# Dendrites Shed Their Dull Image

New techniques are revealing that dendrites, once thought to be mere adding machines, seem to be more actively involved in shaping the responses of neurons

What goes on behind drawn curtains in the tight community of the brain? Consider the lacy, branching appendages of nerve cells known as dendrites. Dendrites have long had a reputation as solid but dull citizens of the neural metropolis: bean counters who passively add up the information they receive through the synapses dotting their surface. But it isn't easy to study dendrites directly, and some researchers have suspected that, like what goes on in the banker's basement at midnight, the secret lives of dendrites are more complex and interesting than their public image suggests.

Recent results indicate that those suspicions may be right. In the past few years, neurophysiologists, aided by new techniques that allow direct examination of dendrites, have begun to penetrate the mystery, producing some of the clearest insights yet into how dendrites work. Their studies, two of which appear in this issue of *Science*, mark the beginning of a "new era in dendritic biology," according to Columbia University neuroscientist Eric Kandel.

NELSON SPRUSTON

**Fine lines.** This CA1 neuron shows highly branched dendrites at both top and bottom.

In that new era, researchers are confirming long-held suspicions that dendrites, far from being bean counters, play an active role in shaping the life of the neuron. Their finely branched network acts as a two-way highway, not only conveying incoming messages to the cell body, but also relaying information from the cell body back to their own outer reaches—information that may modify their responses to future signals. This ability of the dendrites to react and adjust their activity is likely to play an important role in such mental processes as learning and memory. The work has "really put the spotlight on the dendrites," says neuroscientist and neural modeler Terrence Sejnowski of the Salk Institute.

The "bean-counter" image of dendrites stems from the fact that their job as information receivers requires that they pass along to the cell body the synaptic potentials, the little dollops of charge that enter the dendrites when neurotransmitter molecules activate synapses. During the journey to the cell body, each synaptic potential adds up with all the others moving through the dendrites. If their sum is large enough when they reach the cell body, they trigger an action potential by causing sodium ions to flow into the cell. The action potential then sweeps down the axon, the part of the nerve cell responsible for carrying the signal to other neurons.

In the traditional dogma of neuroscience, action potentials were limited to axons, and synaptic potentials to dendrites. "This made a clear distinction between the input and the output of the cell," says Salk Institute neurophysiologist Chuck Stevens. But more than 30 years ago, cracks began to appear in that simple model, as researchers reported evidence of action potentials in the dendrites. Some theorists were intrigued by this possibility and began to consider what action potentials might be doing in the dendrites. Others pooh-poohed the idea, saying that action potentials sweeping through the dendrites would foul up their ability to add up synaptic potentials.

The debate was complicated by the fact that dendrites were considered too fine to be impaled easily with electrodes. Their diameter is a mere 1/1000th the diameter of the squid giant axon, which was used for studies of action potentials in axons, and 1/10th the diameter of a typical neuron cell body, which is where neurophysiologists generally put their electrodes. That meant that, at first, all the evidence for action potentials in the dendrites was gathered indirectly. In the 1970s, however, Rodolfo Llinás's team at New York University poked electrodes directly into dendrites of neurons from the cerebellum and recorded action potentials there. But critics worried that the delicate dendrites may have been damaged by the impaling electrode, producing an erroneous result.

Even those researchers who believed the action potentials were real couldn't agree on which way they were going. Some experiments suggested action potentials may initiate within the dendrites themselves. Others suggested they started in the axon and spread into the dendrites from there. The field was clearly in need of new approaches.

A key advance came last year from Greg Stuart, a postdoc with Bert Sakmann at the Max Planck Institute for Medical Research in Heidelberg, Germany. Sakmann shared the 1991 Nobel Prize for developing a technique called patch-clamping, which replaced sharp, impaling electrodes with smooth-ended electrodes which are pressed up against the neuron's outer membrane to form a tight electrical seal. Stuart had developed methods for patch-clamping dendrites that took advantage of new contrast-enhancing microscopy techniques to bring the dendrites sharply into view.

Using the new method, Stuart put separate patch clamps on the cell body and dendrites of individual neurons in slices of cerebral cortex from rat brains. His results, reported in the 6 January 1994 issue of *Nature*, showed that, when the dendrites were stimulated and the neuron fired, the resulting action potential was registered first by the electrode on the cell body and then, milliseconds later, by the electrode on the dendrites.

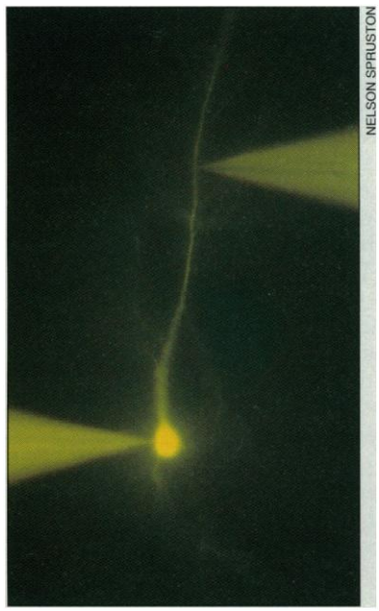
This was the first direct evidence that action potentials travel into the dendrites after being triggered in the axon. "This dual-patch technique that the Sakmann lab introduced really nailed this subject down in a way that wasn't capable of being done in the past," says neuroscientist William Ross of New York Medical College in Valhalla.

The idea of "back-propagating" action potentials (so called because they travel against the main flow of information from dendrite to cell body to axon) had been kicked around among theorists for years. It has a certain appeal, because it could serve as a feedback signal to the dendrites and the synapses on their surfaces.

Researchers have long known that neurons can adjust the strength of their response to incoming signals, a process called plasticity that is thought to be important for learning. For example, in one form of plasticity, synapses that are active when a neuron fires become stronger, so that they give a bigger

response to future signals. Back-traveling action potentials seem "like the ideal way to tell the synapses something happened," says neuroscientist Dan Johnston of Baylor College of Medicine in Houston. "How else will they know the cell fired?"

To find out whether the action potentials might in fact have such a role, Sakmann postdoc Nelson Spruston turned to the neurons in which synaptic plasticity has been most intensely studied, the CA1 neurons of the hippocampus, a brain structure involved in some forms of learning. On page 297, Sakmann's group reports that back-propagation occurs in the CA1 neurons, although they don't yet know if it influences plasticity.



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**Double duty.** Two patch pipettes are in place on a single CA1 neuron, one on the cell body *(bright yellow spot)* and the other on a dendrite.

Although they have not answered that question, they made an unexpected discovery that might relate to plasticity. They noticed that sometimes, after a neuron had fired several times in succession, the electrode on the dendrite would register a much-reduced signal, as if the later action potentials in the series fizzled out before reaching it.

Clarification of what was happening came from Sakmann postdoc Yitzhak Schiller, who was studying action potentials by injecting neurons with calcium-sensitive dyes. Action potentials let calcium into the cell, so Schiller could use the dyes to record the path of the action potentials out to the finest tips of the dendrites. He found that when the neuron fired off a series of action potentials in a row, the first one would spread unhindered throughout the dendrites, but subsequent ones would not make it past some of the dendrites' branch points.

When Schiller and Spruston saw each other's results, "we got really excited," Spruston says. "It all fit together very nicely. ... You have the idea of all these branch points acting like switches that can control the number of action potentials that get through those points." Their finding was confirmed by Joseph Callaway, a postdoc in Ross's lab at Valhalla, who has similar results with calcium-sensitive dyes submitted for publication.

Still, a big question remains unanswered: What is the significance of this switching? If the back-propagating action potentials do contribute to plasticity, says Columbia's Kandel, the fact that branch points can act as switch points means that "one [branch] will [receive] the action potential and one will not. ... You will have the capability in one branch for plasticity that the other branch will not have." That adds to the computing potential of the dendrites, as selective strengthening of some branches would give a boost to signals arising there, leaving other branches unaffected.

Despite their apparent usefulness, backward-traveling action potentials are not universal in dendrites. NYU's Llinás found, in neurons called Purkinje cells, that action potentials begin within the dendrites themselves and travel toward the cell body. But these are not typical action potentials. Purkinje cells lack sodium channels in their dendrites, and the action potentials Llinás observed are carried by calcium ions instead. Indeed, the lack of sodium channels in Purkinje cell dendrites may explain why action potentials that start in the cell bodies of those neurons do not travel backward into the dendrites, a fact that Stuart and Michael Häusser confirmed with dual patch-clamp recording, as reported in a paper in last September's issue of *Neuron*. While the role of the calcium-based action potentials in Purkinje cells is not known, their existence attests to a different "philosophy of [function] of the two cell types," says Llinás.

Besides resolving the question of whether dendrites carry action potentials, recent research is clearing up another long-standing mystery about dendrite action, and that is how synaptic potentials travel through the dendrites. Action potentials travel "actively," which means that, as they pass through the neuron, they open ion channels, allowing positively charged ions to flow into the cell and add their charge to the traveling signal, like springs continually renewing a river's flow. Synaptic potentials, on the other hand, were thought to travel passively, like creeks in dry country, simply flowing along the inside of the membrane with no additional inputs.

The problem is that a potential traveling in that manner loses charge as it goes, and so synaptic potentials from the most distant dendrites would virtually disappear before reaching the cell body. But researchers long ago showed that those distant synapses are able to fire a neuron, which means those synaptic potentials must be able to make the long journey. "You wonder how could these events on the distal dendrites ever make it," says Yale University neurobiologist Tom Brown. "The obvious answer is there has to be some booster out there."

Studies with ion-sensitive dyes had suggested that there are ion channels in the membranes of dendrites that might act as boosters, and on page 301, Baylor's Johnston and postdoc Jeffrey Magee provide more direct evidence that that is the case. They patch-clamped the dendrites and studied individual channels in the patches of membrane beneath the electrode to find out under what conditions the channels opened. "We allowed the cell to experience normal synaptic potentials," says Johnston, "and asked the question of whether or not, in the little patch of membrane, the channels will open during this normal physiological event." They found that voltage-dependent sodium and calcium channels in the membrane open not only in response to action potentials, but also when synaptic potentials pass by on their way to the cell body. "It's like power lines," says Johnston. "You have transformers and amplifiers along the way" to maintain and modify the signal.

Johnston points out that the entry of calcium ions may also be an important cause of plastic changes in the dendrites. Indeed, calcium is a powerful intracellular signal. Whether let in by back-propagating action potentials or by synaptic potentials, it is bound to play a role in shaping the future response of the dendrites. "There are likely to be many, many processes triggered by calcium," says neuroscientist Roberto Malinow of Cold Spring Harbor Laboratory, "synaptic potentiation, ... regulation of ion channels, and even [dendrite] growth."

Despite all the recent revelations, neuroscientists have a long way to go before they understand how all this activity in the dendrites contributes to mental processes. But the next round of experiments addressing that question is already well under way in many labs. For example, Sakmann's group is testing to see whether back-propagating action potentials are necessary to strengthen synapses, and Sejnowski's team at Salk has a paper in press at the *Journal of Physiology* in which they report that the firing of action potentials in CA1 cells strengthens the cells' response to later signals, possibly through bigger boosts to the synaptic potentials as they travel to the cell body.

Ultimately the same techniques will be applied to many other neuron types and will reveal even more variety in the activities of dendrites. "It is all coming together very rapidly," says Sejnowski. And as it does, the staid image of the dendrite is being replaced by something far more intriguing.

**–Marcia Barinaga**