one can retain the giant magnetoresistance up to room temperature.

Groups in at least ten countries have focused attention on these questions. Therefore, we can anticipate rapid developments of both the basic understanding of the physics underlying giant magnetoresistance and the synthesis of new multilayered structures and magnetic precipitates with even larger changes in their electrical resistance for smaller externally applied magnetic fields.

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Dendritic Spines: Convergence of Theory and Experiment

Christof Koch, Anthony Zador, Thomas H. Brown

Dendritic spines, small protrusions covering the surface of many neurons, have fascinated anatomists ever since Ramon y Cajal first described them at the turn of the century. Until recently, their small size has precluded direct measurement of their functional properties. Nevertheless, spines have long been investigated from a theoretical point of view. Experimental and computational studies now seem to be converging toward a common viewpoint—that spines allow biochemical, rather than electrical, compartmentalization within neurons.

Spines are numerous. They represent the major postsynaptic target of excitatory synaptic input. As many as 15,000 spines, at a density of two spines per micrometer of dendritic length, cover the surface of a layer V pyramidal cell in the visual cortex (*1*). In cerebellar Purkinje cells, the number can be as high as 200,000. In contrast, the γ-aminobutyric acid (GABA)–containing stellate cells in the neocortex and hippocampus are characterized by an almost total absence of spines. Spines are the major postsynaptic target of excitatory synaptic input.

Spines are tiny. Their precise morphology has been revealed by three-dimensional electron microscopic reconstructions carried out by Wilson and his co-workers in the neostriatum (*2*) and by Harris and Stevens in the hippocampus (*3*) (Fig. 1). In these rat hippocampal CA1 pyramidal cells, the dimensions of spines are quite variable. Necks range in length from 0.08 to 1.58 μm and in diameter from 0.04 to 0.46 μm. The volume of the spine neck and head ranges from 0.004 to 0.56 μm^2. Spines are so small that at a resting calcium concentration of 80 nM only about three free calcium ions would be found in a spine with the average spine head volume of 0.051 μm^3.

The shape of dendritic spines, in particular the length and diameter of the spine neck, can change during neuronal development or in response to behaviorally significant stimuli (such as light, social interaction, motor activity) (*4*). High-frequency electrical stimulation of specific hippocampal pathways—sufficient to induce long-term potentiation (LTP)—have also been reported to alter spine morphology, leading to larger spine heads, changes in the shape of the spine stem, an increased incidence of concave spine heads, and more synapses on the shaft (*5*). However, it is unclear what direct role, if any, these changes have in causing changes in synaptic efficiency.

What functional role might spines play? Because dendritic spines are so closely associated with excitatory synaptic traffic, they seem ideally suited to modulate information processing in the brain. Thus, they have been subject to analysis by theoreticians. Rall (*6*) argued that the spine neck offers a significant resistance to the electrical charge flowing from the synapse on the spine head to the dendrite and, ultimately, to the cell body. Thus, changing the morphology of the spine neck can lead to significant changes in the somatic excitatory postsynaptic potential (EPSP), providing a possible anatomical substrate for long-term memory. This basic insight was refined and extended (*7*), showing that for fast synaptic inputs the critical factor in determining the spine's electrical behavior is the ratio g_{syn}/g_{neck} [the stimulus-induced conductance increase at the spine head divided by the spine axial (neck) conductance]. If this ratio is small, the synaptic stimulus does not change the membrane potential much and so behaves as a current source. Because the area of a spine is very small, practically no charge loss occurs through the membrane of the spine head or neck; all of the synaptic current injected into the head reaches the base of the spine. Thus, changing the spine dimensions cannot provide a mechanism for potentiation. On the other hand, if g_{syn} is large compared to g_{neck}, the EPSP in the spine will approach the synaptic reversal potential, and the synaptic stimulus will behave as a fixed voltage source. In this case, increasing the spine neck resistance by stretching the spine stem or by reducing its diameter reduces the dendritic EPSP. Crick (*8*) exploited this possibility for his "twitching spine hypothesis": the idea that contractile proteins in the spine provide a mechanism for very rapid (that is, subsecond scale) changes in spine shape that might underlie short-term information storage.

Experimental estimates of the fast [AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)] component of

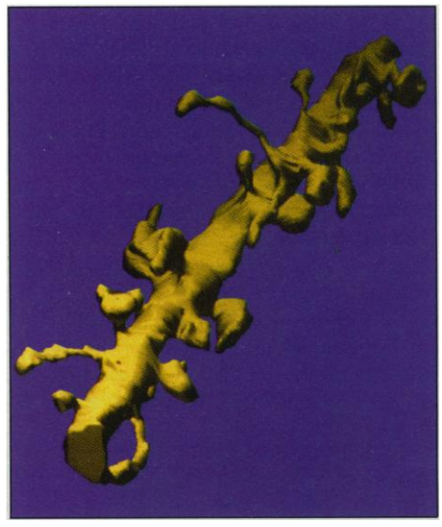

Fig. 1. A dendrite with numerous spines. An 8.5-μm-long dendrite from a CA1 pyramidal cell of the rat hippocampus, with a diameter ranging from 0.51 to 0.73 μm and about three spines per micrometer. [Adapted from (*3*) with permission. © Society for Neuroscience]

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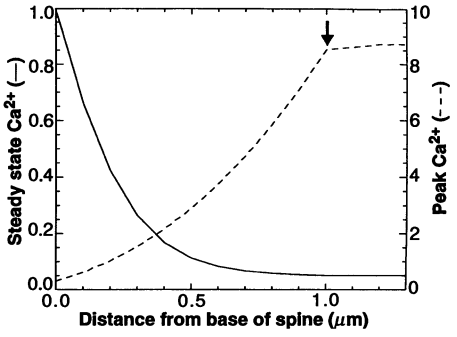

Fig. 2. Simulations of the spatial calcium profile in a dendrite. The abscissa extends from the head of the spine (at the origin) to just below the NMDA channels at the tip of the dendrite (at 1.3 μm). The dotted line shows the peak level of intracellular free calcium after three presynaptic stimuli. While the calcium in the spine rises to about 9 μM, the concentration at the base of the spine is little perturbed from its resting level. In a different simulation illustrating steady state behavior (solid line), the calcium concentration in the dendrite is clamped to 1 μM. In this case, the calcium concentration along the neck rapidly decreases and reaches baseline values at the spine head due to calcium pumps in the spine neck membrane.

g_{syn} from hippocampal slice and culture preparations range from about 0.05 to 0.5 nS (*9*). Values of g_{neck} inferred from spinal morphology fall between 18 to 138 nS (*3*). Thus at these hippocampal synapses the critical ratio g_{syn}/g_{neck} is small, and the synaptic input can be well conceptualized by a current source. Therefore, widening or shortening the spine neck will have little influence on the voltage attenuation properties of the spine.

In contrast, if the membrane of the spine head is endowed with voltage-dependent properties by the presence of fast sodium or calcium channels, computer simulations show that even small synaptic inputs can trigger all-or-none electrical events in the spine head, giving rise to sizable EPSPs in the passive dendrite (*10*). Such spikes do not occur if the neck is too short or too thick, since the associated g_{neck} will then be too large to cause the EPSP to depolarize above threshold levels. At the moment, there is no direct evidence for such spike-like behavior in dendritic spines in cortical cells.

It is known from experimental work that the induction of LTP at some synapses requires a postsynaptic increase in the intracellular calcium concentration; this increase is thought to be mediated by calcium influx through the *N*-methyl-D-aspartate (NMDA) receptor complex (*11*). Thus, computer models—that incorporate either voltage-dependent calcium or NMDA channels—have increasingly focused on the role of spines in modulating calcium dynamics after synaptic input (*12, 13*).

Because of the similarity in the underlying equations, insights obtained from the analysis of membrane potential can be applied to the analysis of calcium dynamics. For instance, due to the small and highly restricted volume of the spine, a small calcium influx after synaptic stimulation causes a large, transient increase in the calcium concentration in the spine; this increase will be much smaller, however, in the dendrite because the large volume of the dendrite acts as a sink for the calcium ions diffusing from the spine head down the neck. Thus, the calcium attenuation between the spine head and base is expected to be large. Furthermore, if the dendritic calcium concentration is "clamped" to 1 μM, the spine head can be protected from the high dendritic calcium concentration by the presence of standard densities of calcium pumps in the membrane of the spine neck (Fig. 2).

Some of these properties have now been visualized by using the fluorescent calcium indicator dye fura-2 in the hippocampal slice. In one study (*14*), calcium accumulates in single spines but not in the parent dendrite of CA3 pyramidal cells after weak presynaptic stimulation of associational-commissural fibers. With stronger stimulation, calcium concentration rises in the dendrite as well. Applying a similar technique to region CA1 pyramidal cells, Guthrie and colleagues (*15*) visualize calcium gradients after a sustained rise in intracellular calcium (to 0.2 to 1.5 μM levels) caused by controllable, photoinduced damage. In a large fraction of spines, the amplitude of the calcium increase in the spine closely parallels that at the parent dendrite; however, in a subset of the spines, changes in spine calcium lag substantially behind the rise in dendritic calcium. Control experiments with injected cobalt suggest that no physical diffusion barrier exists between the dendrite and the spine, supporting the idea that calcium-dependent processes, such as calcium pumps or other uptake systems, are responsible for isolating the spine head. This property would also explain why elevated calcium concentrations in the dendrite in the absence of synaptic stimuli to the spines fail to induce LTP at those spines (*16*).

Thus, both experimentalists and theoreticians are shifting their viewpoint from seeing spines as devices that modulate electrical properties toward a view of spines as devices subserving chemical compartmentalization. One of the key functions of spines, then, would be to amplify and isolate the synaptically induced calcium increases, or any other second messenger, within individual spines. In other words, dendritic spines may be crucial for the induction of information storage in the brain, rather than for its retention.

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