Ion Channel Research Wins Physiology Nobel

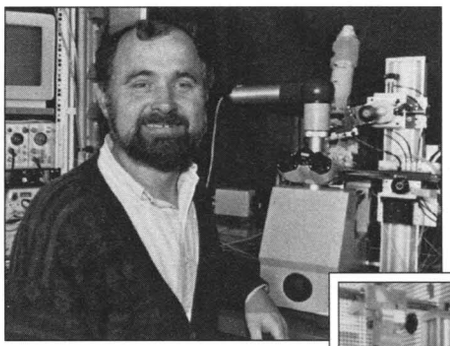
Neher and Sakmann's "patch clamp" method has revolutionized neuroscience and cell biology in the past 15 years

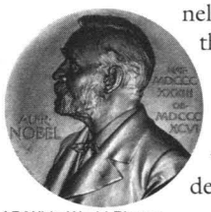
THE NOBEL COMMITTEE'S DECISION TO award this year's prize in physiology or medicine to German neuroscientists Erwin Neher and Bert Sakmann may have come as a surprise to those outside the field of biophysics—but to insiders it was hardly a shock. In fact, many biophysicists have been expecting the award since 1976, when the two investigators invented a technique that would change the face of both neuroscience and cell biology.

Neher and Sakmann's technical advance was mind boggling at first. Using a tiny pipette pressed against the surface of a muscle cell, they measured the ion flow through a channel—a single molecule that acts like a tunnel spanning the cell membrane and allowing ions to pass through its pore. "It was the first time in the history of science that one could look at what a single molecule was doing on a millisecond basis," in a living system, says Bertil Hille, who studies ion channels at the University of Washington. Neuroscientists immediately realized the finding would change their lives. Now they would have a direct way to study the channels that control the ion currents that are absolutely central to the function of nerve and muscle cells.

Before Neher and Sakmann proved that channels existed, their presence was only inferred. For decades researchers had been impaling nerve and muscle cells with sharp electrodes and measuring the total sum of ion currents flowing in and out of the cells. They knew these currents were vital to the cells' electrical excitability, but they didn't know how the ions crossed the membrane. Several teams had used mathematical analysis to predict that ions were passing through channels, but there was no way to study these putative channels directly.

Which brings the tale to 1974, when the 32-year-old Sakmann finished a postdoc in the laboratory of renowned neurophysiologist Bernard Katz in London, and began an assistant professorship at the Max Planck Institut in Göttingen. There, he shared lab space with 30-year-old Neher. In their discussions, Sakmann recalls, the two decided that the question of the nature and behavior of ion channels "was one of the most urgent problems in membrane biophysics." Using a tiny 1-micron-wide pipette hooked up to a shelf full of electronics, they set out in search of the elusive channels.





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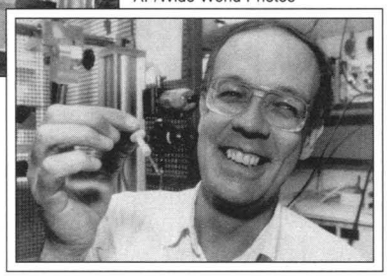

Clamp collaborators. *Erwin Neher* (above), *Bert Sakmann.*

Preparation took a year or so. But, when they applied their pipette to muscle cells, they found they could measure the current flow through the transmembrane channel of a single activated acetylcholine receptor. "It worked the first time," Sakmann recalls. When Neher presented their finding at the Biophysical Society meeting in 1976, the audience cheered.

The next few years were frenzied, as the co-workers and their dedicated team of postdocs refined the technique, known as "patch clamping" for the patch of membrane the pipette contacts. One limitation was the leakiness of the seal between the pipette and the cell surface, which created "noise" that obscured very small currents. Then one weekend in 1980, Neher had a revelation. He watched the noise level on his oscilloscope drop virtually to zero, and realized he had produced an electrical seal 100 times better than normal. He found he could reproduce it by using freshly made and fire-polished pipettes. It was a case of "chance favoring a prepared mind," recalls Yale biophysicist Fred Sigworth, who had joined Neher's lab as a postdoc in 1979. "People had seen this in the past," he says, but Neher was the first to grasp its meaning.

The "gigaseal" (so named because of its gigaohm resistance) multiplied the versatility of the patch clamp. Not only did it cure the noise, but it was so strong a seal that the team found they could use the pipette to tear the patch of membrane right off the cell, making an "inside-out patch" which can be exposed directly to substances to see their effects on the channels in the patch. Or they could suck out the patch, leaving the pipette attached to the cell like a mouth on a balloon, and record ion currents from the whole cell.

"Once we had developed these tools," Sakmann says, "the fun began." Sakmann began working with several other research teams, altering the genes for known ion channels, then using the patch clamp to study the channels formed by the altered genes. Such studies have identified the parts of channel molecules that open or close the ion pore, and those that select which ions can pass through. Neher developed a way to use the patch pipette to find a cell's surface area from its membrane capacitance. This let him observe secretion—which adds membrane to the cell—in real time.

Meanwhile, patch clamping opened the door for studying the electrical activity not only of small nerve cells, such as those in the mammalian brain, but also of non-neuronal cells. "Previously, you had to record from snail neurons because they were big" and could survive being impaled, says Sigworth. "Now you can record from any little cell." Patch clamping in slices of mammalian brain—a trick developed by Sakmann and co-workers—has uncovered clues about memory, and patch clamping of secretory cells revealed the chloride-channel defect in cystic fibrosis.

"The technique really goes far beyond neurobiology," says Hille. For example, the patch pipette can be used to fill a cell with whatever you want—salts, nucleotides, pH or ion indicators, or signaling molecules. Such approaches have answered questions about the signaling pathways in cell membranes and, coupled with Neher's membrane capacitance method, promise to help solve the mystery of how cellular secretion is triggered.

The wide use of the patch clamp reflects the vision of Neher and Sakmann, who kept pushing it to answer new questions, says colleague Walter Stühmer of the Max Planck Institut in Göttingen. Adds Charles Stevens of the Salk Institute in San Diego: "A lot of times people say something is revolutionary, and it's just hype. This time it was really true." ■ MARCIA BARINAGA