# SOMATO-DENDRITIC INTERACTIONS UNDERLYING ACTION POTENTIAL GENERATION IN NEOCORTICAL PYRAMIDAL CELLS IN VIVO

Alain Destexhe,[1] Eric J. Lang[2] and Denis Paré[1]

[1] Laboratoire de Neurophysiologie, Université Laval,
Québec G1K 7P4, Canada

[2] Department of Physiology and Neuroscience, New York University,
New York, NY 10016, USA

In: *Computational Neuroscience: Trends in Research, 1998*, Edited by Bower, J.,
Plenum Press, New York, pp. 167-172, 1998.

Action potential (AP) generation and propagation through the dendritic tree of pyramidal neurons has received much attention lately[1]. Experiments indicate that inhibitory postsynaptic potentials (IPSPs) have a decisive effect in controlling action potential invasion in dendrites[2, 3]. However, these phenomena were observed in slices, and remain to be investigated under *in vivo* conditions where neurons are subject to intense synaptic activity. Here, we have combined computational models with intracellular recordings of neocortical pyramidal cells in order to investigate how spikes can be controlled by IPSPs *in vivo*.

## EXPERIMENTAL OBSERVATIONS

We obtained intracellular recordings of morphologically-identified pyramidal neurons (n=42) from the parietal cortex (areas 5-7) in barbiturate-anesthetized cats and compared APs evoked by synaptic inputs, antidromic invasion, or direct current injection (methods were described in detail elsewhere[4]). The neurons were recorded within 1-2 mm of a ten-electrode array (Fig. 1A).

Evidence was obtained that cortical stimuli delivered at different depths activate partially segregated sets of afferents that preferentially end at corresponding cortical depths, thus exerting maximal effects on different compartments of pyramidal neurons. As shown in Fig. 1B, IPSPs elicited by deep cortical shocks were larger in amplitude (12.4 $\pm$ 2.25 mV compared to 4.8 $\pm$ 1.89 mV), had a shorter peak-latency (23.4 $\pm$ 2.93 ms compared to 41.3 $\pm$ 5.33 ms), a more positive reversal potential (-73.8 $\pm$ 1.64 mV compared to -80.3 $\pm$ 1.75 mV) and were associated with larger decreases in

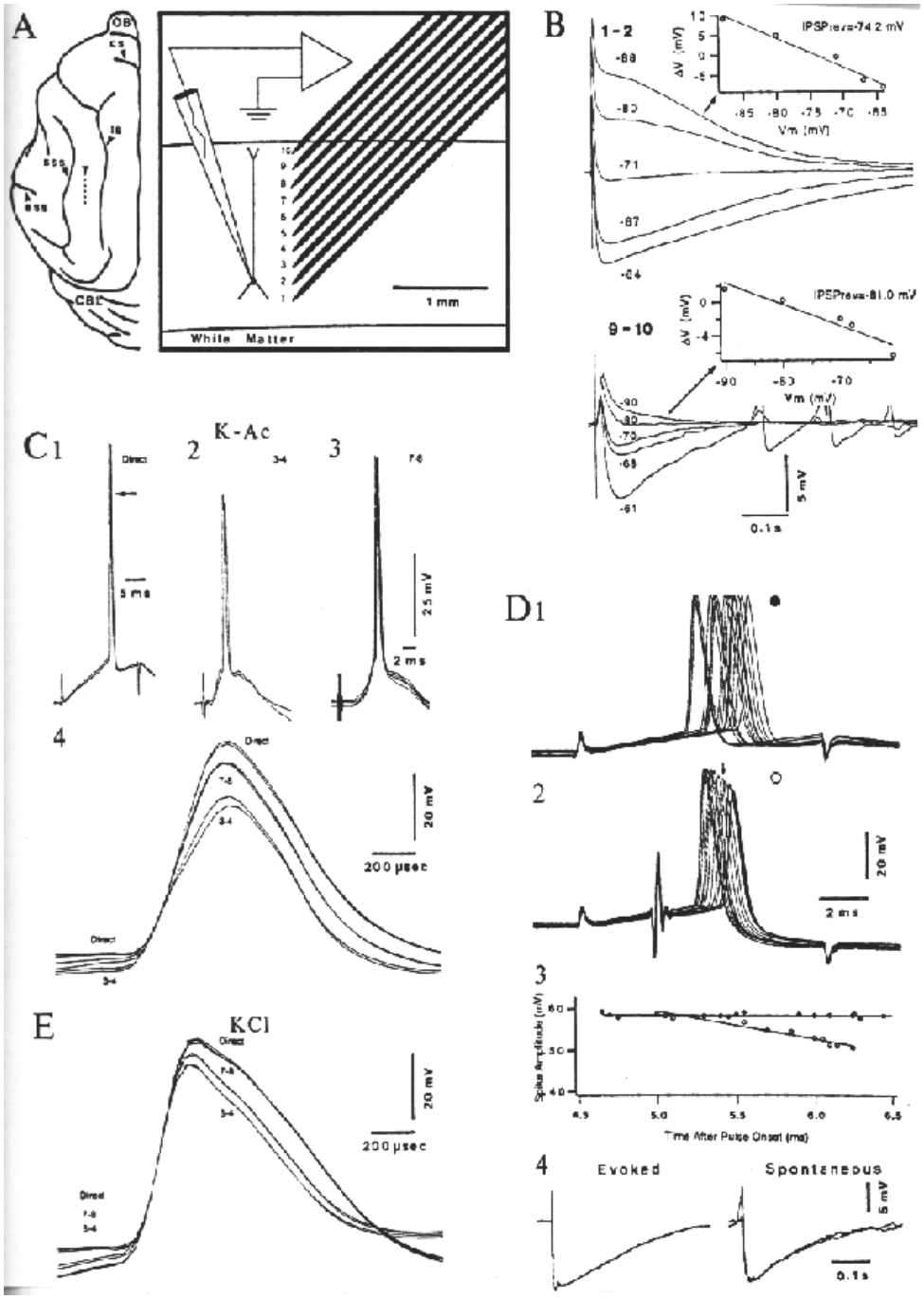


**Figure 1.** Spike attenuation in neocortical pyramidal cells *in vivo*.
A. Experimental paradigm. B. EPSP/IPSP sequences for proximal (1-2) and superficial (9-10) microstimulation. C. Spike attenuation with K-Acetate-filled electrodes (Direct = spike evoked by current injection). D. Spikes evoked by current injection. 1: control, 2: in the presence of evoked IPSP, 3: progressive attenuation of amplitude with latency; 4: comparison between evoked and spontaneous IPSPs. E. Spike attenuation with Chloride-filled electrodes. Modified from a previous study[4].

input resistance (63 ± 8.4% compared to 27 ± 5.1%) than those elicited by superficial cortical stimuli. These differences were statistically significant (paired t-test, $p<0.05$).

Using this paradigm, we investigated the effect of synaptic activity occurring in different somatodendritic compartments on the shape of the somatic action potential. The intensity of the cortical stimuli was adjusted to just above the spike threshold from rest. In pyramidal cells recorded with KAc pipettes (n=29), orthodromic spikes were reduced in amplitude and duration (Fig. 1C2-3) compared to APs elicited by short depolarizing current pulses (Fig. 1C1), consistent with previous findings in the amygdala[5]. The magnitude of the amplitude decrement was a function of the cortical stimulation depth relative to the position of the recorded cells (Fig. 1C). In both deep and superficial cells, maximal spike reductions were obtained with stimuli applied at the soma level.

To ensure that these differences between current-evoked and orthodromic spikes did not reflect differences in the slopes of the depolarization triggering the APs, we investigated the influence of sub-threshold cortical shocks on APs evoked by intracellular current pulses adjusted to elicit spikes in 50% of the trials. As shown in Fig. 1D, the amplitude of the direct spikes remained constant (Fig. 1D1), whereas the amplitude of spikes affected by IPSPs was progressively decreased (by up to 8 mV) as their latency increased (Fig. 1D2).

To assess the relative importance of local changes in input resistance and membrane potential in these phenomena, pyramidal neurons were recorded with KCl pipettes (n=30). Whereas in cells recorded with KAc pipettes the IPSP reversals averaged -78.1 ± 0.77 mV (n=4), in neurons recorded with KCl pipettes they averaged -52 ± 2.89 mV (n=13). Chloride diffusion inside the cells thus caused a 20-25 mV shift in the IPSP reversal potential, bringing it close to the spike threshold. In these conditions, high intensity cortical shocks applied at the soma level produced spike amplitude reductions of 7.45 ± 1.22 mV (n=10; Fig. 1E) compared to 15.58 ± 1.24 (n=9) in cells recorded with KAc pipettes (Fig. 1C).

## COMPUTATIONAL MODELS

Computational models were based on a cellular reconstruction provided by R. Douglas and K. Martin (Fig 2A) and were simulated using NEURON (methods were described in detail elsewhere[4]). The cell was corrected for spines and an axon hillock and initial segment were included. Passive parameters were estimated by fitting the model to a voltage trace from a layer V cortical pyramidal cell recorded in the present series of experiments (Fig 2B). Active currents were inserted into the soma, dendrites and axon with different densities in accordance with available experimental evidence[6]. $Na^+$ channel density was low in soma and dendrites (70 pS/$\mu m^2$ as in adult pyramidal cells[6] – range tested 20-100 pS/$\mu m^2$), but was high in the axon, as indicated by experimental[7] and modeling studies[8, 9]. The delayed-rectifier was also distributed uniformly in the dendrites and no calcium currents were included. All currents were described by Hodgkin-Huxley equations, and two different kinetic models were tested for $Na^+$ and $K^+$ channels[8, 10] with negligible influence on the present results.

The relative density of glutamatergic and GABAergic synapses in different regions of the cell was distributed based on morphological data reviewed previously[11, 12]. Glutamatergic synapses were located exclusively in dendrites at more than 40 $\mu$m away from the soma. GABAergic synapses were located in all compartments of the neuron, with the highest density in the somatic region[11, 12]. Synaptic currents were simulated using kinetic models of postsynaptic receptors [13]. The depth-dependent features of

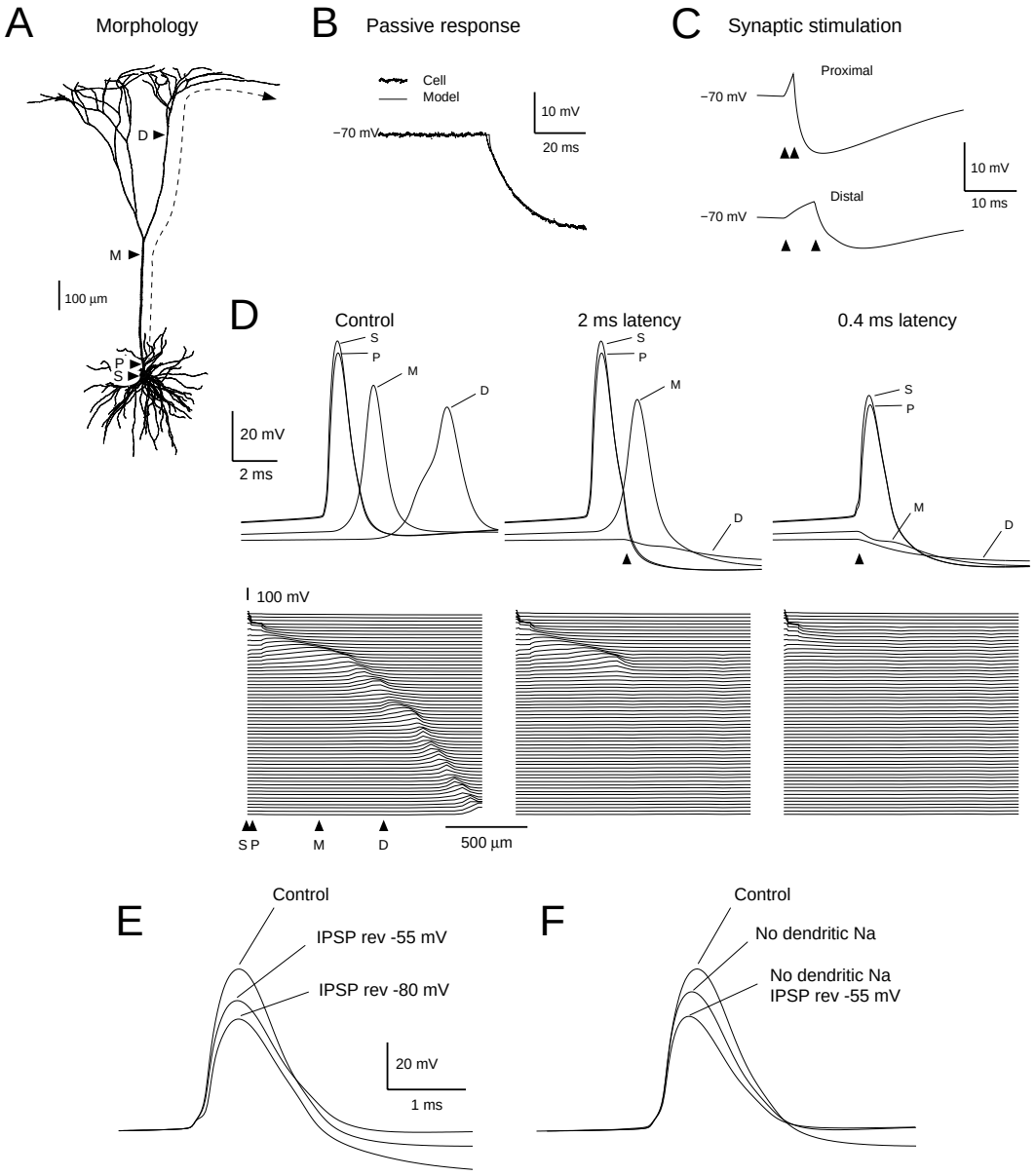


**Figure 2.** Model of spike attenuation in cortical pyramidal cells.
A. Morphology of a reconstructed layer V pyramidal cell. B. Passive response of the model. C. EPSP/IPSP sequences evoked by proximal and distal stimulation. D. Attenuation of spikes by IPSPs. The spike evoked by current injection is shown in control conditions and with IPSP at 2 different latencies. Bottom graphs in D show the spatial profile of membrane potential (path indicated by dotted line in A). These plots were made over a period of 12 ms in steps of 0.2 ms (from top to bottom). E. Effect of IPSP reversal on spike amplitude. F. Effect of removing dendritic $Na^+$ channels on spike amplitude. Modified from a previous study[4].

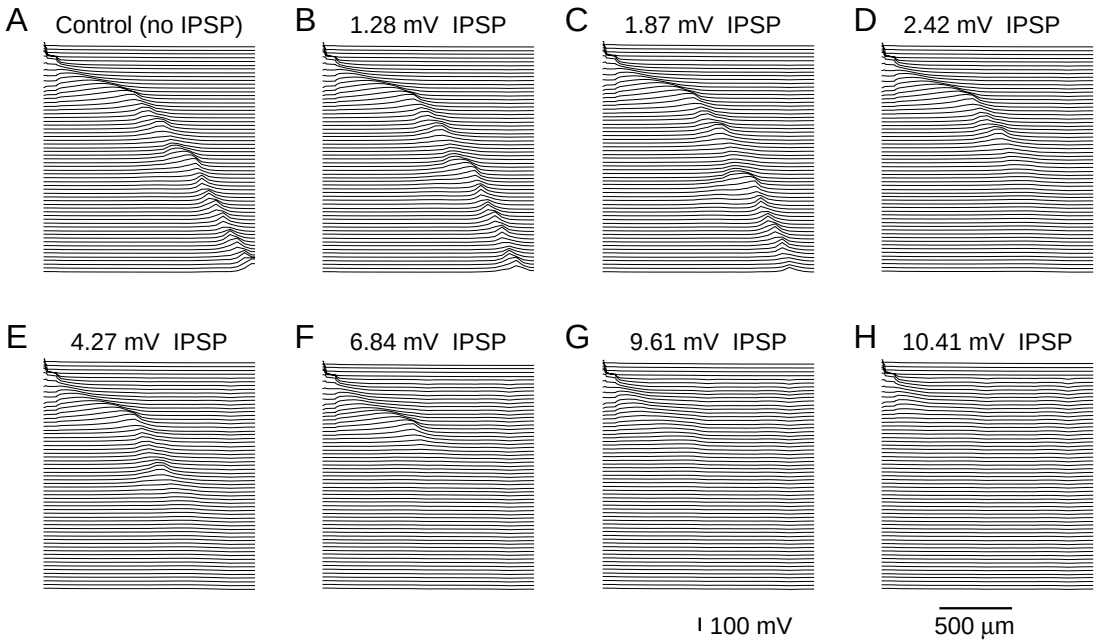


**Figure 3.** Simulated IPSPs are very effective in suppressing backpropagating action potentials. Each plot represents dendritic membrane potential profiles similar to Fig. 2D (0.4 ms latency). A-H: IPSPs of increasing somatic amplitude (indicated in each graph) influenced the velocity of backpropagating spikes (B-C), then suppressed backpropagation (D-H). Modified from a previous study[4].

evoked EPSP/IPSP sequences (Fig 2C) could be reproduced assuming that stimuli activated synapses preferentially in a relatively localized dendritic region[4].

In the absence of other stimuli, spikes evoked by current injection initiated in the initial segment and backpropagated successively to soma and dendrites (Fig 2D, Control). The amplitude and duration of action potentials was markedly affected by IPSPs. IPSPs occurring with small latencies with respect to the spike led to significant reductions up to 25 mV (Fig 2D), with maximal attenuations for IPSPs simulated at the perisomatic level.

To simulate the effect of Chloride injection (Fig. 1E), the IPSP reversal potential was changed to -55 mV. The significant attenuation observed in these conditions (Fig 2E) shows that the increased conductance due to IPSPs (shunt) only accounts for about 60% of spike attenuation. Removing dendritic $Na^+$ channels (Fig 2F) accounted for the remaining 40 % of spike attenuation, showing that dendritic $Na^+$ currents significantly contribute to action potential amplitude. The full attenuation of spike amplitude could be accounted by combining this effect with the shunt described above (Fig 2F, lowermost curve).

The model therefore suggests that spike amplitudes are reduced proportionally to the dendritic area that is "shut-off" by IPSPs, resulting in a spike that contains less or no participation from dendritic $Na^+$ channels. In addition, there is an important current leak through the open channels underlying the IPSPs, resulting in further attenuation. These two factors diminish in importance with more superficial stimuli.

A corollary observation is that, by preventing the participation of dendritic $Na^+$ channels, IPSPs suppress spike backpropagation in distal dendrites (Fig 3). Backpropagating action potentials are fragile[2, 3, 14, 15] and the present simulations show that they can be suppressed by small-amplitude IPSPs. As these IPSPs are well within the range of spontaneous IPSPs occurring *in vivo* (see Fig 1D4), our results corroborate recent optical imaging evidence that spike-related calcium transients remains confined

to proximal dendrites *in vivo*[16].

## CONCLUDING REMARKS

In conclusion, by combining computational models with intracellular recordings of neocortical pyramidal cells *in vivo*, we provided a plausible explanation for our experimental observations on how action potential are controlled by IPSPs in these cells. Models and experiments suggest that IPSPs affect action potentials by two mechanisms: a shunt effect due to the opening of ion channels underlying the IPSPs, and a voltage-dependent effect by preventing dendritic $Na^+$ channels to participate to the somatic spike. Further, we suggest that under conditions of synaptic activity that occurs during active states *in vivo*, the conductance shunt and the voltage-dependent effect of synaptic inputs do not provide favorable conditions for backpropagating action potentials[17].

## REFERENCES


1. Stuart, G., Spruston, N., Sakmann, B. and Hausser, M. Action potential initiation and back-propagation in neurons of the mammalian CNS. *Trends Neurosci.* **20**: 125-131 (1997) .
2. Kim H.G., Beierlein M. and Connors B.W. Inhibitory control of excitable dendrites in neocortex. *J. Neurophysiol.* **74**: 1810-1814 (1995).
3. Tsubokawa H. and Ross W.N. IPSPs modulate spike backpropagation and associated $[Ca^{2+}]$ changes in the dendrites of hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* **76**: 2896-2906 (1996).
4. Paré, D., Lang, E.J. and Destexhe, A. Inhibitory control of somatic and dendritic sodium spikes in neocortical pyramidal neurons *in vivo*: an intracellular and computational study. *Neuroscience*, in press (1998).
5. Lang, E.J. and Paré, D. Synaptic and synaptically activated intrinsic conductances underlie inhibitory potentials in cat lateral amygdaloid projection neurons in vivo. *J. Neurophysiol.* **77**: 353-363 (1997)
6. Magee J.C. and Johnston D. Characterization of single voltage-gated $Na^+$ and $Ca^{2+}$ channels in apical dendrites of rat CA1 pyramidal neurons. *J. Physiol.* **487**: 67-90 (1995).
7. Black J.A., Kocsis J.D. and Waxman S.G. Ion channel organization of the myelinated fiber. *Trends Neurosci.* **13**: 48-54 (1990).
8. Mainen Z.F., Joerges J., Huguenard J.R. and Sejnowski T.J. A model of spike initiation in neocortical pyramidal neurons. *Neuron* **15**: 1427-1439 (1995).
9. Rapp, M., Yarom, Y., and Segev, I. Modeling back propagating action potential in weakly excitable dendrites of neocortical pyramidal cells. *Proc. Natl. Acad. Sci. USA* **93**: 11985-11990 (1996).
10. Traub R.D. and Miles R. *Neuronal Networks of the Hippocampus.* Cambridge University Press, Cambridge (1991).
11. DeFelipe J. and Fariñas I. The pyramidal neuron of the cerebral cortex: morphological and chemical characteristics of the synaptic inputs. *Progress Neurobiol.* **39**: 563-607 (1992).
12. White E. L. *Cortical circuits.* Birkhauser, Boston, MA (1989).
13. Destexhe, A., Mainen, Z.F. and Sejnowski, T.J. Kinetic models of synaptic transmission. In: *Methods in Neuronal Modeling* (2nd ed), edited by C. Koch and I. Segev. MIT Press, Cambridge, MA, pp. 1-26 (1998).
14. Callaway J.C. and Ross W.N. Frequency-dependent propagation of sodium action potentials in dendrites of hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* **74**: 1395-1403 (1995).
15. Spruston N., Schiller Y., Stuart G. and Sakmann B. Activity-dependent action potential invasion and calcium influx into hippocampal CA1 dendrites. *Science* **268**: 297-300 (1995).
16. Svoboda, K., Denk, W., Kleinfeld, D. and Tank, D.W. In vivo calcium dynamics in neocortical pyramidal neurons. *Nature* **385**: 161-165 (1997).
17. Research supported by grants from MRC, NSERC and FRSQ. E.J.L. was supported by a NINDS fellowship.