Topic overview

Single Ion Channels

Discoveries in Modern Science: Exploration, Invention, Technology

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Full Text:

Single Ion Channels

Single ion channels are proteins that control an enormous range of biological function. Life as we know it depends on the ability of a few atoms of channel proteins to control biological functions throughout animals and plants (Alberts et al. 1994; Koeppen and Stanton 2009). The atomic structure of channel proteins has been optimized by natural selection to perform these functions since the beginning of cellular life (perhaps a billion years ago).

ION CHANNELS SELECTIVELY CONTROL THE FLOW OF IONS

Ions—molecules with permanent electrical charge—are hardly able to enter cells except by passing through ion channels, which selectively control their flow. This selective control of ion flow has been apparent since the Nobel Prize experiments and calculations of the English physiologists and biophysicists Alan Hodgkin (1914–1998) and Andrew Huxley (1917–2012), described in delightful historical context by Huxley in *Biographical Memoirs of Fellows of the Royal Society* (1992, 2000). Different ions carry different signals through many different types of ion channels in every cell of animals and plants.

Ions are signals that control different biological functions in different ways. For example, the "bio-ions sodium Na^+, potassium K^+, and chloride Cl^- are single atoms that control the size of cells and the electrical potential ("voltage") across the membranes of cells

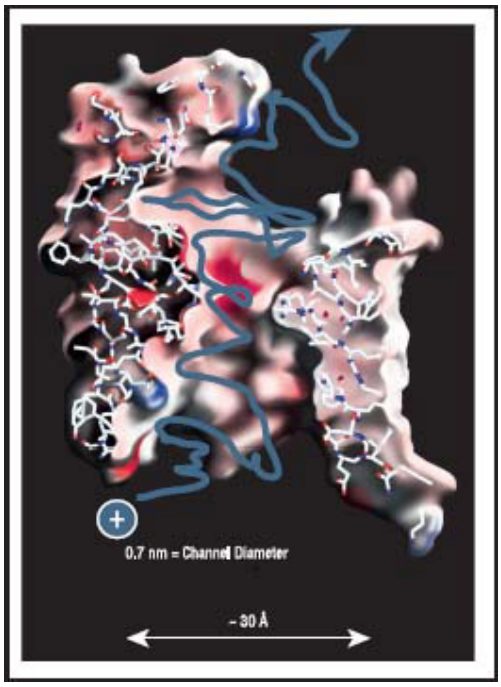

Figure 1. *The real structure of a channel from a bacterial outer membrane with a hypothetical path of a positive ion moving through it. The path is irregular because the motion of all individual atoms is exceedingly irregular going back and forth a tremendous number oftimes in even one billionth of a second.* BASED ON IMAGE BY RAIMUND DUTZLER.

(Ashcroft 2012). Death occurs when the resting electrical potentials across cell membranes disappear and cells swell and burst. These bio-ions are spheres of permanent charge and nearly unchanging diameter.

Calcium Ca^{2+} (with two permanent positive charges) is another particularly important bio-ion. Calcium ions Ca^{2+} are used in nearly every cell to control biological function (Alberts et al. 1994; Koeppen and Stanton 2009) in the same sense that a gas pedal controls the speed of a car. Many functions inside cells are accelerated dramatically when Ca^{2+} flows through calcium channels. The internal concentration of Ca^{2+} near channels is the signal analogous to the position of the gas pedal. Outside cells Ca^{2+} concentrations are nearly one million times larger than inside cells, around 5×10^{-3} molar (M) outside cells compared to less than 10^{-8} M inside cells. Calcium is hardly present in resting cells. The flow of Ca^{2+} through channels raises the internal concentration (near the channel) to around 5×10^{-7} M or higher, sometimes much higher.

Ion channels can control these ionic concentrations and signals because ions cross membranes only through channels. Ions cannot cross lipid membranes. Lipid is the chemical name for the oils found in olive oil, for example. The movement of ions into cells is catalyzed by channels and transporters. Transporters are close cousins of ion channels, with very similar structures, that have historically been described very differently (Eisenberg 1990; Hille 2001) despite their similar structures.

Most biological functions are controlled by channels: Information flow in the nervous system, the contraction of muscle, including the contraction of the heart that allows it to pump blood, and secretion of hormones are controlled by ionic signals regulated by the flow of ions through channel proteins. A substantial fraction of the energy used by a human is determined by detailed properties of the voltage dependence of the sodium channels Na_V of nerve cells in the human brain (Alle et al. 2009; Magistretti 2009).

The function of ion channels has been a central subject in physiology and medicine for more than a century (Huxley 1992, 2000). Many diseases are channelopathies produced by specific malfunctions of specific channels in particular

cells and tissues (Ashcroft 1999), as a web search for “channelopathy” or “channel disease” shows most convincingly.

ION CHANNELS ARE REMARKABLE PROTEINS

A handful of atoms—often in a region smaller across than 5 X 10^{-10} meters (that is, 5 Å)—control biological functions and clinical symptoms that range through an entire animal, over distances sometimes larger than 2 meters, which is some 4 X 10^{9} (four billion) times larger across (and 6 X 10^{28} larger in volume) than the handful of atoms themselves.

Ion channels are the ultimate multiscale device, since their range of control extends nearly twenty-eight orders of magnitude in space (i.e., volume) and twenty-five orders of magnitude in time, from the time scales of atomic motion, 10^{-16} sec, to the time scale of (biological) macroscopic life. Most biological function starts at 10^{-3} sec and sometimes extends 2.52 X 10^{9} sec (80 years) before death. The failure of function in ion channels is one of the main causes of death. The irreversible swelling of tiny nerve terminals in the brain is often the immediate cause of death, and that swelling is produced by a failure of transporters to keep up with leaks through channels. The deadly leak is usually the excessive flow of Na^{+} in and K^{+} out of tiny nerve terminals, which have huge surface-to-volume ratios because they are so small.

The discovery of the structures of ion-channel proteins (MacKinnon 2004), and of their genes and mutant genes (that provide the blueprint for the

structures) (Hille 2001; Nadeau 2011) provides an extraordinary opportunity for all of us. The atomic control of biological function can now be studied in hundreds of (different types of) channel proteins. Atomic manipulation of these proteins can and will allow treatment of disease and extension of productive lifespans. It will allow construction of remarkable technologies making our lives easier and more fun. We simply need to understand and control ion channels as well as we can already control the devices of our semiconductor technology. Before scientists can understand and control, biologists have to describe. Engineering is not possible without a list of parts. Biology is not possible until we know what parts there are in our biological systems and what those parts do.

Biology remains mostly a descriptive science because the parts list is so large and so hard to construct. But the parts list of a human—not including the nervous system—is not beyond our reach. The number of parts in a nuclear submarine that functions in isolation for six months (1.6 X 10^{7} sec, or 16 million seconds) is comparable to the number of parts in a human, outside the nervous system. We can look forward to a quite complete catalog of the parts of a human, including a remarkably precise description of their structure, within the lifetime of our grandchildren, with all that implies.

Ion channels are studied in hundreds of laboratories with remarkable resolution as biologists seek to identify, classify, and describe these crucial parts of our cells and tissues. The genes of scores of channels are now known, and the regulation of the expression of these genes is a topic attracting the attention of large numbers of descriptive biologists (Hille 2001; Nadeau 2011). The different expression of different channel genes in different places governs a large fraction of biology. Different versions of sodium channels Na_V, for example, are found in different parts of the muscle of the heart (e.g., in different locations across the wall of the left ventricle). The slightly different properties ofthese channels allow the heart to pump blood efficiently. Clearly, putting the right channel in the right place in the right amount is essential to building a cell or tissue that works well. Presumably, many pathologies of biological function arise from mistakes in the expression of channel genes and mistakes in the localization of their products, the ion channels themselves.

EXAMINING ION CHANNELS ON THE MOLECULAR LEVEL

Ion channels are studied one molecule at a time as they perform their natural function thanks to two technologies: the patch clamp (Sakmann and Neher 1995) of channels in cells, and the reconstitution of channels into lipid bilayers (Mueller et al. 1962). Both techniques demonstrate that the classical membrane phenomena of physiology arise in channels (Hille 2001). Measurements from single channels give the same results (in detail) whether the single channel is recorded in a biological cell in an animal or isolated in the experimental apparatus used in a laboratory. Single channels have the same properties (in detail) whether synthesized by the wonderful methods ofmolecular genetics and

biologyor by the cell itself. Single-channel recording avoids the horrible confusion produced by measurements all at once ofthe (sum of the) currents produced by the complex mixtures of channel proteins found in cell membranes in their natural state. Progress in understanding the protein enzymes of life required measurements on homogeneous ("clean") systems ("Don't waste clean thoughts on dirty enzymes" was the guiding rule in the heroic age of enzymology); rapid progress in channology required the isolation of the electrical current's flow through single channel proteins. Otherwise scientists must spend most of their time trying to clean up studies of "dirty" mixtures of many channel types.

Single-channel recording is possible because of the contrasting electrical properties of the channel molecule and the surrounding lipid membrane. Lipid membranes are insulators that prevent ion movement; channels are conductors that catalyze the movement of ions (Eisenberg 1990). When recording single channels, significant current flows only through the channels. (The analogy with the channels of transistors in our semiconductor technology is striking 'Eisenberg 2012'. In transistors, channels of silicon with permanent charge '"doping"' conduct current through surrounding insulating SiO_2 glass.) Current through one ion channel can be isolated by the "gigaseal," and then collected and studied by specialized picoammeters ("patch clamp amplifiers") widely available commercially: indeed, many thousands of our version of the amplifier (the Axopatch) are in laboratory use every day. The *gigaseal* is the wonderful name given to describe the gigaohms (i.e., billions of ohms) of shunt resistance needed to seal off a single channel so its single channel current can be measured in isolation from irrelevant currents that flow through other pathways. Gigaseals make dirty mixtures clean and allow quite unambiguous measurements from individual channels.

Because of the ease of single-channel recording, and the importance of the results, descriptive experimental work on ion channels has far exceeded our physical understanding of how channels work. Thousands of research papers on ion channels are published every year. Thousands of presentations are given at international meetings, most notably the annual meeting of the American Biophysical Society. Hundreds of clinicians study channelopathies every day that are responsible for many of the maladies of men and women (and animals and plants for that matter).

Much of the data on ion channels concerns systems of clinical importance with immense financial significance to

the pharmaceutical industry. Nearly every drug of interest to the pharmaceutical industry must be applied to channels of the heart to look for side effects. Many organic compounds have dangerous effects on the Kv11.1 ion channel—encoded by the hERG (KCNH2hRg) gene—that can lead to QT prolongation (i.e., an increase in the duration of time from the start ofthe so-called Q-wave ofthe heart's electrical cycle to the end of the T-wave) as shown in the electrocardiogram of the heart, and proceeding to an often fatal arrhythmia called *torsade de pointes*. Measurements of dangerous effects should be made on single channels of Kv11.1, to avoid ambiguous results, if financially possible.

SINGLE CHANNELS ARE OPEN OR CLOSED

Single-channel recordings show that single channels are either open or closed (to a good approximation). The current through a single channel is independent of the duration of the channel opening, whether the channel is open a few microseconds or many seconds. The current through any type of single channel is a sensitive function of the structure of the channel and of the position of the charges in the channel protein because the channel is so small and its charges are so close to the ions moving through the channel. The conclusion is that the channel does not change structure significantly once it is open, on a time scale of microseconds or longer.

The current through a single channel switches stochastically and forms a random telegraph signal. The biologically important current through membranes is the sum of huge numbers of these stochastically open and closed single-channel currents. In classical cases, channels operate independently, coupled only by the electric field they have in common, so the single-channel currents just sum to make the biologically important macroscopic current.

The biologically important current depends on the total number of channels, the fraction of the time a single channel is open ("open probability"), and the current through a single channel. The currents through biological channels varies with time, and this variation is essential for their function. The time dependence of the biologically important current flow depends on how the open probability varies with time, and the delay with which it responds to stimuli, more than anything else.

Different types of channels open in response to different stimuli because different channel proteins have different structural modules to sense the stimuli. Some channels have modules that respond to voltage. Others have modules that

respond to temperature. Still others have modules that respond to specific chemicals—for example, capsaicin, the ingredient that makes chili peppers taste hot. New channels with new types of sensitivity are constantly being discovered and the diversity is amazing.

Many of the important properties of channels are determined by the time course of the open probability, and so there are many measurements of the kinetics of channel opening in response to stimuli. Although elaborate "Markov" models have been developed to describe the opening of ion channels (Hille 2001; Sakmann and Neher 1995) these have little use in engineering design because they have little predictive value. These models rarely predict what will happen when ion type or concentrations are changed, or the electrical potential or other variables vary.

The widely held view of channel opening as a "conformational change" (i.e., a change in the channel's shape) is more metaphor than model. It is not a physical model that yields predictions. Physical models ofchannel opening are not yet available that allow such predictions. Ostensibly, a physical model must deal with the central fact that the open channel has only one conformation (on the biological time scale) independent of the duration of the opening.

SELECTIVITY OF THE OPEN CHANNEL

The open channel has been analyzed successfully with physical models in a few cases: the EEEE (glu glu glu glu) Ca_V or L-type calcium channel, the DEKA (asp glu lys ala) voltage activated sodium channel, and the ryanodine receptor (Eisenberg 2011).

The successful model of the selectivity of an open channel must deal with the variables important for macroscopic function—for example, the concentration of ions in the mixtures in which channels function in animals and plants. (The solutions inside and outside cells are derived, roughly speaking, from seawater. They are always mixtures of bio-ions in which calcium plays an important role.) A successful model must actually predict the current through a channel under a variety of conditions, on the biological time scale.

Simulations including all the atoms of the channel are not yet successful models. All atom simulations have grave difficulties (Eisenberg 2011) dealing with the enormous gap between the time scale of atomic motion and biological function. They cannot yet deal in a calibrated way with the properties of ionic mixtures, or solutions containing calcium. Still required is the maturation of all atom simulations into calibrated and thus useful models of biological function.

The successful models of open channels (Eisenberg 2011) have used an "all spheres" approach introduced by the German American physician and biophysicist Wolfgang Nonner and the American physiologist and biophysicist Robert Eisenberg, which grossly oversimplifies the structure ofthe channel. In these models relevant side chains appear as charged spheres, kept within the channel, but otherwise free to move to the position of lowest free energy. Such models, much to the surprise of their originators, using crystal radii

of the bio-ions and just one or two parameters (never adjusted once they are set) can account for the selective binding properties of both the EEEE calcium channel of the heart (Ca_V) and the (very different) selective binding properties of the DEKA sodium channel over five orders of magnitude of concentration of calcium in many mixtures of ions. The diameter of the channel is mostly responsible for the selectivity of these models. The solvation properties (i.e., dehydrating desolvation from water and re-solvation by side chains of the protein) are handled by the dielectric coefficients as in implicit solvent models of ionic solutions, that are primitive but nonetheless used successfully in much of physical chemistry (Fawcett 1999). Calcium selective channels have been built and have the properties expected (Vrouenraets et al. 2006). Models ofthe ryanodine receptor in the same spirit produce current voltage curves that match experiments and predict detailed properties of those curves before the measurements were made (Gillespie 2008). Indeed, engineering these channels is possible.

FUTURE OF ION CHANNELS AS NANODEVICES

As engineering reaches to make nanodevices, it is useful to remember that we have the ultimate multiscale nanodevice already (literally) in our hands: our fingers, like the rest of us, contain billions of ion channels. The description of ion channels has been and will be the work of generations of biologists. Engineers know that building things requires

numbers and equations. The development of useful models of ion channels will require the knowledgeable interactions of those who know what to describe with those who know how to analyze the descriptions with numbers.

SEE ALSO *Cell Signaling ; Neuronal Structure And Plasticity ; Neurons, Electrical Properties Of ; Neurotransmission* .

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