

Signal enhancement in distal cortical dendrites by means of interactions between active dendritic spines

(synaptic efficacy/dendritic integration/neural modeling/saltatory conduction/memory mechanisms)

G. M. SHEPHERD*, R. K. BRAYTON†, J. P. MILLER‡, I. SEGEV§, J. RINZEL§, AND W. RALL§

*Section of Neuroanatomy, Yale University School of Medicine, New Haven, CT 06510; †IBM Watson Research Center, Yorktown Heights, NY 10598; ‡Department of Zoology, University of California, Berkeley, CA 94720; and §Mathematical Research Branch, National Institutes of Health, Bethesda, MD 20205

Communicated by Edward V. Evarts, December 4, 1984

ABSTRACT Pyramidal neurons in the cerebral cortex characteristically give rise to an apical dendrite, whose distal dendritic branches in layer I are covered with spines. These spines are known to be sites of synaptic connections, but the physiological properties of the spines and the functional significance of their responses are still largely unknown. The main function attributed thus far to these synaptic responses, situated at a great distance from the neuronal cell body, is slow background modulation of impulse output in the axon. In pursuing computer simulation analysis of electrical properties of dendrites, we have obtained results suggesting interactions between distal dendritic spines. If the heads of dendritic spines have excitable membrane properties, the spread of current from one or several spines could bring adjacent spines to their thresholds for impulse generation. This could give rise to a sequence of spine head action potentials, representing a saltatory propagation, from one or more excitable spine heads to nearby excitable spine heads, in the distal dendritic branches. Both the amplification due to several spine action potentials and the possibility of propagation into more proximal branches would increase the efficacy of distal synaptic inputs. Because of nonlinear dependence upon several modifiable parameters (such as spine stem resistance and membrane excitability) and upon the spatio-temporal pattern of synaptic input, such contingent synaptic enhancement would be particularly relevant to cortical functions underlying information processing and to plasticity underlying learning and memory.

The main type of neuron in the cerebral cortex is the pyramidal neuron. Its cell body gives rise to several basal dendrites and a single apical dendrite, which ascends toward the cortical surface where its branches course laterally and terminate within lamina I (see Fig. 1A). Both basal and apical dendritic branches are covered by a large number of very small knob-like processes, termed spines. The spines are known to be sites of synaptic connections to the pyramidal neurons (cf. ref. 1).

The apical dendrite with its spine-covered branches is perhaps the most characteristic feature of cortical dendritic architecture; however, its contribution to pyramidal neuron activity, and thereby to cortical function, is little understood. The traditional view has been that synapses on the cell body and basal dendrites mediate rapid control of impulse generation in the axon hillock, whereas those on the distal apical dendritic spines, because of the distant location, mediate mainly slow background modulation of impulse generation.

Recently we have explored the possibility that dendritic spines may have excitable properties (2-7). In pursuing this work, we have found that such properties not only amplify

the response of the individual spine but also lead to interesting interactions between spines. These interactions could greatly enhance the contribution of distal apical dendrites to the control of pyramidal neuron activity. They also suggest unique hypotheses concerning the neural substrate for information processing and memory functions in the cortex.

METHODS

Because direct experimental analysis of distal spine properties is beyond the reach of present techniques, we employ a computational modeling approach, which has become routine in correlating morphological and electrophysiological data from neurons (8-15). For this purpose we have introduced the use of general electrical network analysis programs (13-15), which permit neuronal structures with complex morphologies and distributed physiological properties to be simulated with relative ease. The present computations were carried out by using the ASTAP program at the IBM Watson Research Center (cf. ref. 13), SPICE (16) (with the assistance of B. Bunow) at the National Institutes of Health, and NEUROS, modified from SPICE by P. B. Guthrie.

The neuronal structures represented by the model in our analysis consisted of three spines arranged along a length of terminal dendritic branch (Fig. 1B). This morphology was simulated by a system of 14 compartments, as indicated in Fig. 1C (see legend for details). The compartmental analysis was carried out in the usual way (8), with a specific membrane capacitance of $1 \mu\text{F}/\text{cm}^2$ and specific membrane resistance ranging from 2000 to 8000 $\text{ohm}\cdot\text{cm}^2$. In addition, each spine head membrane area incorporated a Hodgkin-Huxley model of the nerve impulse, based on previous adaptations of this model to central neurons (refs. 10-12; see Fig. 1 legend and below).

RESULTS

In previous theoretical (2) and modeling (13) studies it has been shown that synaptic depolarization in a spine head can spread passively with only modest decrement into a neighboring spine head. If the neighboring spine was presynaptic, transmitter release could be evoked (13). Here, we have tested the hypothesis that an impulse in one spine head could trigger an impulse in a neighboring spine head. The results are shown in Fig. 2. It can be seen that an impulse with a clear threshold and an all-or-nothing spike was generated in the first spine head in response to a current pulse. When the impulse fired, it led to the generation of an impulse in the second neighboring spine head. This in turn triggered an impulse in the third spine. In other computations, results similar to those in Fig. 2 have been obtained when the initial spine head impulse was generated in response to an excitatory synaptic conductance change.

It is important to note that the only sites containing active,

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

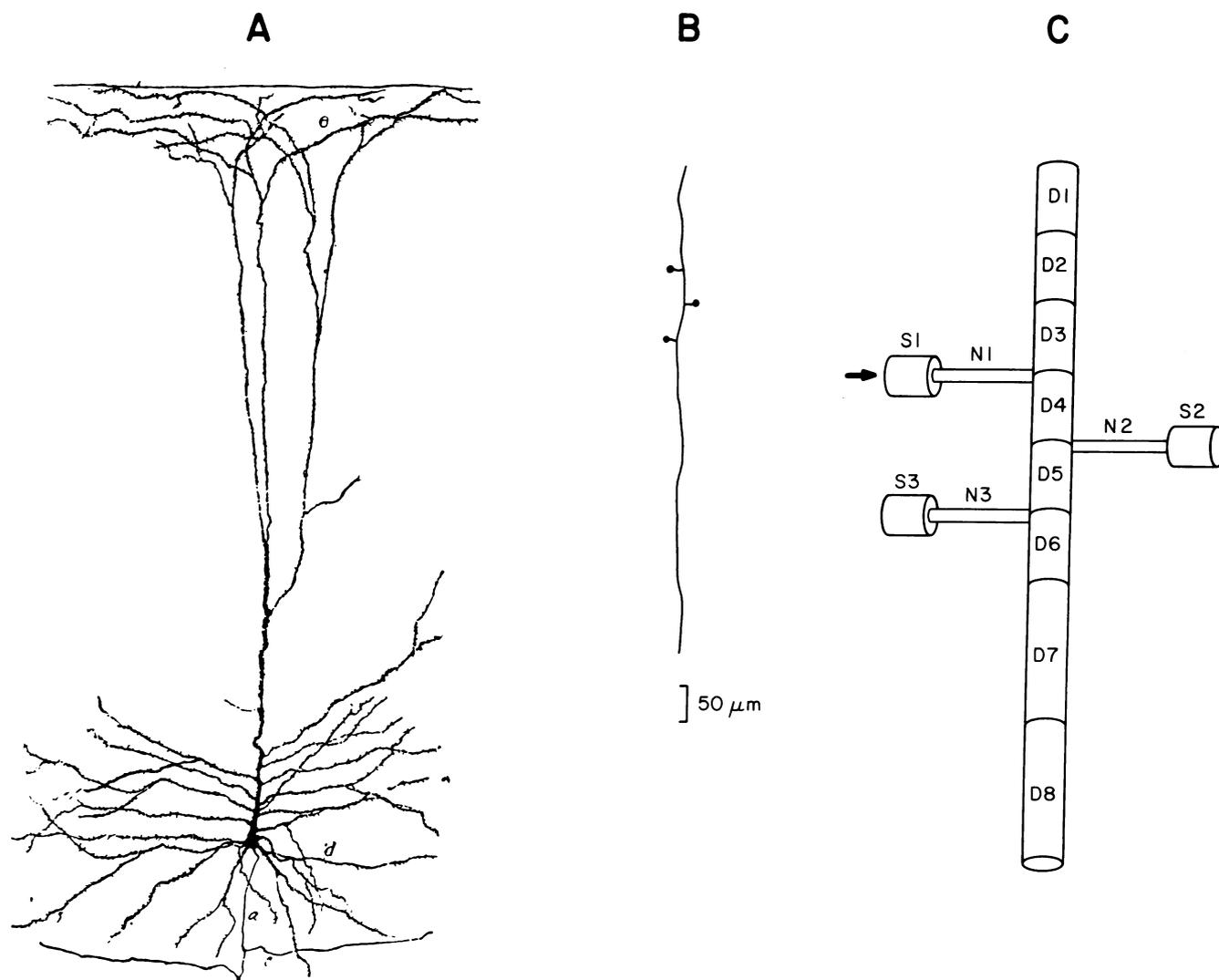


FIG. 1. (A) Pyramidal neuron in the cerebral cortex; Golgi impregnation (17). (B) Schematic diagram of the terminal segment of an apical dendritic branch in the most superficial cortical layer in A. Only three spines out of the total array are indicated, spaced 50 μm apart. This represents the system that was modeled. As can be seen by comparison with A, this model had a much smaller number of spines, with much greater spacing, than the actual case. (C) Diagrammatic representation of the compartmental model of B. D, dendritic compartments. Each compartment consisted of a membrane capacitance ($1 \mu\text{F}/\text{cm}^2$) in parallel with a membrane resistance ($2000 \text{ ohm}\cdot\text{cm}^2$) and a voltage source for the resting membrane potential (-70 mV); intracellular resistivity was $80 \text{ ohm}\cdot\text{cm}$. The dimensions of each compartment were dendrites D1–D6, diameter = $1 \mu\text{m}$ and length = $50 \mu\text{m}$; dendrites D7 and D8, diameter = $1 \mu\text{m}$ and length = $200 \mu\text{m}$ (D7 and D8 represent the extension of the branch toward the soma); spine stems N1–N3, diameter = $0.2 \mu\text{m}$ and length = $3 \mu\text{m}$; spine heads S1–S3, diameter = $1 \mu\text{m}$ and length = $2 \mu\text{m}$. Each spine head included a model for the nerve impulse, based on the Hodgkin–Huxley model (cf. refs. 10–12). For this particular case, maximal sodium conductance (g_{Na}) was $500 \text{ mS}/\text{cm}^2$, maximal potassium conductance (g_{K}) was $100 \text{ mS}/\text{cm}^2$, and the rate constant function α_m was four times that for squid axon [see Dodge and Cooley (10) for these and other parameters estimated for mammalian central neurons]. The arrow indicates that stimulation was by depolarizing current injection or membrane conductance change in spine head S1.

voltage-dependent conductances were the spine heads; all other membrane was passive. Thus, the active propagation depicted in Fig. 2 was discontinuous and resembled in this respect the saltatory conduction that takes place from node-to-node in myelinated nerve.

The interspine interactions were heavily contingent on multiple factors. Active channel densities and kinetics were obviously important. For example, the all-or-nothing response of the spine head was critically dependent on the number of sodium channels and the maximal value for the rate constant α_m in the Hodgkin–Huxley model. We explored the ranges of values estimated previously for mammalian motoneurons by Dodge and Cooley (10). Within those ranges, higher values for both of these parameters enhanced interspine interactions; lower values led to lower excitability, requiring simultaneous synaptic inputs to several spines

in order for an initial impulse to be generated and activation of neighboring spines to occur.

Other factors included especially the dimensions of the spine stems and dendritic branches and the electrical properties of their membranes. A crucial property was that with narrower spine stems or larger diameter dendritic branches (or both), it was necessary to have several spines receiving synaptic excitation in near-synchrony, in order that the resultant impulses could generate sufficient current to trigger spines further along the dendrite (6, 7). Precise placement and timing of excitatory synapses along the dendrite enhanced spread, whereas inhibitory synapses opposed it (ref. 7; unpublished data). These factors also affect passive spread of synaptic potentials into and out of dendritic spines (cf. refs. 2–6, 13, 18, 19); action potential generation provides for additional properties of amplification and propaga-

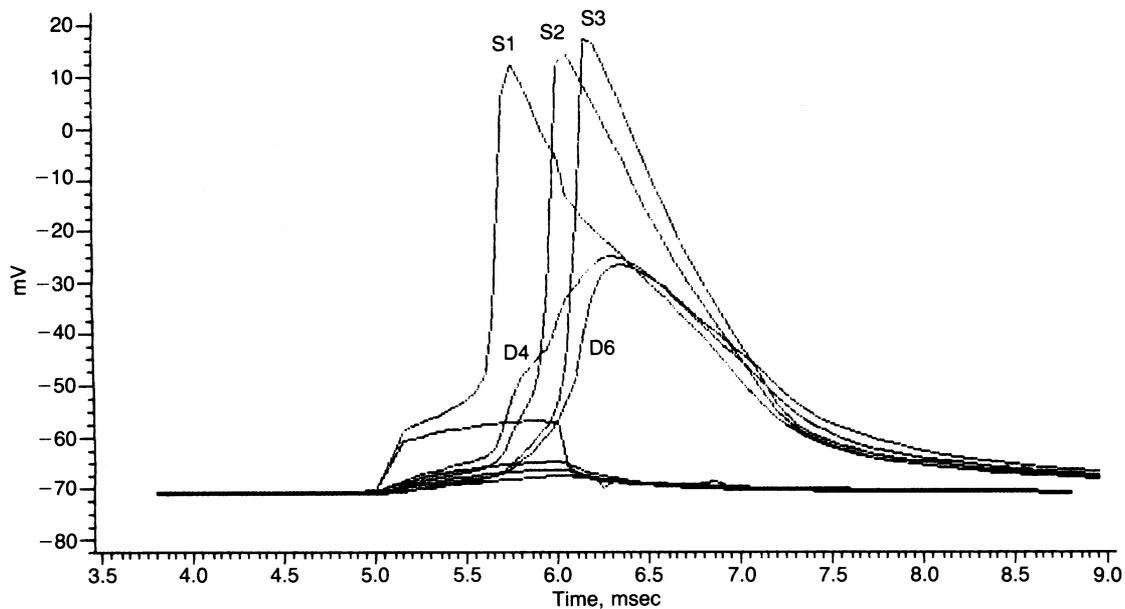


FIG. 2. Saltatory impulse spread between spines in the distal dendritic spine model. A suprathreshold current pulse (or synaptic conductance change, not shown here) in spine head S1 elicited an impulse, which spread passively through dendritic segment D4 to trigger an impulse in spine head S2. This in turn spread through D5 to elicit an impulse in S3. Spread into dendritic compartment D6 could elicit impulses in spines further along the dendrite, dependent on multiple factors as noted in the text. Superimposed on the tracings are the small responses in each compartment to just-subthreshold current stimulation in spine head S1. Note the all-or-nothing character of the impulse responses in each spine head and the conduction delays, which were equivalent to a conduction velocity between S1 and S2 of 0.15 m/sec and between S2 and S3 of 0.3 m/sec.

tion. In other computations (see ref. 7), active propagation beyond branch points to a parent dendrite generally did not occur unless there was summation with activity in the sister or parent branch.

DISCUSSION

As a mechanism for initial processing of dendritic synaptic inputs, spine interactions by means of excitable properties could have considerable functional significance. First, the relative efficacy of distal dendritic inputs would be greatly enhanced. Second, as shown in Fig. 2, the transients within the model spines and dendrite are rapid and do not have the slow, low-amplitude time course of synaptic potentials recorded experimentally at a distance in the cell body. Within the distal dendrite, information might thus be processed through precise timing of specific inputs to different neighboring spines (cf. ref. 20). These precise interactions would greatly increase the complexity of information processing that can take place in distal dendrites.

Active spines appear to provide a basis not only for multiply-contingent processing of synaptic inputs as outlined above but also for storage of information. The spine stem resistance as a parameter for varying the effectiveness of spine input to the parent dendrite has been recognized as a likely locus for plasticity underlying learning and memory (18, 19, 21, 22). This could also regulate the effectiveness of interactions between excitable spines. In addition, it is attractive to postulate that excitable spine heads may provide a locus for activity-dependent changes. Much work has indicated that, in presynaptic terminals, voltage-gated channels undergo activity-dependent changes (cf. ref. 23). Our results suggest that if similar changes occur in voltage-gated channels in spines, they could provide the basis for postsynaptic nonlinear interactions and thus contribute to heterosynaptic associational mechanisms for learning and memory.

Previous studies have provided evidence for "pseudosalvatory" conduction from active booster regions in dendrites

of certain neurons; these regions have been presumed to be located in dendritic branches or branch points (24–26). Our simulations indicate that, under appropriate assumptions about dendritic branch and spine morphologies, some of the active dendritic responses could be attributed to spines. Further experimental analysis, combined with the present modeling approach, is necessary to determine the relative contributions of activity in spines, branches, and branch points to dendritic spikes and intradendritic conduction. We have focused here on the Hodgkin–Huxley model as a basis for this activity, but it should be emphasized that the results have more general implications for the possible contributions of other types of voltage-dependent ionic channels to spine functions. Of particular interest in this regard are voltage-dependent calcium channels. The present approach may therefore be useful in helping to direct future experiments toward obtaining evidence for membrane properties and active channels of dendritic spines and interpreting their contributions to cortical processes underlying higher brain functions.

We thank Barry Bunow for assistance with development of computer programs and Art Belanger, of the Biomedical Computing Unit at Yale, for assistance with the computations. This work has been supported in part by Research Grant NS-07609 from the National Institute of Neurological and Communicative Disorders and Stroke (to G.M.S.) and by Research Grant BNS-8202416 from the National Science Foundation and a Sloan Foundation Fellowship (to J.P.M.).

1. Jones, E. G. & Powell, T. P. S. (1969) *J. Cell Sci.* 5, 509–529.
2. Jack, J. J. B., Noble, D. & Tsien, R. W. (1975) *Electric Current Flow in Excitable Cells* (Oxford Univ. Press, Oxford).
3. Miller, J. P., Rall, W. & Rinzel, J. (1985) *Brain Res.*, in press.
4. Perkel, D. H. & Perkel, D. J. (1985) *Brain Res.*, in press.
5. Shepherd, G. M., Brayton, R. K., Belanger, A., Miller, J. P., Malinow, R., Segev, I., Rinzel, J. & Rall, W. (1984) *Soc. Neurosci. Abstr.* 10, 547.

6. Malinow, R. & Miller, J. P. (1984) *Soc. Neurosci. Abstr.* **10**, 547.
7. Rall, W. & Segev, I. (1985) in *New Insights into Synaptic Function*, eds. Edelman, G. M., Gall, W. F. & Cowan, W. M. (Wiley, New York), in press.
8. Rall, W. (1964) in *Neural Theory and Modelling*, ed. Reiss, R. F. (Stanford Univ. Press, Palo Alto, CA), pp. 73–97.
9. Rall, W. & Shepherd, G. M. (1968) *J. Neurophysiol.* **31**, 884–915.
10. Dodge, F. A., Jr., & Cooley, J. W. (1973) *IBM J. Res. Div.* **17**, 219–229.
11. Traub, R. D. (1977) *Biol. Cybern.* **25**, 163–176.
12. Pellionisz, A. & Llinas, R. (1977) *Neuroscience* **2**, 37–48.
13. Shepherd, G. M. & Brayton, R. K. (1979) *Brain Res.* **175**, 377–382.
14. Fleshman, J. W., Burke, R. E., Glenn, L. L., Lev-Tov, A. & Miller, J. P. (1982) *Soc. Neurosci. Abstr.* **8**, 414.
15. Fleshman, J. W., Segev, I., Cullheim, S. & Burke, R. E. (1983) *Soc. Neurosci. Abstr.* **9**, 343.
16. Nagel, L. W. & Pederson, D. O. (1973) *Simulation Program with Integrated Circuit Emphasis (SPICEZ)*, ERL-M382 (Univ. California Press, Berkeley, CA).
17. Ramon y Cajal, S. (1911) *Histologie du Systeme Nerveux de l'Homme et des Vertebres*, (Maloine, Paris).
18. Rall, W. & Rinzel, J. (1971) *Soc. Neurosci. Abstr.*, 64.
19. Rall, W. (1978) in *Studies in Neurophysiology*, ed. Porter, R. (Cambridge Univ. Press, Cambridge, UK), pp. 203–209.
20. Shepherd, G. M. (1981) in *Neurons Without Impulses*, eds. Roberts, A. & Bush, B. M. H. (Cambridge Univ. Press, Cambridge, UK), pp. 255–267.
21. Fifkova, E. & van Harrevald, A. (1977) *J. Neurocytol.* **6**, 211–230.
22. Crick, F. (1982) *Trends Neurosci.* **5**, 44–46.
23. Klein, M., Shapiro, E. & Kandel, E. (1980) *J. Exp. Biol.* **89**, 117–157.
24. Eccles, J. C., Libet, B. & Young, R. R. (1958) *J. Physiol., (London)* **143**, 11–40.
25. Spencer, W. A. & Kandel, E. R. (1961) *J. Neurophysiol.* **24**, 272–285.
26. Llinas, R. & Sugimori, M. (1980) *J. Physiol., (London)* **305**, 197–213.