All Grown up and Ready to Rumble

Ion Channels of Excitable Membranes, 3rd Edition
By Bertil Hille
Sunderland, MA: Sinauer Associates (2001).
814 pp. $85.00

Potassium Channels in Cardiovascular Biology
Edited by S.L. Archer and N.J. Rusch
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"..we know what we are, but
know not what we may be."
Ophelia in *Hamlet*, 4.5.43–44 (W. Shakespeare)

Ion channels let us see, hear, feel, move, and dream. Impressive. But, is it really time for two more (big) books on the subject? The answer is a vigorous "Yes." This reflects the awesome attributes that make these proteins pivotal to biology and how rapidly we have gained new knowledge since the advent of recombinant DNA methodologies.

Ion channels form portals across cell membranes that open and close to allow specific ions to pass. It is essential that they operate only at the correct time, location, and level of activity. Why the litany of restrictions? Because they are extremely efficient.

We exist out of equilibrium. Our cells are high in potassium and low in sodium, chloride, and calcium. This uneven arrangement is achieved by the slow steady labor of energy-driven pumps, carrier class transport proteins present in plasma membranes in great abundance. A cell can harbor 10^7 sodium-potassium pumps, each hydrolyzing one ATP molecule to power influx of two potassium ions and efflux of three sodium ions about 150 times a second. Pumps create ionic imbalance and electrical inequality ensues: the cell interior is negative relative to its surroundings primarily because small amounts of positively charged potassium ions leak out. These asymmetries are an immediately available reservoir of stored electrochemical energy, held in check, poised for abrupt release.

Ion channels reside at this dynamic interface as the agents of excitability. Their activity is no serene affair. In response to a stimulus, such as a puff of neurotransmitter, ion channels undergo conformational changes, open water-filled pores that span the membrane, and allow specific ions to explode through the pores down their electrochemical gradients. With no direct link to input of metabolic energy or coupling between changes in protein structure and individual translocation events, as many as 10^8 potassium ions can rush through a single potassium-selective channel each second—no wonder some cells have just a dozen.

Among classes of proteins, the functional attributes of ion channels are, perhaps, the best described. Biochemical methods were not the first source of this knowledge. Indeed, before they were even known to

be proteins, the astounding efficiency of ion channels allowed their role in producing action potentials to be delineated using electrical recordings of the exceedingly large axons in squid (Curtis and Cole, J. Cell. Comp. Physiol. *19*, 135–144, 1942; Hodgkin and Katz, J. Physiol. *108*, 37–77, 1949). Thereafter, methods to record from tiny membrane patches made it routine to examine single ion channels operating in real time in native cells (see *Single-Channel Recording*, B. Sakmann and E. Neher, eds, New York: Plenum Press, 1995). Later, a few channel types with rich natural sources, such as skeletal muscle or *Torpedo* electric organ, were purified and reconstituted in functional form, allowing both their study free of confounding cellular influences as well as direct biochemical assessment (see *Ion Channel Reconstitution*, C. Miller, ed., New York: Plenum Press, 1986).

The cloning of ion channel genes, first by classical molecular biological techniques and now via searches of genetic databases over the internet, has produced a deluge of revelatory information: hundreds of molecules that form ion channel pores and scores of proteins that regulate ion channels are now known. DNA sequences allow prediction of protein sequences, motifs that may participate in specific functions, and membrane topology. Genes expressed in cultured cells have allowed biophysical characterization of a plethora of ion channels in wild type form and again after site-specific mutation to define relationships between sequence and function. Induced overexpression of ion channel parts is now permitting isolation, crystallization, and high resolution imaging, for example, of a bacterial potassium channel pore (Doyle et al., Science *280*, 69–77, 1998), catapulting discussions of the structural basis for function from the inferred to the determined.

Novel molecular approaches are rapidly moving the field beyond its biophysical origins. Now, the bevy of regulatory proteins that interact with individual ion channels to determine their native behavior are being enumerated. Levels of expression of ion channel genes in different tissues, during normal development and in response to stress, can now be quantified. High-throughput strategies to rapidly assess thousands of compounds are now regularly applied to discovery efforts seeking medications that alter ion channel function. Molecular methods applied to the genetics of human disease are revealing a spectrum of ion channel diseases; in some cases, inherited mutations cause a disorder (for example, cystic fibrosis), in other cases, our individual genetic differences (polymorphisms) predispose to a poor outcome when faced with a secondary challenge (for example, drug-induced cardiac arrhythmia). In response to this veritable onslaught of new information, the two new books seek to describe where we are, show how we got here, and speculate on where we are going.

Ion Channels of Excitable Membranes, 3rd Edition, by Bertil Hille. Earlier versions were notable achievements for their clarity and broad utility. The third edition is markedly expanded, remarkably up to date, and stands as an unmitigated tour de force. Complete and enthusiastic, but not overwhelming, the text builds intuitively from the biophysical roots of the discipline. By maintaining a historical flavor, the reader is cleanly offered the essential ideas and concepts that remain key even as the field evolves. As only a single author can, the book offers a coherent worldview, moving from action potentials and single-channel recordings to crystal structures and the mechanistic basis for disease. While not seeking to present at an "expert level," the work bravely travels (with requisite forewarning) to the very edge of current knowledge; indeed, at this precipice where differing opinions still vie for dominance, some of us will disagree with the enunciated expectations—just as we should. The book is thus ideal for any student beyond a basic undergraduate science curriculum. It remains a resource for practitioners of the craft and the essential guide to the electrophysiological universe.

Potassium Channels in Cardiovascular Biology, edited by S.L. Archer and N.J. Rusch. The heart is a pump. Its every beat is orchestrated by wavelets of sodium, potassium, calcium, and chloride ions moving through ion channels to yield excitation, contraction, and relaxation. The beats come faster as we run, slower when we sleep, and recur some 100,000 times a day. This activity maintains blood pressure and circulation through the vascular system, delivering oxygen and removing waste products from our organs. The brain is particularly sensitive to diminished blood flow. Pump failure for a few seconds causes loss of consciousness; after minutes, permanent brain damage and death result.

Potassium channels are required contributors to the electrical impulses that maintain normal cardiac pump function and blood vessel tone. Because potassium ion efflux restores cells to negative resting potentials, potassium channel activity limits excitation, decreasing the frequency and duration of heart beats and promoting vasodilation. Still, one might well wonder about a book exclusively on potassium channels, and only those in the heart and vessels. The explanation lies in part with the vast diversity of potassium channels that allow for cardiovascular function: over 30 types of pore-forming potassium channel subunits (many of which manifest splice variation) that form a single pore by assembly in groups of four often nonidentical subunits. These complexes show uneven geographical and temporal expression at both the cellular and subcellular levels. Moreover, normal ion channel function depends on interaction of pore-forming subunits with one or more regulatory subunits that can be constant or occasional companions. More than 15 of these regulators are now known; some soluble, others integral membrane proteins—these too show geographic and temporal diversity. Variation in potassium channel function is also observed during healthy development and secondary to disease due to altered gene expression. Indeed, the functional diversity that results from inheritance of ion channel genes in wild-type, mutant, and polymorphic form reveals that normal cardiovascular physiology absolutely depends on the exquisite timing and normal activity level of potassium channels.

In this context, Archer and Rusch offer a rich tapestry in 899 pages of nonredundant, thoughtful prose. The compilation covers all the key areas and moves nicely from the general to the specific. Particularly wonderful is the half of the book that covers the vascular system. This is an important subject (indeed, the endothelial cells lining our blood vessels comprise the single largest organ in the body) that is not adequately considered

elsewhere. Topics covered include the roles of potassium channels of endothelial cells, smooth muscle, and the vasculature of skeletal muscle, brain, heart, lungs, and kidneys in health and disease. In large measure, the general subject chapters and those on potassium channels in the heart are truly excellent; only a few do not meet the standard of existing resources or suffer from out-of-date or parochial viewpoints. Such limits do not detract from the overall strength of the compendium. It serves as intended as a comprehensive review of potassium channels for those who study the heart and vasculature.

These two books herald the maturation of our discipline. Our inquires no longer focus solely on biophysics and a few great mysteries, for example, by what means can an ion current cross an insulating lipid membrane. The interrogations are now more subtle; we must seek to understand the specifics: how, when, why, and why not. These books make it clear that the work ahead is just as exciting as what has come before.

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