PHYSIOLOGY NOBEL

Celebrating the Synapse

Arvid Carlsson first started thinking that he might win a Nobel Prize nearly 40 years ago. Since then, he says, "I've been up and down about it many times." Carlsson need not have fretted. His pivotal discovery—that dopamine is a key neurotransmitter in the brain—not only led to treatments for Parkinson's disease and schizophrenia, but also sparked a revolution in neuroscience that has helped keep the field on a constant high ever since.

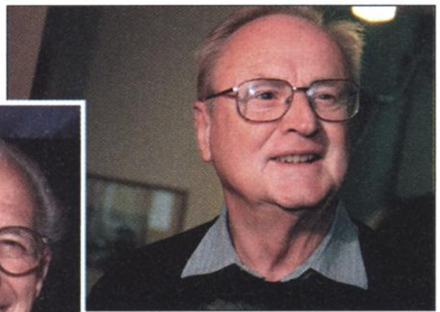
Last week, the Nobel Assembly recognized those achievements, awarding the Nobel Prize in physiology or medicine to Carlsson of the University of Gothenburg in Sweden and to two other pioneers in the study of nerve cell communications: Paul Greengard of Rockefeller University in New York City, who figured out how dopamine and other neurotransmitters trigger their target neurons when they bind at the synapse, the junction between two nerve cells; and Eric Kandel of New York's Columbia University, who built on these insights to demystify some aspects of learning and memory.

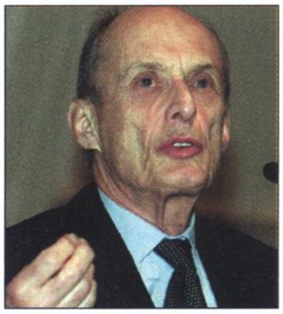
"This prize is really a celebration of the synapse," says neuroscientist Corey Goodman of the University of California, Berkeley. He and others applaud the Nobel committee's decision to honor nearly a half-century of neuroscience research. "These people are all towering figures" in the field, says neurobiologist Charles Stevens of the Salk Institute for Biological Studies in La Jolla, California.

The story of this year's prize began in the 1950s, when Carlsson, now 77, overturned conventional wisdom by proving that dopamine—once thought to be merely a precursor in the synthesis of the neurotransmitter norepinephrine—is an important nervous system messenger in its own right. In one key experiment, he and his colleagues gave rabbits a drug that depletes norepinephrine in the brain, putting the animals into a temporary stupor. Carlsson found that the rabbits could be roused with injections of L-dopa, which the brain converts to dopamine. According to the then-prevailing view, the dopamine should have been converted to norepinephrine. But he found only dopamine in the animals' brains—indicating that it was responsible for the rabbits' recovery.

Carlsson and others later discovered that Parkinson's disease, which causes rigidity and tremors, results from degeneration of dopamine-producing neurons in a brain region involved in movement control. That finding led to the use of L-dopa as a therapy for Parkinson's patients. Further studies on the connections between neurotransmitter levels and mental states spawned a wealth of drugs, including Prozac, that fight psychosis and depression.

In the 1960s, Greengard, 74, took Carlsson's insights several steps further by exploring how dopamine, norepinephrine, and serotonin trigger responses in their target neurons. Back then, Greengard says, most neuroscientists believed that nerve transmission was purely electrical, propagated by the flow of charged ions across nerve cell membranes. But he showed that this is only half of the story.





Neuro trio. Eric Kandel, Arvid Carlsson, and Paul Greengard (*clockwise from left*).

In most neurons, Greengard found, the neurotransmitters exert their effects biochemically, by triggering a so-called second messenger inside the target cells. This in turn activates an enzyme that adds phosphate groups to cellular proteins, thus setting off a chain of events that alter nerve cell properties—for example, heightening or damping sensitivity to electrical stimulation. To date, Greengard and his colleagues have identified more than 100 brain proteins phosphorylated as a result of neurotransmitter activity, including one that serves as a kind of master control switch for dopamine.

The link between phosphorylation and nerve cell signaling inspired the research of Kandel, 70, into how the brain learns and remembers. Kandel, who started his career as a psychiatrist, began dabbling in learning and memory research as a postdoc at the National Institutes of Health in the late 1950s. But although his work there recording electrical impulses from the hippocampuses of cats resulted in some "very nice papers," Kandel says, he wanted a system that was easier to work with. So he went to Paris to study with Ladislav Tauc, an expert on the sea slug *Aplysia*, famous for its giant neurons. "With *Aplysia*, you can just record from those cells until the cows come home," Kandel says.

Over the following years, Kandel demonstrated that the responses of *Aplysia*'s nerve cells to various stimuli—such as touching the animal's tail or giving it an electrical shock—were amplified according to the strength and duration of the stimuli. These heightened responses could last for days or weeks, thus demonstrating a form of learning and memory. In general, weak stimuli gave rise to short-term memory, and stronger stimuli to long-term memory.

Kandel, sometimes in collaboration with Greengard, went on to show that short-term memory is created by means of phosphate addition to proteins that make up the pores in the cell membrane that calcium and other ions involved in nerve transmission flow through. Long-term memory, he found, forms when stronger stimuli trigger the synthesis of new proteins that change the shape of the synapse and its sensitivity to further stimuli.

This finding helped solved a long-standing puzzle: why protein synthesis is necessary for long-term memory but not for short-term memory. It was also the culmination of decades of work that began with Carlsson's pioneering discoveries in the 1950s. When asked how winning the Nobel Prize might change their lives, all three recipients told *Science* they hoped the impact would be minimal. "I will try very hard not to let it affect my life," says Kandel. "I already like my life."

–MICHAEL BALTER

PHYSICS NOBEL

Achievements Etched In Silicon

Silicon, rather than gold, might be an appropriate material for this year's Nobel Prize in physics. For it was with silicon that the three recipients—Jack Kilby of Texas Instruments in Dallas; Herbert Kroemer of the University of California, Santa Barbara; and Zhores Alferov of the A. F. Ioffe Physico-Technical Institute in St. Petersburg, Russia—made their crowning achievements. Computers, cell phones, and CD players rely on technology they made possible.

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