The Selfish Spike: Local and Global Resets of Dendritic Excitability

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Dendritic spikes are local events that occasionally propagate successfully to the soma, triggering axonal action potentials that backpropagate into the dendrites. In this issue of *Neuron*, Remy et al. show that single dendritic spikes in hippocampal pyramidal neurons transiently inhibit further dendritic spikes in the same branch, while backpropagating action potentials trigger a widespread reduction of dendritic excitability. Thus, dendritic spikes can cause local and global resets of dendritic spike generation, which can be exploited for computation and plasticity.

> "It is not enough to succeed. Others must fail."
>
> —Gore Vidal

Dendrites compute. The repertoire of dendritic computations depends in part on the number of independent functional compartments in the dendritic tree, and on how they interact. One of the most dramatic examples of such functional compartmentalization is the dendritic spike. These occur when synaptic input is sufficiently clustered in time and space on a dendritic branch to trigger regenerative activation of dendritic Na^+, Ca^{2+}, or NMDA receptor channels, producing a sharp voltage deflection and strong local calcium influx (Gasparini et al., 2004; Golding and Spruston, 1998; Losonczy and Magee, 2006; Schiller et al., 1997, 2000; Williams and Stuart, 2003). Successful initiation of a dendritic spike thus represents a form of coincidence detection, reporting when a threshold level of spatiotemporal input clustering has been crossed. This local decision-making process allows single dendritic branches to act as independent computational compartments, greatly enhancing the computational power of single neurons (London and Hausser, 2005; Mel, 1993). Moreover, dendritic spikes—by delivering calcium to the dendrite—may act as a trigger for synaptic plasticity (Golding et al., 2002; Remy and Spruston, 2007). Since dendritic spikes can also propagate with variable efficacy to the soma, they also enhance the efficacy of distal synapses and the probability and precision of axonal action potentials (Ariav et al., 2003; Gasparini et al., 2004). Thus, dendritic spikes can serve multiple important roles in neuronal function.

The biophysical mechanisms and necessary conditions driving the initiation of dendritic spikes have been well characterized in recent years. This new level of understanding has been won by exploiting important recent technical advances, including patch-clamp recordings from fine dendrites, two-photon dendritic calcium imaging, and particularly multisite glutamate uncaging techniques, which allow synaptic inputs to be activated in defined spatiotemporal patterns (Gasparini and Magee, 2006; Losonczy and Magee, 2006). However, our current knowledge has been focused on understanding initiation and spread of a dendritic spike in isolation. While this is clearly important, it neglects the fact that communication between neurons in the brain is a highly dynamic and history-dependent process: channels inactivate, receptors desensitize, synapses facilitate and depress, and every integration event will be shaped by the state of the variables on which it depends. How does this apply to dendritic spikes? How does the history of activity in the neuron and its dendrites influence local spike generation? Moreover, what happens next: does initiation of the spike itself change subsequent integration? As revealed in this issue of *Neuron*, Remy et al. (2009) have now taken an important step toward answering these questions.

Using multisite two-photon glutamate uncaging to activate patterned synaptic input on CA1 pyramidal neurons in hippocampal slices, Remy et al. first asked how triggering a local spike influences the generation of further dendritic spikes. They delivered temporally and spatially clustered input to multiple spines in individual basal dendritic branches, a paradigm that reliably evokes fast Na^+-channel-mediated dendritic spikes (Gasparini and Magee, 2006; Losonczy and Magee, 2006), and repeated this stimulation pattern at frequencies up to 10 Hz. At low frequencies (1 Hz), the dendritic spike was consistently triggered, but stimulation at 5–10 Hz led to a pronounced reduction in the spike amplitude and eventual failure. This "spike depression," which can be considered a form of refractoriness or short-term plasticity, was maintained for several hundreds of milliseconds after a spike, taking almost 5 s to fully recover, and was restricted to the stimulated branch (Figure 1A). Indeed, the authors found that other dendritic branches that shared the same parent dendrite as the depressed branch were fully capable of supralinear integration, and so were protected from the depressing effect of the dendritic spike in the sibling branch.

In the first set of experiments, the dendritic spike was restricted to the stimulated branch. However, dendritic spikes vary in their ability to propagate to the soma, and strong spikes can trigger somatic action potentials (Ariav et al.,

2003; Golding and Spruston, 1998; Losonczy et al., 2008; Stuart et al., 1997). By increasing input strength, Remy et al. next investigated what happens when local spikes trigger action potentials, which efficiently backpropagate into the dendritic tree of pyramidal cells. In contrast to the local effect of local dendritic spikes, triggering a backpropagating spike led to a widespread inhibition of dendritic spikes (Figure 1B). The authors then asked if any backpropagating action potential—even one not triggered by a previous dendritic spike—could cause such attenuation. Using action potential patterns obtained from in vivo recordings from CA1 pyramidal cells exhibiting place-related firing in freely moving animals, Remy et al. directly elicited action potentials with somatic current injection and found a similar global attenuation of dendritic spikes. Thus, successful initiation of a dendritic spike leads to failure of subsequent spike generation, either in neighboring regions of the same dendrite, or across the dendritic tree if the dendritic spike is strong enough to generate axonal output. Interestingly, Remy et al. demonstrate that success and subsequent failure of dendritic spike initiation are products of the same biophysical process. By examining the properties of voltage-gated Na^+ channels in dendritic cell-attached patches, they show that activation of these channels by dendritic spikes triggers prolonged inactivation that limits the availability of sodium channels for subsequent spike generation. Similar mechanisms underlie the fatigue in backpropagation efficacy during trains of action potentials (Colbert et al., 1997; Jung et al., 1997).

The work of Remy et al. raises a number of new issues. First, dendritic spikes come in a wide range of different flavors, depending on the local complement of inward and outward voltage-gated and NMDA conductances. Dendritic spikes that do not rely primarily on Na^+ channel activation, such as those in cerebellar Purkinje or cortical pyramidal cells, are likely to exhibit less depression, or achieve it via different mechanisms. Second, either neurons exhibiting high firing rates will have tonically inhibited dendritic spikes, or the global reset mechanism described by Remy et al. must be tuned differently from that in CA1 pyramidal cells. Third, the ability to switch between a local and global reset refocuses attention on the factors modulating successful propagation of dendritic spikes to the soma; and in turn, since backpropagation is itself modulatable, so might be the strength and extent of the global reset produced by the backpropagating spike. In this context it will also be particularly important to consider the impact of inhibition, in particular to understand the extent to which it can regulate the switch between the local and global reset and mitigate the extent of the global reset. Finally, although dendritic spikes have also been observed in vivo in anaesthetized animals (Kamondi et al., 1998), the real challenge is now to show directly that the high degree of input clustering required to trigger them also occurs during, and is relevant to, behavior.

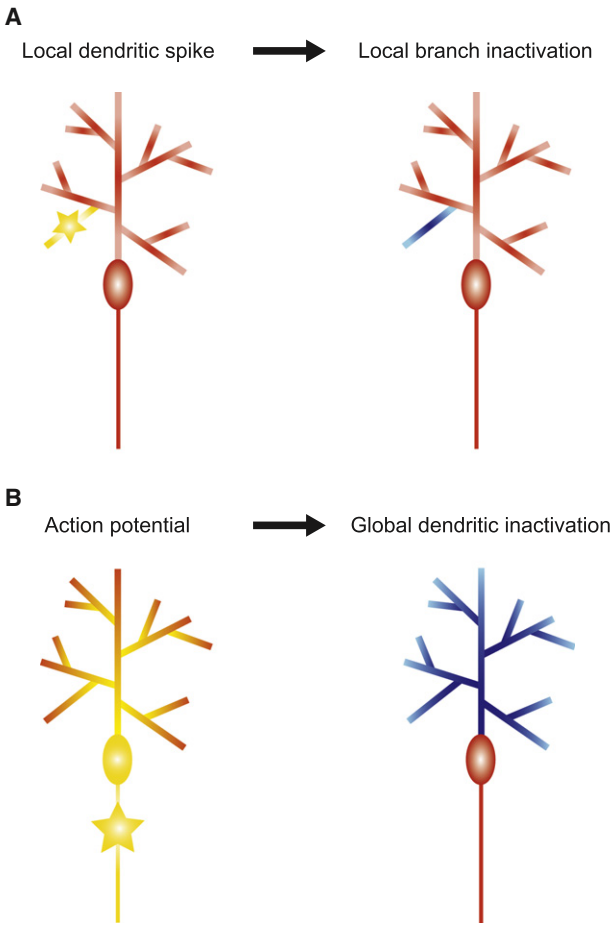

Figure 1. Local and Global Resets of Dendritic Excitability by Dendritic Spikes and Backpropagating Action Potentials

(A) Activation of a local dendritic spike that does not propagate effectively beyond its own branch reduces the ability of inputs to the same branch to trigger subsequent dendritic spikes.

(B) When an action potential is triggered in the axon (either by a dendritic spike or by distributed input), its backpropagation into the dendritic tree causes a widespread reduction in the probability of dendritic spike generation.

What are the computational implications of these findings? Remy et al. show that dendritic spikes can trigger a local and global reset that temporarily dampens the ability to trigger additional dendritic spikes. This is analogous to surround inhibition, with the strength and spatial extent depending on whether the spike is exclusively local or triggers a somatic action potential. Why might dendritic spikes selfishly inhibit each other? One interesting possibility is that the temporary local reset after a dendritic spike increases the effective signal-to-noise ratio of the inputs that triggered the spike. During the prolonged time window of depression, other inputs in the same branch will have unequal opportunities for supralinear summation, diminishing their influence on synaptic integration as compared with that of the "local hero" dendritic spike. In the event that a group of inputs triggers a somatic action potential (via a dendritic spike or not), and assuming that supralinear integration is frequently used, those inputs become the most prominent ones in the entire cell for hundreds of milliseconds after their onset, at the expense of others (a "winner-take-all" scenario). This process can also have a long-term impact given

that dendritic spikes leave a synaptic plasticity trace, even following a single trial (Remy and Spruston, 2007), and also trigger long-term changes of intrinsic excitability that favor further dendritic spike generation by the same input pattern (Losonczy et al., 2008). First, this makes the "win" of the activated inputs a more emphatic and durable one: not only have they succeeded in triggering a local spike that will potentiate their strength, but they also reduce the chances of other inputs being potentiated, providing the winning inputs with a long-term advantage. Second, reducing the overall frequency of potentiation-triggering events (particularly if the failure of subsequent events to trigger dendritic spikes might be linked to long-term depression) might be a good way of implementing dendritic gain control and ultimately homeostasis of synaptic strength, both locally and globally. Also, as noted by the authors, this mechanism sets a limit on the number of input patterns that can be stored with dendritic spikes, as well as how frequently those patterns can be retrieved, to a maximum of ~1 pattern per second. Thus, placing dendritic spikes in context shows that they depend crucially on the history of activity, and decisively shape the future of synaptic integration in the same neuron, over both short and long timescales. This sharpened focus on competition between different cooperative groups of synaptic inputs that drive dendritic spikes also allows one to speculate that Gore Vidal's characteristically tart and cynical observation about human endeavor may also apply to synaptic integration.

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Nipping Fear in the Bud: Inhibitory Control in the Amygdala

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Cortical and thalamic inputs to the lateral amygdala are recruited during auditory fear conditioning. In this issue of *Neuron*, Pan et al. describe a new mechanism of GABA-mediated modulation at these synapses, involving target-specific suppression of glutamate release through differential activation of GABAb receptors on glutamatergic inputs to neurons and interneurons.

The amygdala is a subcortical brain structure, consisting of several interconnected nuclei (Pitkanen et al., 1997), which is critically involved in fear-related behavioral responses both in humans and animals (Fanselow and LeDoux, 1999; Davis and Whalen, 2001; Maren and Quirk, 2004). Given that interneurons in the amygdala, specifically in its lateral nucleus (LA), receive massive excitatory inputs (Smith et al., 1998), they are well positioned to control the firing rate of principal neurons by releasing the inhibitory neurotransmitter GABA on them. The latter is also promoted by the intrinsic membrane properties of interneurons in the LA allowing these cells to maintain high-frequency spiking in response to postsynaptic depolarization without a significant frequency accommodation (Mahanty and Sah, 1998). The inhibitory neurotransmitter γ-aminobutyric acid (GABA), released by local circuit interneurons, mediates inhibition in different regions of the brain, including the amygdala, through its binding to either ionotropic $GABA_A$ or G protein-coupled GABAb receptors. While activation of