BERT SAKMANN AND THE PATCH CLAMP

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Any biologist will tell you that all metazoan life begins with a change in membrane potential. A successful sperm-egg fusion reaction quickly results in a dramatic change in membrane potential which in turn prevents additional sperm from entering the fertilized egg. Rapid changes in membrane potential are induced by the flux of ions through molecular tunnels known as ion channels which are localized on the cell surface and span the entire width of cell membrane. Some ion channels open up in response to certain ligands (ligand-gated) whereas others are activated by changes in membrane potential (voltage-gated); different ion channels have selectivity filters which permit only certain types of ions to pass through. All cells of the human body have distinct sets of ion channels that allow them to function in specific ways. Cell-cell communication in the brain (neuronal transmission) in particular is heavily dependent on the production and timely release of a variety of neurotransmitters and the presence of their cognate receptors, a majority of which are ionotropic. So dependent is this process on ion channels that mutations which debilitate their function invariably culminate in neurological disorders that are collectively known as "channelopathies."

Over the past decade, x-ray crystallographic studies together with biochemical and electrophysiological work have done much to enhance our understanding of the biophysics associated with ion channels function. Back in the 1960s, however, our knowledge of ion channels was rudimentary at best, largely due to the fact that sensitive techniques were not available to cell physiologists who were keen to explore how electrically charged ions could influence processes such as vision, transmission of nerve impulses and muscle contraction. At that time, the presence of ion channels had only been inferred from contributions from several laboratories but beyond that nothing was known about them.

The elegant and ground-breaking work of Bert Sakmann and Erwin Neher resulted in the development of a highly sensitive patch clamp technique in the 1970s which was employed to demonstrate unequivocally that ion channels exist on the cell membrane and are indeed responsible for allowing ions to move across the membrane.

Bert Sakmann - Recipient of the 1991 Nobel Prize in Physiology or Medicine

Born in Stuttgart (Germany) in 1942, Bert Sakmann grew up in Lindau and subsequently returned to his hometown to obtain higher education. Although physics and engineering were his passions, Sakmann seemed to think that biological systems could be explained in engineering terms and became immensely interested in the area of cybernetics in his final year. Ambivalent about whether to pursue a career in biology or physics, he finally decided to go to medical school in Tubingen. The first two years of his broad-based medical curriculum exposed Sakmann to physiology and biochemistry, and he decided to do his doctoral thesis in electrophysiology - an area he felt was closest to engineering. Subsequently, he joined the laboratory of Otto Creutzfeldt in Munich to work on the electrophysiological basis of pattern recognition. After carrying out his postdoctoral work in Bernard Kartz's laboratory at University College London, Sakmann then moved to the Max Planck Institute for Biophysical Chemistry in Göttingen which Erwin Neher had also joined. While there, both Sakmann and Neher teamed up to study different subtypes of acetylcholine receptors with biophysical methods. Their initial studies on the frog neuromuscular junction convinced them that denervated muscle fibers served as an excellent system for using extracellular pipettes to record ion channel activity.

One of the problems that confronted Sakmann and Neher in their early days was the background “electrical noise” which made it impossible to register signals emanating from a single ion channel. To reduce this noise they employed a glass micropipette approximately one micron wide and fitted that to their recording electrode; this ingenious modification worked beautifully. Subsequently, introduction of high-resistance “gigaseals” between fire-polished microtips and cell membranes (the “patch”) further refined their technique, permitting even more microscopic (picoamperes in magnitude) currents to be detected in any type of ion channel in any cell. In 1991, both Sakmann and Neher were awarded the Nobel Prize in Physiology or Medicine for their pioneering work through which the function of single ion channels in cells can be studied.

The gift of Sakmann and Neher has truly revolutionized cell biology. Since its discovery, cell biologists have relied heavily on this technique and gained valuable insights into important biological processes such as cell-cell communication, hormone regulation and insulin production. The combination of patch clamping with that of recombinant DNA technology has proven to be especially powerful; specific ion channels can be expressed in cultured cells and their biophysical and pharmacological properties studied by patch clamp. Patch clamp has also been instrumental in enabling pharmaceutical companies to develop drugs for the treatment of heart disease, epilepsy, and many other neurological disorders. Once thought to be a laborious and low-throughput technique, patch clamp has now been automated permitting investigators to rapidly screen thousands of candidate drug molecules at once.