

# "Home-Grown" Proteins Build Synaptic Strength

**M**any neuroscientists believe that synaptic strength—the ease with which a signal traverses the synapse, which is the gap between two neurons—plays a central role in learning and memory. When a music student first reads “C major 7 chord” on a score, for example, it takes considerable effort to strike the correct keys on the piano. After reading and playing the chord 500 times, however, the neural pathway that translates a visual image into a musical concept and then into a fingering pattern becomes established, enabling the fingers to strike the keys faster and more accurately. At the molecular level, the “wearing in” of this neural pathway translates into the building-up of synaptic strength and a more powerful signal.

The cell biology of this process has posed a paradox, however. To build synaptic strength, new proteins are needed immediately at the dendrites, the synapse-forming branches emerging from the body of the neuron. These proteins must be transported from elsewhere because, according to conventional wisdom, they are made in ribosomes inside the cell body, not in the dendrites. If so, how are the proteins transported to the correct synapse quickly enough to account for learning?

Erin M. Schuman, an HHMI investigator at the California Institute of Technology, has investigated this apparent anomaly and now offers another view. “Since we know that all synapses are individual, protein would have to be shipped to each, and that would be a traffic nightmare,” she says. Instead, Schuman concludes that dendrites use a “home-grown-protein” approach that is considerably swifter and surer than the problematic “manufacture-and-ship” tactic. Using a technique that she invented, she has shown that dendrites make the proteins themselves,

when and where they’re needed, rather than import the proteins from the cell body.

Proving this hypothesis required considerable experimental dexterity. Schuman’s studies used green fluorescent protein (GFP), derived from jellyfish, to signal that protein synthesis was occurring. Her team built a “reporter” molecule containing the GFP messenger RNA (mRNA), which carries the DNA’s instructions for synthesizing proteins in the ribosomes. The team flanked the GFP with two key elements: one that causes the reporter mRNA to travel from the cell body (where it is made) to the dendrite, and another that responds to the neuron’s signal to “make protein” by regulating the synthesis of GFP on the mRNA template.

To start the protein synthesis, Schuman used a growth factor called BDNF. After a few minutes, reporter protein levels in many parts of the dendrites did rise, as shown by the increased brightness of GFP under a light microscope.

To prove that the proteins were being synthesized in the dendrites, Schuman and her graduate students Bryan Smith and Girish Aakalu tried several hundred times to keep dendrites alive after being severed from the cell body. The neurons came from the rat hippocampus—a part of the brain that is essential for learning and memory. Roughly a dozen dendrites survived, and each showed protein synthesis after stimulation with BDNF, indicating that the synthesis must have occurred in the dendrite rather than the cell body.

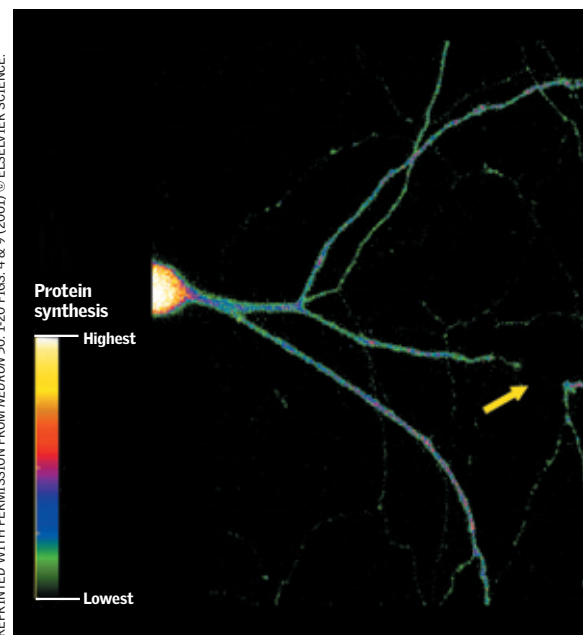
The data were intriguing. For one thing, throughout the experiment, protein synthesis occurred at the same spots within the dendrite, suggesting that locally synthesized proteins might be delivered to only a few synapses. These experiments, Schuman stresses, show the simplicity of a process that’s essential to learning and memory. “Our data show that protein is made right in the

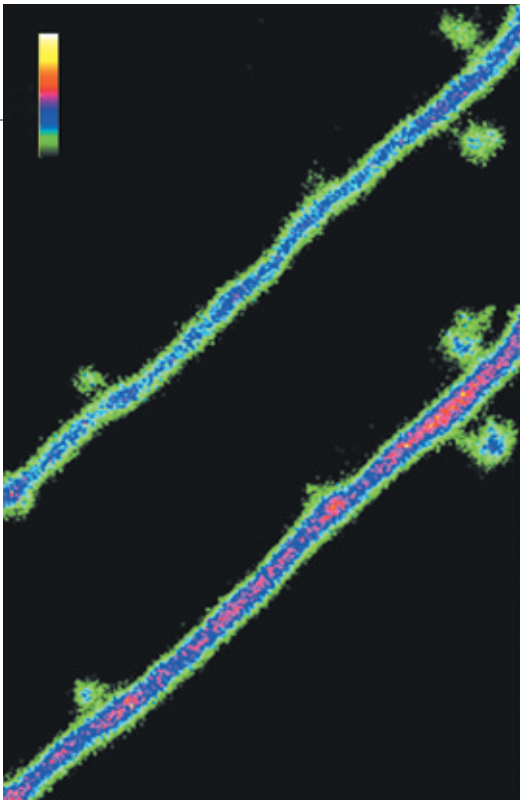
dendrite. This means that an activated synapse need not send a signal to the cell body to make new protein and ship it back. There is a local control mechanism. The events at the synapse are in very close proximity to the protein-synthesis machinery.”

In practical terms, Schuman notes that the protein involved in fragile X syndrome, a genetic abnormality that causes mental retardation, is an RNA-binding protein found in dendrites. “Understanding dendritic protein synthesis may help us understand, somewhere down the line, what goes wrong with fragile X syndrome,” Schuman says. If that hope is not realized, there is still a broader benefit: Every step toward understanding the transmission of nerve signals across synapses produces a clearer picture of learning and memory.

— DAVID TENENBAUM

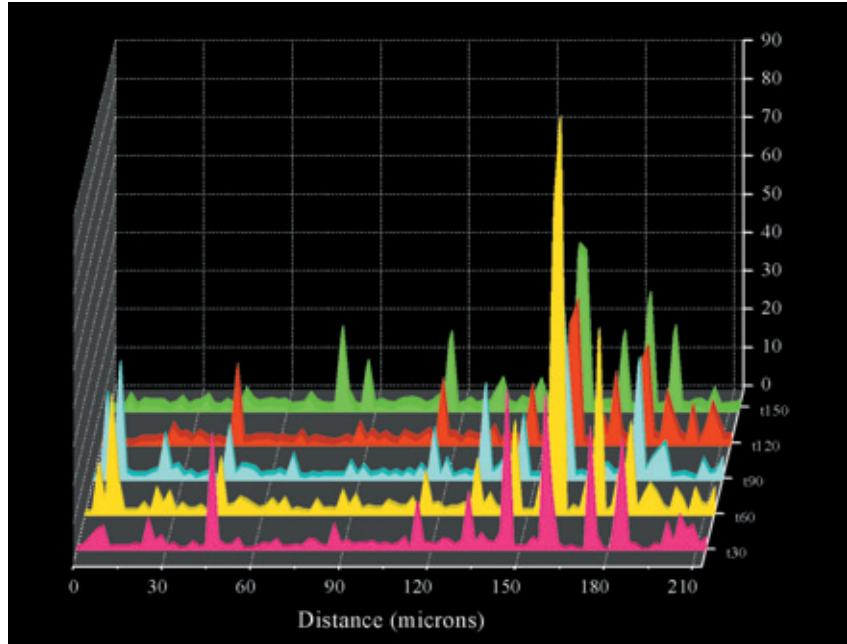
**T**hese images show protein synthesis occurring at the dendrite, where proteins are ultimately needed to build synaptic strength. They reveal an efficient system for learning and memory. Instead of proteins being produced in the neuron cell body and shipped to the far-flung dendrites, they are synthesized locally, right where they do their work.





ERIN M. SCHUMAN

▲ Protein synthesis along dendrites, seen at high magnification. Upper: part of a dendrite before stimulation with BDNF. Lower: same dendrite after stimulation. The location of synthesis does not change, but it intensifies after stimulation, as shown by the transition from blue to red and the appearance of blue in the dendritic spines.



▲ On a single, severed dendrite, protein synthesis lasts hours after the BDNF stimulus. The five colored trails indicate protein synthesis at 30-minute intervals after stimulation. Distance from the cell body (bottom scale) shows synthesis taking place in the same locations—possibly at synapses.

▼ Dendrites before (left) and 120 minutes after (right) BDNF treatment. Arrow shows where the dendrite was severed from the cell body.

