Dendritic Spikes versus Cable Properties

As their major evidence for propagated dendritic spikes, Llinás *et al.* (*1*) utilize the shift in latency of a field potential peak with distance down the dendritic trees of cerebellar cortical neurons. Several authors have suggested, however, that such field potential latency shifts could be merely due to the passive cable properties of the dendrites (*2*). Since the peak of a passively spreading postsynaptic potential (PSP) occurs later as one records further away from the synapse, it would seem reasonable first to eliminate this passive peak shift as the source of the phenomena before assuming propagated dendritic spikes.

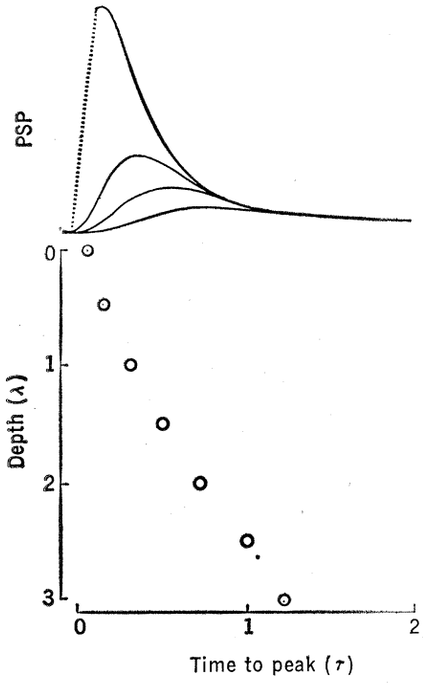

Fig. 1. Delay in the peak of simulated postsynaptic potentials (PSP). (Top) The PSP shape at various distances (0.5, 1.0, 1.5, and 2.0 λ) from a synapse is seen to exhibit the following characteristics: delay in peak, delay in foot, decrease in peak height, and increase in half-width. (Bottom) Plotting the time (in time constants τ) at which the PSP peak occurs against the distance (in space constants λ) from the synapse leads to the illusion that the PSP is actively propagated (using compound action potential reasoning) at the rate of 2 to 4 space constants per time constant. Values of $\lambda = 0.5$ mm and $\tau = 5.0$ msec yield rates in the 20 to 40 cm/sec range, the same as the "conduction velocities" measured by Llinás *et al.* (*1*) and assumed to represent propagated dendritic spikes. These results were simulated on a passive cable with 0.5 λ compartments, with a conductance change at the origin lasting 0.2 τ.

In the experiment of Llinás *et al.*, the extracellular potential should obey the cable equation (*3*) because of the geometry of cerebellar cortex (*4*). Since the synapses in their experiments are on the distal tips of the dendritic tree, and since the conductance change associated with synaptic activity is usually much briefer than the membrane time constant, we can represent the PSP by the impulse response of the cable equation (*5*):

$$V(X,T) = \tfrac{1}{2}\pi^{-\frac{1}{2}}T^{-\frac{1}{2}}e^{-T}e^{-X^2/4T}$$

where $X = x/\lambda$ is the axial distance in space constants (λ) from the synapse, and $T = t/\tau$ is the time in time constants (τ) since the instantaneous conductance change. If we set $\partial V/\partial T$ equal to zero, the location of the PSP peak with time is found (*6*):

$$X_{\max} = (4T^2 + 2T)^{\frac{1}{2}}$$

Thus the peak will be 2.45 λ from the synapse after 1 τ. Values of $\lambda = 0.5$ mm and $\tau = 5$ msec yield an apparent propagation rate of about 25 cm/sec, although the peak will travel somewhat faster nearer the synapse (Fig. 1). Since the conduction velocities of Llinás *et al.* are in the 10 to 40 cm/sec range, the passive peak shifts are of the correct order of magnitude to account for this feature of their results (*7*).

Other characteristics of passively spreading PSP's with distance from the synapse are (i) a delay in the foot of the PSP, (ii) prolongation of the half-width, and (iii) decrease in peak height. Although interactions between biphasic components of field potentials can complicate their interpretation, it is significant that the late negative peak in figure 1C of Llinás *et al.* (*1*) from which conduction velocities were measured, demonstrates all of these passive characteristics. It is interesting to note that if their synaptic input had been widely diffused throughout the depth of the dendritic tree (instead of being neatly restricted to a narrow beam at the distal 100 microns of the dendritic tree), such passive characteristics would be obscured (although temporal dispersion of the synaptic inputs could mimic them).

For these reasons then, we conclude that passive spread cannot be eliminated as a source of the peak shift phenomenon. Since all dendrites should exhibit such passive peak shifts, whether they also have spikes or not, we believe that the parsimonious explanation of such field potential data is passive spread, rather than propagated dendritic spikes.

As further evidence for an all-or-nothing process, Llinás *et al.* use inhibition of the second response in a paired-stimulus experiment and occasional observations of spikes in superficial layers. Although such results are consistent with—but not unique to—active dendritic events, they cannot distinguish between active and passive propagation for such a dendritic spike. Since a passively spreading spike will also cause a passive peak shift in the same manner as a PSP will (*8*), peak shifts alone cannot be used to establish active propagation even if dendritic spikes themselves are more firmly established.

While dendritic spikes may exist, the present evidence of Llinás *et al.* does not appear to establish the spike hypothesis—much less the propagated spike hypothesis—as preferable to other well-known explanations for such data.

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4. In the experiment of Llinás *et al.* surface-parallel currents from different dendrites tend to cancel, whereas translaminar currents add, giving rise to a parallel extracellular current distribution. Under such conditions, the *cable model* (although not necessarily the cable equation) applies to extracellular as well as intracellular and transmembrane potentials [J. Clark and R. Plonsey, *Biophys. J.* **6**, 95 (1966)]. According to this model, the intracellular media are modeled as resistors running parallel to the dendritic axis, connected to each other at short intervals by resistors and capacitors representing the membrane; the *membrane potential* obeys the cable equation. But the intracellular potential is much greater than the extracellular potential; hence it is approximately equal to the membrane potential and obeys the cable equation. From the symmetry of the model, the interior and exterior potentials must have the same waveshape. Therefore, the extracellular potential obeys the cable equation.
5. The dendrite is stimulated with a very brief conductance change at one point, so that as much charge enters the dendrite as would flow into a dendrite 1 λ long during 1 τ if a potential of 1 volt were to be maintained across the membrane.
6. Two methods exist in the literature for measuring propagation rates from field potentials: spatial maxima and temporal maxima. Stevens, for example, calculates the spatial maxima of the membrane current (*I*) by setting $\partial V^3/\partial X^3 = \partial I/\partial X = 0$. Thus, for each value of *T*, the

different depths are compared to find the depth with the largest response. Llinás *et al*, however, ask *when* does the largest response occur at each depth and then compare these peak latencies between depths. To calculate this temporal maximum, we set $\partial V/\partial T = 0$.

7. For longer conductance changes, the rate is not significantly altered. In figure 1, for example, we use a square conductance change of 0.2 τ duration.
8. The apparent propagation rate for a passively spreading spike will be faster than for a PSP. For example, a biphasic current stimulus which produces a spike of 0.2 τ duration at the origin will spread with an apparent propagation rate about twice as fast as a PSP caused by a monophasic pulse.
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Calvin and Hellerstein claim that the negativities observed at the molecular layer of the alligator cerebellum after parallel fiber activation are generated by the synaptic current as the synaptic potentials are decrementally conducted toward the soma of the Purkinje cells. They state a well-known set of equations for the electrotonic decrement of amplitude and change of time course for the intracellularly recorded synaptic potentials, but these are not directly applicable to the case in question.

The spatial orientation of the Purkinje cells is of the open-field type (*1*) so that it permits a simplification of the dendritic trees to a series of vertical core conductors (*2*). This particular organization resembles closely a muscle-nerve preparation, where the only region in which an excitatory synaptic current generates a negative extracellular field is in the vicinity of the synaptic region (*3*). The inward current across the postsynaptic-subsynaptic membrane is simultaneously accompanied by an outwardly directed current which generates the postsynaptic potentials and which produces in the extracellular media a positive field as the external longitudinal current moves toward the synaptic sink. This type of field is, in fact, the most commonly observed in other vertebrate cerebella (*4, 5*). Our findings, however, relate to a negative field recorded extracellularly, that is, a sink which moves in time from its origin at the surface of the molecular layer to the layer of Purkinje cell somas. Furthermore, their argument is faulty, even if it were to be applied to an extracellular positivity. The extracellular field potentials are generated by transmembrane currents and not by transmembrane potentials. To calculate the time course of the extracellular field one should take the second derivative of the intracellular potential with respect to space in order to estimate the transversal current density along the cable (*6*). The results would have reminded them that there is a marked phase shift between the transmembrane potential and the transmembrane current and thus that the time course of an electrotonically conducted EPSP does not reflect directly the time course of the extracellular field potential.

The aforementioned negativity is blocked by a preceding stimulus to the surface of the cerebellar cortex. This stimulus generates large inhibitory synaptic potentials in alligator Purkinje cells (*5*) similar to those observed in other species (*4*). Excitatory synaptic currents are increased, not blocked, by membrane hyperpolarization since the electromotive force is larger under such conditions than at the normal resting potential level. Since our negative fields are blocked by a preceding parallel fiber stimulation which does not have any presynaptic action on the test EPSP (*7*), the large dendritic negativity cannot be ascribed to synaptic currents.

As shown in figures 1, B and C, and 2A of our paper (*8*), the amplitude of the negativity does not reach its maximum value at the region of synaptic impingement but at an appreciable distance from this site; thus it cannot be generated by decrementally conducted potentials, given that, in such a situation, the maximum amplitude of the potential should correspond to the locus of synaptic input.

For the reasons cited in the first paragraph, if the negativity recorded at the molecular layer were generated by synaptic currents, a reversal to a positive field should be evident as the microelectrode moves away from the site of synaptic impingement along the length of the cell. Such reversal was never observed. A reversal from a negative field at the surface of the molecular layer to a positive field at 100 μ and all levels below this depth was shown, however, for the synaptic currents generating the dendritic spikes after these spikes were blocked by a preceding local stimulation (Fig. 2B).

Finally, the presence of large all-or-none negativities at the level of the Purkinje cell dendrites (*8*, figure 2, E to I) and their inhibition by a preceding local stimulation is, in fact, a direct demonstration of dendritic spikes in Purkinje cells. The other neuronal elements of the molecular layer, the stellate cells, display a very different behavior following paired Loc stimulation (*9*).

We do not consider the criticisms of Calvin and Hellerstein as truly pertinent to the question of dendritic spikes, and we feel that our data can best be explained by the presence of propagating dendritic spikes in Purkinje cells.

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Educational Status and Risk of Coronary Heart Disease

Hinkle *et al.* (*1*) have investigated the occurrence of death and disability from coronary heart disease (CHD) in relation to occupational and educational status. Their sample includes few men with angina pectoris as the only manifestation of CHD because angina often does not result in prolonged absence from work. Thus, their observations have direct relevance primarily for the epidemiology of myocardial infarction and sudden death, the other two major clinical forms of CHD. However, Hinkle *et al.* generalize their results to risk of CHD without qualification. They seem to overlook the possibility that angina pectoris may be related to the antecedent conditions in a different manner than is myocardial infarction and sudden death.

Previous investigations (*2*) have shown that a factor can be related to one clinical form of CHD but not another. Excess body weight in the Framingham study bears little relation to risk of myocardial infarction, although it is associated with occurrence of angina pectoris and sudden death. Cigarette smoking is related to increased risk of myocardial infarction but is unrelated to risk of angina pectoris.