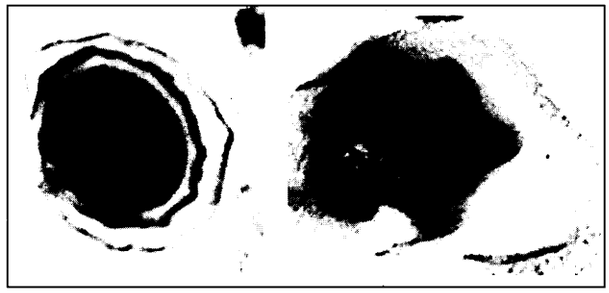
that kill by rupturing cell membranes. Trial and error led Baker's team to two formulations that demonstrate potent antimicrobial action. An emulsion including the detergents Triton X-100 and tributyl phosphate took out gram-positive bacteria and the vast majority of viruses sheathed in protein envelopes. (Naked RNA viruses are not susceptible, because they have no membrane for the emulsions to disrupt.) A second preparation killed a different spectrum of bugs: gram-negative bacteria and fungi. Combining the armaments yielded a potent killing machine. Exposing a variety of fungi, bacteria, and enveloped viruses to a 1000-fold dilution of the double-barrel emulsion for 15 minutes annihilated the life-forms, the researchers concluded from the absence of colonies in suitable growth media.



Decommissioned. *Bacillus cereus* spore, about 1 micrometer in diameter, before (left) and 4 hours after exposure to new emulsion.

To Baker's initial surprise, the emulsions proved effective against bacterial spores—a form of suspended animation in which the bacteria produce a hard protective coat—which tend to resist all but the harshest chemicals. "It appears that the oil acts as a nutrient that tricks the spores to start producing cell membrane, a process that the emulsions disrupt quite easily," said Baker. In one experiment, he and his colleagues infected skin wounds on mice with spores of *Bacillus cereus*, a cause of food poisoning and severe infections. One hour later, the wounds were rinsed with either a 10% solution of the two emulsions or with salt water. The wounds in the treated mice healed, while those in the control animals festered.

Sperm and red blood cells are the only animal cells that Baker's team has found to be susceptible to the emulsions. Other cells are studded with carbohydrates that appear to somehow prevent the emulsion droplets from fusing to the cell membrane. This gentleness is a nice surprise considering that membrane-disrupting antimicrobial peptides have shown unexpected toxicity in animal tissues, says microbiologist Jill Adler Moore, director of the Institute of Cellular and Molecular Biology at California State University in Pomona. The bottom line, says Baker, is that the emulsion mixture is a drug candidate mainly for external uses, such as for treating skin ulcers.

This expectation will soon be put to the test. The National Institute of Child Health and Human Development in Bethesda, Maryland, is planning a clinical trial to see if the emulsions will work as a vaginal contraceptive cream that wards off sexually transmitted diseases. And the U.S. military intends to try to detoxify contaminated equipment by hosing it down with the emulsions, a procedure that could save the equipment from becoming expensive scrap—or paperweights. **–JOSEPH ALPER**

Joseph Alper is a writer in Louisville, Colorado.

NEUROBIOLOGY

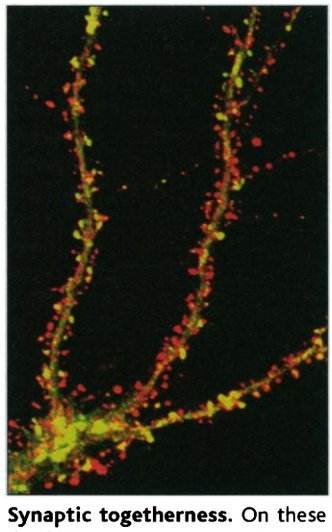
New Clues to How Neurons Strengthen Their Connections

New results point to the AMPA receptor for glutamate as playing a key role in the changes underlying long-term potentiation in brain neurons

Neurobiologists who study how the brain adapts and learns have long known that synapses—the specialized regions where one neuron receives chemical signals from another—are where the action is. For example, learning seems to be associated with an increase in the strength of those synaptic connections. Now, three teams—two of which report their results in this issue of *Science*, while the third published in the May issue of *Nature Neuroscience*—implicate a new player in the biochemical changes underlying a type of synapse strengthening known as long-term potentiation (LTP).

The neurons that undergo LTP respond to the neurotransmitter glutamate. Their synapses contain two kinds of glutamate receptors, but researchers studying LTP have largely focused on the one known as the NMDA receptor. That's because glutamate binding to this receptor is the first step in LTP. Exactly what happens after that is unknown—and the subject of fervent study and debate. The new work fingers the other, less famous glutamate receptor, the AMPA receptor, as a player in those synapse-strengthening events.

Previously, neurobiologists had thought that AMPA receptors are present at relatively unchanging levels in the vast majority of synapses on glutamate-sensitive neurons. But that no longer appears to be the case. Two of the teams, led by Roberto Malinow of Cold Spring Harbor Laboratory on New York's Long Island and Robert Malenka at the University of California, San Francisco, show that AMPA receptors move into and out of synapses as synaptic connections strengthen and weaken. The third team, led by Peter Seeburg and Bert Sakmann of the Max Planck Institute for Medical Research in Heidelberg, Germany, provides indirect evidence that the movements are needed for LTP to occur. Taken together, says Richard Huganir, who studies receptors at Johns Hopkins University School of Medicine in Baltimore, the results give "incontrovertible evidence" that "the regulation of AMPA receptors in general is going to be very key" to modulating synapse strength.



Synaptic togetherness. On these dendritic spines, AMPA receptors are stained green, NMDA receptors are red, and synapses where both are present are yellow.

The current findings are also likely to influence a long-standing debate over whether the changes that occur in LTP take place postsynaptically, that is, in the cell that receives the signal, or presynaptically, in the cell that dispenses it. They imply that at least part of the changes are postsynaptic. Ironically, however, the new findings trace back to an experiment done 9 years ago that was long viewed as strong evidence for presynaptic change.

At that time, the NMDA receptor had already been implicated in LTP, a task for which it is remarkably well suited. Brain neurons usually have thousands of synapses for

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receiving signals from other neurons. NMDA receptors become activated only if a glutamate signal arrives when the receiving neuron has just been activated by a signal from another source. That gives NMDA receptors the ability to strengthen synapses that receive closely timed signals, a trait thought to be important for learning. Once NMDA receptors have been activated and LTP triggered, the synapse is stronger, meaning it allows more ions to flow into the neuron in response to incoming signals, even if they don't activate NMDA receptors. But exactly how that happens was unknown.

One possibility is that the presynaptic neuron releases more glutamate into the synapse every time it fires. This could then trigger the AMPA receptors, also presumed to be present in the synapse. In 1990, two teams provided evidence for that model in the form of statistical analyses of the responses of individual synapses in brain slices or cultured neurons in response to low-level stimulation (*Science,* 29 June 1990, p. 1603). One of the studies, by neurobiologist Richard Tsien at Stanford University School of Medicine and Malinow, who was then a postdoc in his lab, also contained the first hints of another possibility, however.

This was an analysis of what they called "failures of transmission," when synapses don't transmit a signal at all. Malinow and Tsien interpreted those failures as cases in which no glutamate was released. The failures dropped dramatically once LTP was triggered, suggesting that the probability of glutamate release had risen.

But that logic was based on the assumption that every synapse had a steady level of AMPA receptors that would respond to glutamate if it were there. Later, Malinow and others began to question that assumption. If, contrary to expectations, some synapses had only NMDA receptors, they would appear to be "silent," not responding to glutamate until conditions were right to trigger the NMDA receptors and LTP. The number of silent synapses would drop if LTP caused AMPA receptors to move into those synapses. Indeed, an influx of AMPA receptors would strengthen any glutamate synapse, not just those that had been silent before.

A handful of labs began recording from neurons of the hippocampus, the brain area where LTP is most often studied, looking for synapses that were silent under normal conditions and only responded to glutamate under conditions that activate NMDA receptors. In 1995, Malinow's and Malenka's labs reported evidence for such synapses, followed in 1996 by a similar paper from Arthur Konnerth and his colleagues at the Universität des Saarlands in Homberg, Germany.

But there were alternative explanations for those data, such as the possibility that the amount of glutamate released into the silent synapses was simply too low to trigger AMPA receptors that were there. Then more recently, another line of research appears to have clinched the case for AMPA-less synapses: In the past 2 years, five research groups have used microscopy and differential staining techniques for AMPA and NMDA receptors and found synapses in the hippocampus that have only NMDA receptors.

Even so, a bigger question remained: Could AMPA receptors move into any synapses—silent or not—quickly enough to account for any part of LTP? The latest work answers that question in the affirmative. "The big advance" made by Malinow's and Malenka's groups in the present papers, says Huganir, "is to show that [AMPA receptor content] can be modulated rapidly."

Newborn. These spine-like structures grew within 20 minutes of LTP. (The scale bar equals 3 micrometers.)

Malenka's group used cultured neurons for its work. LTP can be difficult to induce in cultured neurons, so the team instead studied long-term depression (LTD), a synapse weakening akin to neuronal forgetfulness that is also triggered by NMDA receptors and may serve to weaken synapses when the conditions for LTP are no longer met. The researchers stimulated the cultured neurons in a way that induces LTD, and 15 minutes later stained the neurons with antibodies to the AMPA receptor and with other antibodies that highlight synapses. As they report in the May *Nature Neuroscience,* they found that LTD brought about a decrease in the percentage of synapses containing AMPA receptors. "This is a cool way of adjusting synaptic strengths, being able to throw AMPA receptors in there or take them away," says Malenka, who recently moved to Stanford's medical school.

Malinow's team, whose report appears on page 1811 of this issue, used a relatively new microscopic technique known as two-photon laser scanning microscopy, which allows researchers to see inside living cells structures as small as dendritic spines, the little knobs that form the receiving end of synapses. The team created a gene consisting of a sequence coding for one of the subunits of the AMPA receptor fused to a sequence encoding a fluorescent protein, and used a virus to insert that gene into neurons in cultured rat brain slices. In neurons expressing the gene, the team saw fluorescent-labeled AMPA receptors clustered at the base of the dendritic spines—"as if," says Malinow, "they are waiting for something."

LTP seems to be what they are waiting for. Within 15 minutes after stimulation to induce LTP, labeled AMPA receptors flooded into some of the dendritic spines. What's more, closer inspection showed the receptors inserted into the membrane at the tip of the spine, where the synapse is found. Malinow notes that the AMPA receptors don't just move into spines that appear empty of AMPA receptors, but also into those that already contained AMPA receptors. "We ... have always suggested that LTP would involve delivery into both types of synapses," he says.

Indirect evidence that the movement of AMPA receptors into synapses is in fact necessary for LTP comes from the Max Planck's Seeburg and Sakmann and their colleagues. In work described on page 1805, the group bred engineered mice that lack GluR-A (also known as GluR1), one of the four protein subunits that make up the AMPA receptor. The four subunits are interchangeable, so the mutant mice still had AMPA receptors composed of the other three subunits, and these seemed to function normally under non–LTP-inducing conditions. But the team could not induce LTP in the CA1 subset of hippocampal neurons where LTP is commonly studied.

The researchers argue that the effect can't just be due to the absence of GluR-A, because other types of hippocampal neurons still undergo LTP in the mutant mice. Instead, there appears to be a shortage of AMPA receptors in the CA1 neurons, where the GluR-A subunits normally make up a particularly high percentage of the available subunits, says Seeburg. That, he says, suggests that the neurons suffer from "a need for spare AMPA receptors to make LTP go."

These new findings are far from the whole story on AMPA receptors and postsynaptic changes during LTP. Huganir's group at Johns Hopkins, as well as Thomas Soderling and his colleagues at the Vollum Institute in Portland, Oregon, has shown that kinase enzymes activated during LTP add phosphate groups to the GluR1 subunit of the AMPA receptor. This increases the ease with which ions flow through

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the receptor's channel, a change that should enhance the strength of the synapse. Huganir says his lab has unpublished data that other AMPA subunits are phosphorylated as well. "It is clear that the AMPA receptors are getting highly regulated" at several levels, he says, adding that he suspects phosphorylation may turn out to help with the transport of the receptors to the synapse as well.

Other recent work suggests that LTP may create striking postsynaptic changes in the form of whole new synapses. Two teams, one led by Malinow and Karel Svoboda of Cold Spring Harbor, and the other by Tobias Bonhoeffer of the Max Planck Institute of Neurobiology in Munich, Germany, recently reported that within 20 minutes after the start of LTP, tiny new structures appear in the postsynaptic neuron that may become new dendritic spines (*Science*, 19 March, p. 1923, and *Nature*, 6 May, p. 66). The work is preliminary and the fate of the structures isn't certain, but Bonhoeffer believes they will turn out to be new spines. "Eventually those newborn spines will each have a synapse," and the movement of AMPA receptors triggered by LTP may eventually fill those new synapses as well.

Although it remains to be seen how all these pieces will fit together, the case for migrating AMPA receptors playing an active role in modulating synapses is "very compelling," says Stanford's Tsien. But he and others say that doesn't mean that all of LTP will be accounted for by changes in the postsynaptic neuron. LTP occurs within a minute, and the receptor movements have not been confirmed to occur that quickly. That means, says Tsien, that there are likely to be "other mechanisms taking place to fill in what is happening" during the first moments of the process.

Unpublished work from his group suggests that one of these is increased glutamate release occurring within the first minute after LTP has been triggered. This result also bolsters the view that there will be presynaptic and postsynaptic contributions to the synapse-strengthening process. "I think what the field is telling us is it is both" pre- and postsynaptic, says Richard Scheller, who studies synapses at Stanford's medical school. But wherever the balance of pre- and postsynaptic mechanisms turns out to be, the idea that AMPA receptors modulate synapse strength is likely here to stay. **–MARCIA BARINAGA**

HUMAN RESOURCES

Efforts to Boost Diversity Face Persistent Problems

More groups are going to bat for underrepresented minorities in science and engineering. But can they do better than past efforts to make a difference?

Time is a precious commodity for Diann Brei, an assistant professor of mechanical engineering at the University of Michigan, Ann Arbor. With her biological clock ticking, the 35-year-old Brei and her husband decided last year to have a second child even though she knew it might cost her a chance at tenure when she comes up for review in 18 months. "The informal rule is that one child before tenure puts you at risk," says Brei. "I've heard I'm the only woman in the engineering school to have had two children before tenure." Last month the Alfred P. Sloan Foundation came to the rescue, awarding her its first pretenure faculty fellowship. The money will allow Brei to attend meetings, retain a graduate student whose industrial funding had ended, and resume a full research schedule as quickly as possible.

Mariana Loya isn't thinking about children or tenure just yet. Instead, the 20-year-old materials engineering major divides her time among classes at the University of Washington, an undergraduate research project on biomaterials, and tutoring inner-city kids. Loya, whose father is Latino and Native American and whose mother is Asian, also talks up the importance of science and math at scores of public appearances as Miss Washington, the state's representative in last fall's Miss America pageant. Such outreach brought her to the attention of the National Academy of Engineering (NAE), which showcased her at its 2-day summit last month on women in engineering. Officials hope that Loya's glamorous image will help attract other minority women into what NAE president William Wulf calls a "pale, male profession."

Role model. Engineering student Mariana Loya, the current Miss Washington, has been presented as the new face of engineering. Yet even she says she may not pursue an engineering career.

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The Sloan program and the NAE summit represent two fresh efforts to tackle the chronic underrepresentation of women and non-Asian minorities in the scientific work force. They are joined by a new federal Commission on the Advancement of Women and Minorities in Science, Engineering and Technology. On 24 June, at the National Science Foundation (NSF), the commission will hold the first of two public hearings to collect information for a report to Congress. NAE's follow-up to its summit, which drew 200 leaders from academia, industry, and government, is a new Committee on Diversity in the Engineering Work Force that will hold a workshop next month to discuss how diversity can boost a company's bottom line.

These activities are meant to continue chipping away at a problem that, experts say, begins with negative messages in elementary school, continues through undergraduate and graduate programs that erect barriers—financial, academic, and cultural—to all but the best candidates, and persists into the workplace. And the stakes are getting higher all the time, says one commission member. "If we don't solve this problem soon, we'll reach a crisis point in our ability to compete in a global economy," says George Campbell, president of the National Action Council for Minorities in Engineering (NACME).

A new NSF report on women, minorities, and persons with disabilities, the ninth in a biennial series, describes the uneven progress to date (www.nsf.gov/sbe/srs/nsf99338). In some areas, gains have been substantial. For example, women now receive 12% of the doctoral degrees awarded in engineering—up from a mere 2% in 1978. Even so, Texas A&M University associate dean Karan Watson has calculated that such an output provides only enough women Ph.D.s for each of the 1500 U.S. engineering departments to hire a new female faculty member once every 6 to 12 years.

And the changes in the percentages of underrepresented minorities in most disciplines have been slight, although Asians