10.3 Synaptic Amplification by Active Membrane in Dendritic Spines (1985), *Brain Res.* 325:325–330

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The suspected functional role of dendritic spines as loci of neuronal plasticity (possibly memory and learning) is greatly enriched when active membrane properties are assumed at the spine head. Computations with reasonable electrical and structural parameter values (corresponding to an optimal range for spine stem resistance) show that an active spine head membrane can provide very significant synaptic amplification and also strongly non-linear properties that could modulate the integration of input from many afferent sources.

Many synaptic contacts between neurons are located on dendritic spines. The possible functional significance of these spines has excited the interest of theoretical and experimental neuroscientists. Based upon the assumption that spine head membrane is passive, previous studies concluded that the efficacy of a synapse onto a spine head would be less than or equal to the efficacy of an identical synapse directly onto the 'parent' dendrite[2,4,8,12,16–21,24,32]. However, for an *active* spine head membrane, early steady state considerations suggested that a spine might act as a synaptic amplifier[8]. Here we present transient responses computed for transient synaptic conductance input. We address two questions: (1) What would be the difference in efficacy between a synapse onto a *passive* spine and onto an *active* spine? and (2) How would the efficacy of a synapse onto an active spine depend upon structural and electrical parameters of the spine? Our transient calculations demonstrate that: (1) the efficacy of a synapse onto an active spine could, indeed, be *much greater* than the efficacy of an identical synapse onto the parent dendrite or onto a passive spine; and (2) such amplification would occur only for certain ranges of spine parameters. A maximal efficacy could be attained, corresponding to a narrow optimal range of these parameters.

Calculations were performed using a commonly available program called SPICE[34] running on an IBM 370 computer. SPICE simulates the behavior of complex circuits of electrical components, and can calculate the non-linear, transient responses of circuits to time- and voltage-dependent conductance changes. The methods for modeling the structural and electrical properties of spines and dendrites, including the formulation of the action potential kinetics of active membrane[7,23], were essentially those described by Shepherd and Brayton[27]. Numerical accuracy was tested in several cases for which analytical solutions could be derived; deviations never exceeded 2%. Here, the spine head is assumed to be isopotential and the spine stem is reduced to a lumped resistance connecting the spine head to the dendrite, represented as a passive membrane cylinder of infinite length. Parameters specifying the morphology of the spine and dendrite were chosen to fall within the range of anatomical measurements reported in the literature[1,3,5,6,9,10,13,15,26,33]. The values for these parameters, as well as the electrical, synaptic and action-potential conductance parameters, are listed in Table I.

In order to compare the functional properties of an active and a passive spine, the responses of each to

TABLE I

Parameters for computations

Parameter	*Value*
Resting membrane resistivity	5000 Ωcm²
Cytoplasmic resistivity	100 Ωcm
Membrane capacitance	1 μF/cm²
Dendrite diameter	1 μm
Dendrite length	infinite
Spine head diameter	0.75 μm
Spine stem resistance	0, 200, 400, 800 MΩ (see figure legends)
Synaptic conductance transient	
Time course proportional to $te^{-\alpha t/\tau}$	$\alpha = 50$, $\tau = 5$ ms
Peak conductance	0.25 and 0.50 nS (see figure legends)
Action potential (3 variable model)[7,23,27]	
Kinetic coefficients	$k_1 = 10^5$, $k_2 = 6 \times 10^4$, $k_3 = 25$, $k_4 = 0.2$, $k_5 = 1$, $k_6 = 0.01$, $k_7 = 5$.
Resulting maximal inward conductance (for an isolated active spine head)	16 nS
Reversal potential for active inward current (relative to rest)	125 mV

identical synaptic inputs were computed. The results are presented graphically in Fig. 1, for two synaptic conductance amplitudes. For the smaller synaptic input the computed excitatory postsynaptic potentials (EPSPs) were all qualitatively similar and remained in the linear regime (dashed curves in all panels). For both passive and active cases, the EPSP in the dendrite (spine base) was substantially lower in amplitude than the EPSP in the spine head (note difference in voltage scales). This voltage attenuation from head to base corresponds to the I × R drop across the relatively large resistance presented by the spine stem.

When the amount of the synaptic conductance was doubled, the EPSPs shown as solid lines were obtained. In the passive case, the EPSP amplitudes are nearly doubled and the EPSP shapes are qualitatively similar to the dashed curves. However, the solid curves in the active case are qualitatively different, because the EPSP in the spine head exceeded the threshold for initiation of regenerative currents by the active spine head membrane. These regenerative

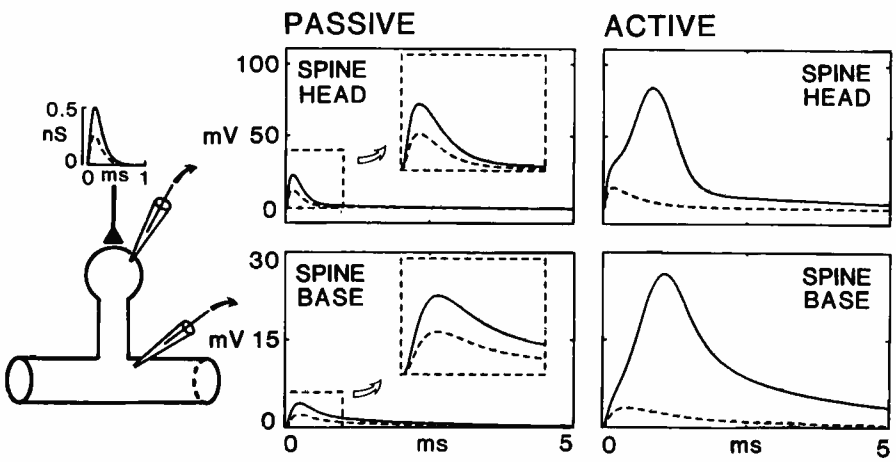

Fig. 1. Spines with active heads can greatly augment synaptic efficacy. Calculations were performed using a model representing a spine on a dendrite cylinder, shown diagramatically at the left. All model parameters are listed in Table I. Directly above the spine diagram are the time courses of the two synaptic conductances used: the dashed curve has a peak amplitude of 0.25 nS; the solid curve has peak conductance of 0.5 nS. The dashed and solid curves in the enclosed panels are the corresponding voltage transients (EPSPs) resulting from these two conductance transients, computed at two different locations (spine head or spine base) for two different types of spine head membrane (passive or active). The insets in the two left panels (passive spine membrane) are enlarged views of the areas enclosed with dashed boxes. Note that the 0.5 nS conductance transient is a suprathreshold for action potential generation in the active head (upper right panel), resulting in a substantial augmentation of the current entering the spine. This results in a much-enhanced EPSP at the base of the active spine (lower right panel).

currents have several consequences that can be described as synaptic amplification or augmentation relative to the passive case: (1) much more charge enters the spine head membrane, resulting in a spine head EPSP having a much larger amplitude and duration; and (2) the charge delivered through the spine stem into the dendrite is substantially larger, resulting in an EPSP (at the spine base) that is augmented in both amplitude and duration. The *peak amplitude* of the EPSP at the base of the active spine was 6.5 times greater than at the base of the passive spine. The *net charge* delivered to the dendrite by the active spine (proportional to the area under the EPSP at the spine base) increased 10-fold over that delivered by the passive spine (for time duration shown in Fig. 1). Thus, by either of these two criteria, synaptic efficacy was *substantially increased* by incorporation of active properties into the spine head membrane.

Previous theoretical studies have shown that changes in the structural and electrical parameters of passive spines could change synaptic efficacy[8,12,16–21,24,32]. An 'operating range' was identified within which synaptic efficacy could be increased or decreased — relative to an 'operating point' — by decreasing or increasing the spine stem resistance. (An increase in stem resistance would result, for example, from decreasing stem diameter, increasing stem length, or partially occluding the stem.) It was suggested that such changes could contribute to plasticity in central nervous systems[8,16–21,24]. Subsequently, significant activity-dependent changes in morphological parameters of spines have been reported[1,3,5,6,13]. Here we extend our study of the dependence of synaptic efficacy upon stem resistance to the case of an *active* spine head. The transient computations, illustrated by Fig. 2, show the effect of changing spine stem resistance, when the spine head and dendritic parameters remain unchanged. The amplitude and time course of the synaptic conductance (leftmost panel) was equal to the larger input (solid curve)

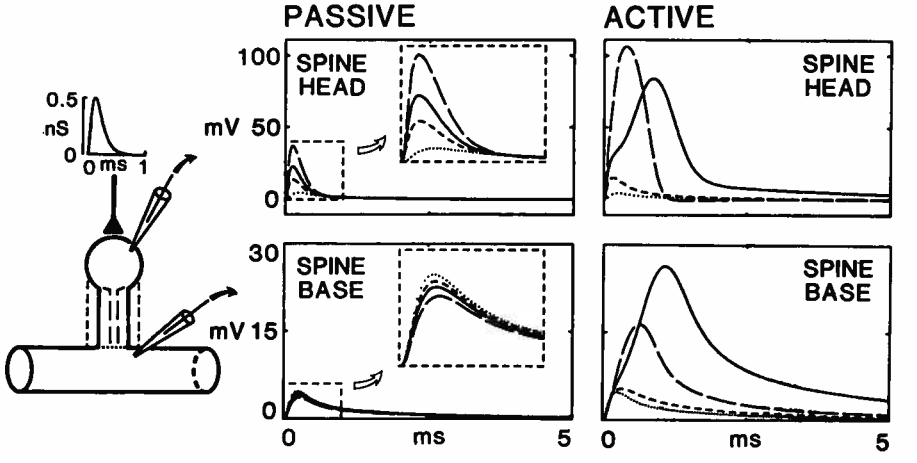

Fig. 2. There is an optimal stem resistance for maximal synaptic efficacy. The diagram at the left represents the spine model. All structural and electrical parameters of the spine and dendrite *except* spine stem resistance were as in Fig. 1. Variations in stem resistance are represented on the diagram as different spine stem diameters, although changes in length and partial occlusion could also change this resistance. Dotted curves are for the case of zero stem resistance (i.e. synapse directly on the dendrite). Resistance values of 200, 400 and 800 MΩ are represented with short-dashed, solid, and long-dashed lines, respectively (i.e. the thinner the stem, the higher the resistance). Directly above the spine diagram is the time course of the synaptic conductance used for all calculations; peak conductance was 0.5 nS. In each of the 4 enclosed panels are the voltage transient (EPSPs) corresponding to the 4 spine stem resistance values. The EPSPs were calculated at two different locations (spine head or spine base) for two different types of spine head membrane (passive or active). The insets in the two left panels (passive spine membrane) are enlarged views of the areas enclosed with dashed boxes. Note that the 400 MΩ stem results in a suprathreshold response for the *active* head (solid curve, upper right), yielding the largest EPSP at the base of the spine (solid curve, lower right). Stems of either higher or lower resistances give lower amplitude EPSPs at the base.

used in Fig. 1. The solid curves in Fig. 2 are the EPSPs calculated for a stem resistance of 400 MΩ. (These curves are identical to the solid curves of Fig. 1.) Doubling spine stem resistance yielded the curves shown as long dashes in Fig. 2; halving spine stem resistance yielded the curves shown as short dashes in Fig. 2. The dotted curves are for the limiting case of zero spine stem resistance, for which there can be no difference of potential between spine head and spine base. (The dotted curves in the upper and lower panels are identical EPSPs plotted to different voltage scales.) These dotted curves represent the reference case, corresponding to a synapse placed directly on the dendrite.

For the passive spine, comparison of the upper and lower panels of Fig. 2 shows the expected effects. For successive increases in spine stem resistance, the EPSP amplitude in the spine head (upper panel) grows successively larger than the (dotted) reference EPSP, while the EPSP amplitude at the spine base (lower panel) becomes successively smaller. The difference between these upper and lower EPSPs corresponds to the I × R drop of voltage for current flowing through the spine stem. Thus, for a passive spine, the effect of these increases in spine stem resistance is to reduce the EPSP amplitude and area at the spine base, and hence the efficacy of the synapse.

For the active spine, the computed results at the right side of Fig. 2 show more complicated (very nonlinear) effects for identical increases in spine stem resistance. For an increase from 0 to 200 MΩ, the increased depolarization in the spine head does not reach the threshold for generation of an action potential; however, some regenerative response is revealed by the augmentation of both amplitude and duration of the EPSP (short dashes) at the base of the active spine, compared with the passive case. Doubling the spine stem resistance to 400 MΩ has a very dramatic effect (solid curves). In this case, the spine head depolarization exceeds threshold, resulting in a substantial regenerative augmentation of voltage amplitude and duration in the spine head, and producing a large EPSP at the spine base. Note that a further doubling of spine stem resistance to 800 MΩ causes the spine head membrane to reach threshold earlier. Even though the resulting action potential has a larger peak amplitude, its shorter latency and duration result in a smaller area under the curve. Less charge is delivered through the spine stem to the dendrite, and the resulting EPSP at the spine base has a smaller amplitude and area. Because further increase of spine stem resistance causes further reduction of the EPSP at the spine base, it follows that the optimal (maximal) EPSP occurs for an intermediate spine stem resistance value (around 400 MΩ in this example). Because this optimum corresponds to conditions where the spine head depolarization just exceeds threshold, it is clear that these optimal conditions must correspond also to an intermediate value of synaptic conductance amplitude; that is, optimal efficacy occurs with respect to both synaptic conductance and spine stem resistance. The idea of such an optimum was briefly noted in the early steady state considerations of Jack et al.[8]; transient computations leading to similar conclusions have recently been done independently also by Perkel and Perkel[14].

An intuitive understanding of how synaptic efficacy is decreased by larger values of spine stem resistance depends upon recognizing the effect of voltage saturation in the spine head. The reversal potential sets an upper limit for the spine head EPSP amplitude and for the I × R voltage drop from spine head to spine base. Thus when R is increased while the I × R drop remains almost unchanged, the value of I, the spine stem current, must decrease almost inversely with R. This decreased current delivers less charge to the dendrite and produces a smaller EPSP there. Note that this intuitive explanation holds also for the effect of large spine stem resistance values upon a passive spine; this applies to the early steady state and transient results of Rall and Rinzel[17–21,24], and Jack et al.[8], and has also been recognized in two recent analyses of passive spines[12,32]. Negligible dependence of synaptic efficacy upon spine stem resistance results when non-linear voltage (saturation) effects in the spine head are avoided, either by treating synaptic input as a current injection[11], or by keeping synaptic conductance very small[12,32]. The small attenuation reported by Turner and Schwartzkroin[30] resulted from using a small value for the ratio of spine stem resistance to dendritic input resistance[17,18,24].

Measurements of the stem resistance in real spines have not been reported in the literature. Estimates of stem resistance based upon recently reported ranges of stem dimensions (assuming a uniform cytoplasmic resistivity) yield values at the low end of the range

used in our calculations. For example, an unobstructed stem 0.1 μm in diameter and 1.0 μm in length would have a resistance of 100 MΩ. However as pointed out by Wilson et al.[33], such calculations would substantially *underestimate* the true stem resistance. A significant proportion of a spine stem may be occluded by extensive cytoskeletal structures and by large membrane-bound vesicles called the spine apparatus (SA)[28,29,31-33]. For example, occlusion of two-thirds of the volume along half the length of the above stem would double its resistance, to 200 MΩ. The resistance of this partially occluded stem would then be very sensitive to further changes in diameter of either the SA or the stem itself. For example, a 13% increase in SA diameter (or 9% decrease in stem diameter) would increase stem resistance to 400 MΩ. A further increase in SA diameter of only 5% (or a further stem diameter decrease of 5%) would increase stem resistance to 800 MΩ.

Thus, a dendritic spine could theoretically function as an EPSP amplifier, *if* the membrane in its head were active, and *if* the stem resistance and other biophysical parameters lay within the appropriate ranges. The 'gain' of the spine would be variable, and would be sensitive to small changes in stem resistance around an optimal value. Also, if such active spines were placed at distal dendritic locations, the augmentation produced by the active spine head membrane could compensate for the disadvantage of distal location. Still another kind of augmentation might take place in distal dendritic arbors. The large local depolarizations expected there would spread with negligible decrement into small branches[19,22,25] and spine heads[8,11,12,27], and those spine heads which have active membrane might thus be brought to threshold without any direct synaptic input (or they might reach threshold for a synaptic input that would be insufficient by itself). If this happens, it might be best for only some spines to have active membrane, because the distribution of active and passive spines would determine the extent to which a chain reaction of spine firings might occur, resulting in an all-or-none, and possible large, composite EPSP (for an arbor or for an entire neuron). All of these possibilities have significant functional implications for local interactions, synaptic efficacy and plasticity that merit continued attention by neurobiologists.

We thank Barry Bunow for assistance with development of computer programs, Idan Segev and Gwen Jacobs for valuable discussion. This work was supported in part by NSF Grant BNS-8202416 and a Sloan Foundation Fellowship, both awarded to J.P.M.

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