A change of mind

One protein appears to control neurons' ability to react to new experiences, MIT scientists show.

Anne Trafton, MIT News Office

March 24, 2010

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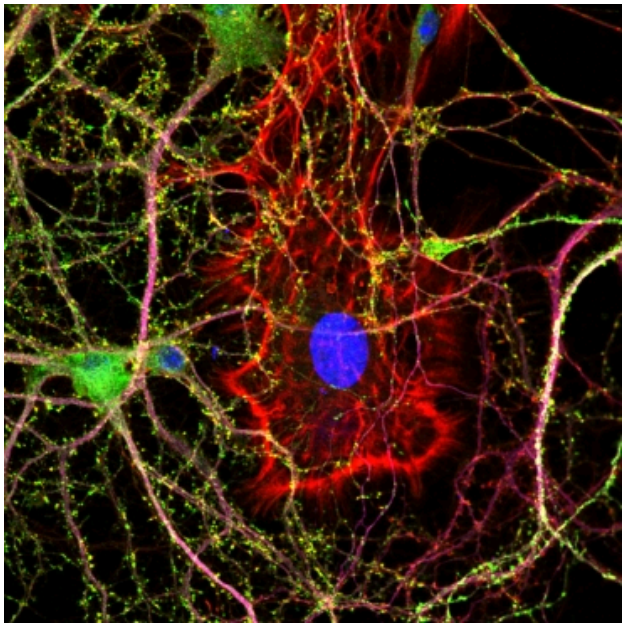

MIT neuroscientists have shown that the protein Arc is necessary for neurons like this one to adjust their responses to new sensory stimuli. (The blue circle is the neuron's nucleus, and the red strands are actin filaments.)
Image: Jason Shepherd

Plasticity — the brain's ability to change in response to external input — is critical for most cognitive functions, including learning and memory. Those changes usually involve a strengthening or weakening of synapses, the connections between brain cells (neurons).

MIT neuroscientists have now found that a single protein, known as Arc, appears to control neurons' ability to strengthen and weaken their synapses by regulating the number of neurotransmitter receptors on their surfaces. The finding could help researchers identify new drug targets for Fragile X and Angelman syndromes — inherited forms of mental retardation that have been linked to deficits of Arc.

"The more we understand the chain of cellular events that Arc is involved in, the more we can identify particular targets where we could intervene," says Mriganka Sur, head of MIT's Department of Brain and Cognitive Sciences (BCS).

Sur and Mark Bear, the Picower Professor of Neuroscience, are senior authors of a paper on the work that appeared in the March 14 online edition of *Nature Neuroscience*.

A surprising discovery

Jason Shepherd, co-lead author of the paper and a postdoctoral associate in Bear's lab, began studying Arc as a grad student at Johns Hopkins University. He and his colleagues showed that Arc weakens synapses by removing receptors for glutamate, a neurotransmitter that stimulates neuron activity, from neuron cell membranes. They also discovered that when the Arc gene is turned off in mice, they lose their ability to form long-term memories.

In the new study, Shepherd and co-lead author Cortina McCurry, a recent PhD recipient in BCS, did a series of experiments designed to pinpoint the role of Arc in the visual cortex of mice. They started with a classic experimental setup that involves sealing one eye for two days, depriving the eye of visual input. In normal mice, this strengthens synapses in the part of the cortex receiving input from the open eye, and weakens them in cortical cells wired to the closed eye.

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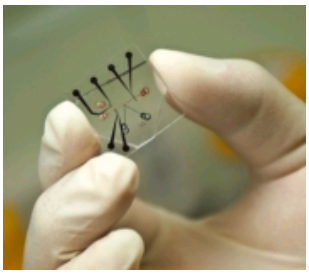

A single unit of the new desalination device, fabricated on a layer of silicone. In the Y-shaped channel (in red), seawater enters from the right, and fresh water leaves through the lower channel at left, while concentrated brine leaves through the upper channel.
Photo: Patrick Gillooly

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Shepherd and McCurry performed their experiments on mice with a mutation in the Arc gene that renders the protein ineffective. Because of Arc's known role in weakening synapses, they expected mice without Arc not to show any synaptic weakening from the closed eye. That prediction came true, but to the researchers' surprise, they found that the synaptic strengthening normally seen from the open eye also disappeared.

"If you knock out the gene, you don't get either response," says Shepherd. "The brain is not responsive at all to the changes in sensory input."

They observed the same lack of plasticity in studies of Arc-deficient mice that were repeatedly exposed to the same visual stimulus (for example, a horizontal bar), which normally provokes neurons to enhance their response to that particular stimulus.

The results suggest that Arc has an indirect role in inserting glutamate receptors in the cell membrane, as well as its previously known role in removing them, according to the researchers. "It's remarkable to find one single gene and its protein to be so responsible" in different types of plasticity, says Sur.

While others have shown in experiments with neurons that Arc appears to have a role in both suppressing and stimulating synapses, this paper is the first to demonstrate the effect in living animals, says Hey-Kyoung Lee, associate professor of biology at the University of Maryland, who was not involved in the research. "The current paper clearly shows that Arc plays a critical role in shaping cortical synapses with sensory experience," she says.

Shepherd is now planning experiments to image the Arc protein in single cells in the visual cortex. He also plans to further investigate the protein's role in Fragile X and Angelman syndromes.

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