, 2001; McAllister et al., 1999). AP backpropagation provides the dendritic arbor with a modified copy of the axonal AP pattern and could promote the stabilisation of initial synaptic connections between those neuronal assemblies that fire together. At early postnatal stages the relative contribution of NMDAR-mediated synaptic currents is larger than in the adult CNS (Crair and Malenka, 1995) and at nascent excitatory synapses the postsynapse contains only NMDARs (Washbourne et al., 2002) and presumably these nascent synapses are electrically very weak or even silent. Highly localised calcium inflow into dendrites via postsynaptic NMDA receptors may still occur if the $Mg^{2+}$ block of NMDARs (Mayer et al., 1984) is transiently relieved by backpropagating APs. This putative function of AP backpropagation in refining the specificity neuronal circuits by coincident pre- and postsynaptic APs in neuronal assemblies during early postnatal development has yet to be studied in detail.

## Acknowledgements

We thank Greg Stuart, Nelson Spruston, Nathan Urban, Arnd Roth, Troy Margrie, Fritjof Helmchen, Mike Häusser, and Srdjan Antic for comments on the manuscript, Srdjan Antic, Dax Hoffman and Arnd Roth for permission to use their data and Ramon Granadillo for bibliographic assistance.

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