Learning by Diffusion: Nitric Oxide May Spread Memories

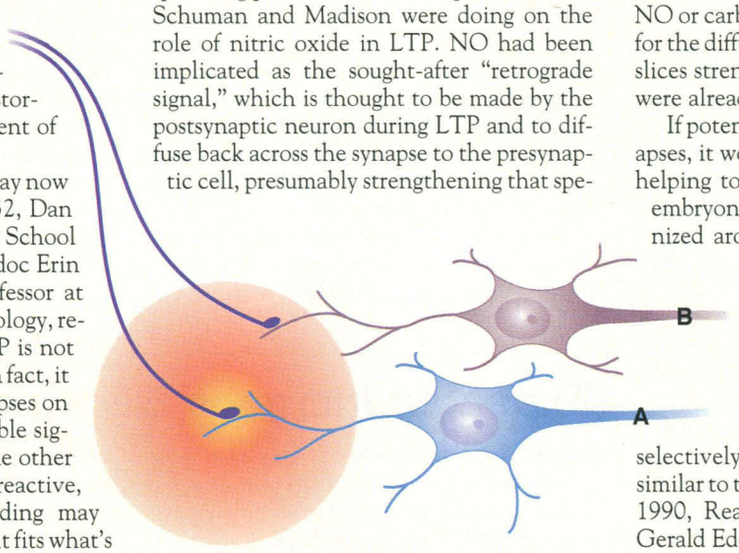
For an esoteric phenomenon, long term potentiation (LTP), has received a lot of attention in recent years. That's because this process strengthens the synapses that provide the functional links between neurons. Consequently, it may be central to both brain development and memory storage. Part of LTP's appeal has been that it appeared to be exquisitely specific, able to pick out and strengthen one synapse from among the thousands that dot a particular neuron. To brain modelers, that specificity meant each synapse could function as an independent memory-storage unit—the biological equivalent of the computer bit.

But that view of the synapse may now be forced to change. On page 532, Dan Madison of Stanford University School of Medicine and his former postdoc Erin Schuman, now an assistant professor at the California Institute of Technology, report findings suggesting that LTP is not as specific as had been thought. In fact, it can apparently be spread to synapses on neighboring neurons by a diffusible signal—and that signal may be none other than nitric oxide (NO), a highly reactive, soluble gas. Although this finding may shatter the former image of LTP, it fits what's known about NO, which has already been implicated as a diffusing signal in LTP (*Science*, 29 November 1991, p. 1296).

Finding that potentiation can spread to nearby synapses provides "a phenomenal new insight into the nature of LTP," says Columbia University neuroscientist Eric Kandel. Says Roger Nicoll, a neuroscientist at the University of California, San Francisco: "This is without a doubt the most direct evidence that there is some transfer of potentiation through a diffusible message." And he adds that the finding is "very provocative. Nature has gone to elaborate lengths to create a structural edifice that can give you synapse specificity. To then just degrade the process and let it spread around a bit, makes it seem like Nature blew it somehow."

The first evidence for spreading potentiation came in 1989 from Tobias Bonhoeffer, Volker Staiger, and Ad Aertsen, at the Max Planck Institut für Biologische Kybernetik in Tübingen. LTP can be triggered in a single synapse by simultaneously stimulating both the "presynaptic" neuron, which sends a signal across the synapse, and the "postsynaptic" neuron, which receives the signal. When the Bonhoeffer group used this technique to induce LTP in a synapse in a slice of rat hippocampus (a brain region involved in some types of learning), they found that the responses at synapses on neighboring neurons appeared to be strengthened as well.

At the time, LTP was thought to be highly specific, and their result was so iconoclastic that it didn't win rapid acceptance. Then, 2 years later, independent evidence of spreading potentiation came up in work that Schuman and Madison were doing on the role of nitric oxide in LTP. NO had been implicated as the sought-after "retrograde signal," which is thought to be made by the postsynaptic neuron during LTP and to diffuse back across the synapse to the presynaptic cell, presumably strengthening that specific synapse. But Schuman and Madison found that if they blocked NO production in a specific synapse, that synapse could still be strengthened, provided that others nearby were undergoing LTP. It seemed that NO from those synapses could rescue the synapse whose NO production was blocked.



Sphere of influence. NO may spread the effects of LTP to nearby synapses.

ILLUSTRATION: K. SUTLIFF

To explore this idea further, Schuman and Madison triggered LTP in single synapses in slices of rat hippocampus. Using more precise detection methods than Bonhoeffer's, they measured the effect on nearby synapses on neighboring neurons and found, as Bonhoeffer had, that the synapses were strengthened. Their painstaking methods and the sheer number of neurons they sampled in 3 years of work on the project won over many researchers who had been reluctant to buy the notion of spreading potentiation. "I was very skeptical initially," says neuroscientist Michael Stryker of the University of California, San Francisco, "but technically the new work seems really sound."

Madison and Schuman went on to test the role of NO in spreading potentiation, and found that when they blocked production of the gas in the postsynaptic neuron, they also blocked the strengthening of neighboring synapses. But Madison cautions that these findings don't prove that NO is the signal; it might instead trigger formation of another molecule that does the actual signaling.

Whatever the signal that wafts out from a potentiated neuron, a large number of synapses on many other neurons will be within its reach. Schuman and Madison had no way of telling whether all or just some of those synapses would be strengthened. But data from another research group does address that question. Last June, Kandel and his colleagues Min Zhuo, Scott Small, and Robert Hawkins reported in *Science* that spritzing NO or carbon monoxide (another candidate for the diffusible message) onto hippocampal slices strengthened only those synapses that were already receiving nerve impulses.

If potentiation spreads only to active synapses, it would be ideally suited to the job of helping to refine nerve connections in the embryonic brain. The mature brain is organized around clusters of neurons that respond to similar stimuli: such as the columns of neurons in the visual cortex that all respond to input from the same eye. To achieve that organization, embryonic neurons start with excess connections, then prune back, selectively keeping those that receive input similar to that received by their neighbors. In 1990, Read Montague, Joseph Gally, and Gerald Edelman of the Neurosciences Institute in New York City predicted that a diffusible substance such as NO could help determine which neurons are kept by broadcasting the news that a potentiating signal had been received, and triggering other neurons to strengthen any synapses active at the same time. So far, however, there are only preliminary—and conflicting—reports on whether NO actually performs such a function in developing brains.

Another intriguing question is what spreading potentiation means for learning and memory. For starters, it means the individual synapse cannot be the "computer bit" of the brain. "Instead of thinking of a synapse as representing a piece of information, you can now begin thinking of a population of [potentiated] synapses" acting together, says Salk Institute neural modeler Terrence Sejnowski. And while that reduces the storage capacity of the brain, Sejnowski believes that spreading out the storage may confer unknown advantages. He and Montague, who is now at Baylor College of Medicine in Houston, are developing computer models to test that hunch. So it may turn out that Nature didn't make such a mistake after all.

–Marcia Barinaga