between sorting motifs and adaptors to design reagents to manipulate sorting in living cells—could also be used to elucidate the machinery that directs axonal sorting.

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Dendritic Spikes Veto Inhibition

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How inhibition regulates dendritic excitability is critical to an understanding of the way neurons integrate the many thousands of synaptic inputs they receive. In this issue of *Neuron*, Müller et al. (2012) show that inhibition blocks the generation of weak dendritic spikes, leaving strong dendritic spikes intact.

Neurons come in two flavors: excitatory and inhibitory. Because excitatory neurons usually outnumber inhibitory neurons in most brain regions, it's not surprising that we know more about excitation than inhibition. This extends to our understanding of how inhibition regulates dendritic excitability. Although originally thought of as passive integrators of incoming synaptic inputs, we now know that dendrites express a range of voltage-gated channels and, as a result, can perform a variety of active forms of synaptic integration. This includes the generation of dendritic "spikes"—all-or-none, active responses initiated in localized dendritic regions or branches following the activation of dendritic voltage-gated sodium and/or calcium channels, as well as NMDA receptors, which derive their voltage dependence via external magnesium block. These active forms of dendritic integration have been studied in great detail over the last

two decades, primarily due to advances that have allowed dendrites of neurons to be investigated directly using either electrophysiological or imaging techniques. What has been missing from the puzzle is an understanding of how this dendritic excitability is regulated by inhibition. In the current issue of *Neuron*, Müller and colleagues (2012) investigate the role of inhibition in regulating dendritic excitability in hippocampal CA1 pyramidal neurons. The authors focus on "recurrent" or "feedback" inhibition, evoked following antidromic activation of CA1 pyramidal neuron axons via stimulation of the alveus. Previous work indicates that stimulation of the alveus evokes at least two forms of recurrent inhibition, with a single stimulus recruiting primarily somatic and proximal dendritic inhibition, whereas brief trains (as used in the study by Müller and colleagues) also recruit a distal dendritic form of inhibition mediated by stratum oriens and lacunosum-

moleculare (OL-M) cells (Pouille and Scanziani, 2004). The somatic and proximal dendritic inhibition evoked by alveus stimulation is likely to be mediated by a variety of interneuron subtypes, including axo-axonic cells, which target the axon initial segment, basket cells, which are primarily somatic, and bistratified cells, which target oblique and basal dendrites (Somogyi and Klausberger, 2005).

To generate dendritic spikes, the authors use local glutamate iontophoresis targeted to oblique and basal dendritic branches. Consistent with earlier work using glutamate uncaging (Losonczy et al., 2008), they find that glutamate iontophoresis generates localized dendritic spikes in a subset of basal and apical oblique branches of hippocampal CA1 pyramidal neurons. These local dendritic spikes can be detected at the soma as an abrupt change in the rate of rise of the somatic membrane potential,

and they had similar properties to events generated by glutamate uncaging or local synaptic stimulation. Presumably the authors chose to use glutamate iontophoresis rather than uncaging in these experiments because of the capacity of caged glutamate to block GABA receptors (Fino et al., 2009). As observed previously (Losonczy et al., 2008), the authors find that these dendritic spikes come in two classes, weak and strong, with strong dendritic spikes more effective in generating action potential output. The main new finding from the study (Müller et al., 2012) is that while recurrent inhibition is effective in blocking the generation of weak dendritic spikes, it is ineffective in blocking the generation of strong dendritic spikes. The authors go on to show that this is also the case after conversion of weak dendritic spikes to strong dendritic spikes following the pairing of dendritic spikes with bursts of somatic action potentials. Finally, the authors investigate the impact of recurrent inhibition during theta-burst stimulation, used to mimic the natural theta rhythm, showing that an activity-dependent reduction in inhibition during theta-burst stimulation reduces the capacity of inhibition to block the generation of dendritic spikes.

The data show that recurrent inhibition is relatively ineffective in blocking the generation of strong dendritic spikes, which begs the question: What is it about these events that makes them so powerful? Previous work indicates an important role of dendritic A-type potassium channels in regulating the strength of localized dendritic spikes in hippocampal CA1 pyramidal neurons (Losonczy et al., 2008). This work suggests that A-type potassium channels are at lower densities in dendritic branches with strong dendritic spikes and that the conversion of weak dendritic spikes to strong dendritic spikes is associated with downregulation of A-type potassium channels in specifically dendritic branches. Consistent with this idea, earlier work has shown that localized downregulation of dendritic A-type potassium channels can occur during induction of long-term potentiation (Frick et al., 2004). In both cases, downregulation of dendritic A-type potassium channels has been shown to require activation of NMDA receptors. Earlier

work indicated that A-type potassium channels have a range of effects on dendritic integration in CA1 pyramidal neurons, acting to either linearize or suppress excitatory postsynaptic potential summation (Cash and Yuste, 1999; Hoffman et al., 1997).

One of the most interesting findings in the paper is that the capacity of recurrent inhibition to reduce the amplitude of dendritic glutamate-evoked depolarizations that are subthreshold for generation of dendritic spikes is weaker in dendritic branches that generate strong dendritic spikes. This result is even more surprising given that much of the recurrent inhibitory input recruited by stimulation of the alveus will be located at the soma. Application of GABA to these dendritic branches suggested that the difference in the impact of recurrent inhibition on different dendritic branches is not due to differences in the density of GABA receptors or the reversal potential for GABA. These data suggest that the number or release probability of GABAergic inputs recruited during recurrent inhibition is lower in dendritic branches that generate strong dendritic spikes. How this occurs is unclear, but it may involve the release of a retrograde signal, possibly in response to generation of dendritic spikes. Because the conversion of weak dendritic branch spikes to strong dendritic branch spikes did not influence the capacity of recurrent inhibition to reduce the amplitude of subthreshold glutamate-evoked depolarizations, this process presumably takes time to develop and occurs subsequent to downregulation of A-type potassium channels in these dendritic branches. Whether this is associated with similar, or perhaps opposite, changes in feedforward inhibition on these dendritic branches is unclear.

Finally, it is worth commenting on the impact of the findings on the overall excitability of CAI pyramidal neurons. Earlier work has shown that pairing dendritic spikes with action potentials can convert weak dendritic spikes to strong dendritic spikes (Losonczy et al., 2008), thereby enhancing dendritic excitability. The current work by Müller and colleagues (Müller et al., 2012) adds to this data, showing that dendritic branches that generate strong dendritic spikes are

also associated with weaker recurrent inhibition. This would be expected to further enhance dendritic excitability. The following question thus arises: What mechanisms are in place to stop runaway dendritic excitability? In conventional forms of synaptic plasticity, long-term potentiation is opposed by long-term depression and vice versa, allowing these two forms of plasticity to coexist. One would expect that there are also mechanisms in place to curb runaway dendritic excitability. One such mechanism could be via an activity-dependent increase in expression of dendritic HCN channels (Fan et al., 2005). Other possibilities include changes in expression of A-type potassium channels or the efficacy of feedforward inhibition.

In summary, the paper adds to the growing recent literature on the capacity of inhibition to modulate dendritic excitability (Lovett-Barron et al., 2012; Murayama et al., 2009; Palmer et al., 2012). The main result is that dendritic branches showing strong dendritic spikes can veto inhibition compared to branches with weaker dendritic spikes. This effect is enhanced by a reduced efficacy of recurrent inhibition on dendritic branches with strong dendritic spikes. Given that it has been proposed that local dendritic spikes in CA1 pyramidal neurons may act as a storage mechanism coding features of the synaptic input (Losonczy et al., 2008), the study by Müller and colleagues indicates that recurrent inhibition will act to refine this information storage, preserving only information coded by dendritic branches that generate strong dendritic spikes. These finding further enhance our knowledge of the way inhibition acts to shape the impact of dendritic excitability on neuronal output.

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