Book Review

Handbook of Membrane Channels, edited by Camillo Peracchia

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Reviewed by Louis J. DeFelice, Anatomy and Cell Biology, Emory University

When Bertil Hille first published *Ionic Channels of Excitable Membranes* in 1984, he speculated that a single cell might contain as many as 10 different kinds of channels. The human genome, he wrote, "probably codes for more than 50." Since then biologists have discovered so many channels that no one can count them, much less organize them. Trying to collect channels like stamps in a book raises several questions. Would it be better to focus on differences, such as ion selectivity or regulatory mechanisms? Or would it be better to concentrate on similarities, such as molecular structure or tissue of origin? This quandary recalls a comparison that Alan Hodgkin made in his autobiography, *Chance and Design*, between zoologists (who thrive on differences) and physiologists (who concentrate on what is similar). Camillo Peracchia has collected and organized ion channels according to both of these strategies. Section I of the *Handbook* begins with chapters on K, Na, Ca, and Cl channels and then moves to ligand-gated channels (ACh, glutamate, glycine, and GABA), cyclic nucleotide-sensitive channels, calmodulin-regulated channels, and gap junction channels. Section II encompasses intracellular membrane channels including Ca-release channels, mitochondrial channels, and vesicle fusion channels. Overall this collection aims toward a synthesis of the biophysics and the molecular biology of ion channels. However, do not look for a comprehensive treatment of ion channels; the subject is too broad, and the narrative character of this book does not permit it. Nor is there a uniform style or consistent depth of treatment of different ion channels, attributes that are difficult to achieve in a book written by many authors. The *Handbook* takes a refreshingly broad view of ion channels, and it contains many useful summaries of particular topics. However, in spite of an excellent index it fails as a true handbook of ion channels because of its limited scope and its ambiguous organization.

The *Handbook* begins with an overview of gene families, using the K channel as a framework. The use and misuse of molecular descriptors such as "homology" and "similarity" concern the authors. Nonetheless, they themselves fall into traps such as "primary sequence homology." Hydropathy plots and structural motifs nevertheless emerge clearly in this first chapter, which provides a basic overview of these subjects. The chapter ends with a hypothesis that gene subfamilies diverge into independent channel systems. Left dangling, however, is the definition of subfamily (as well as the definition of family and superfamily), which reduces the hypothesis to a tautology. The positive point here is that this chapter, like others, is more than an overview of the subject at hand. In some respects, chapters in the *Handbook* amount to novel research articles that frame new ideas. This feature is a strength, because some articles are first rate. However, it is also a weakness because the descriptive style and the speculative nature of the articles preclude the creation of a true handbook. Another possibility for such a volume might have been a comprehensive digest of facts about ion channels–molecular structure, toxicology, regulation, kinetic rate constants, unitary conductance, and biological significance–but that is not the layout of the present work.

The chapters on voltage-gated K channels and on Ca-activated K channels constitute a main strength of the *Handbook*. Permeation, gating currents, and maxi-channels receive a comprehensive and up-to-date treatment, setting a standard for excellence that is not always maintained throughout the book. The chapters on Na channels seem dated in comparison; in spite of that, they manage to summarize Na channel permeation, kinetics, and toxicology. The Ca channel chapters begin with an overview of molecular biology and subunit structure, and they end with the pharmacology of Ca channels in heart and nerve. However, the *Handbook* essentially ignores Ca-mediated inactivation, which is surprising considering the prominence of this mechanism in Ca channel function. Happily, Cl permeability receives as much space as the other ion channels. This once-poor relation of Na, K, and Ca channels deserves its new popularity because of its probable wide-ranging influence over cell physiology and its certain role in disease. This section begins with an excellent summary of fast Cl channels that contains a practical analysis of how the channel works. The next two chapters compete for the cystic fibrosis transmembrane conductance regulator Cl channel. In spite of this attention, these chapters do not adequately address the field. The emphases on Cl channel regulation and the focus on genetic approaches to channel structure partly compensate for this deficiency.

Midway through the *Handbook*, ligand-gated channels make their appearance. Not by surprise the well-studied nicotinic channel-receptor complex leads the way, but in an unexpected fashion. The familiar five-potato model appears nowhere. Instead, the first chapter focuses on the pharmacology and the distribution of ACh-Rs in the mammalian central nervous system. Although this topic was a welcome change, it also illustrates the spotty selection that eventually becomes a frustration throughout the *Handbook*. Glutamate-,

GABA-, and glycine-gated channels follow ACh in appearance. These articles focus on subunit classification, tissue comparison, and family trees. Molecular biophysics, however, which dominates the field of voltage-gated channels, is noticeably absent in the section on ligand-gated channels. This is a curious omission because the molecular biology and biophysics of ligand-gated channels represent a highly developed subject that in many ways has set the standard for voltage-gated channels.

The section on cyclic-nucleotide sensitive channels, like the section on ligand-gated channels, charts an uneven course. An ion pathway known foremost as a voltage-gated conductance falls under the category of a cyclic-nucleotide sensitive channel, which points to the difficulties involved in channel classification. This section includes cGMP-activated channels in the retina, but it ignores the analogous channels in the olfactory bulb. These related topics form an exciting new area in comparative ion channel biophysics that might well have been explored further in the *Handbook*.

The section on gap junction channels starts out well, but ends poorly. Molecular models of these channels have proliferated in recent years, and the first two chapters present state-of-the-art information on the biophysics and molecular biology of gap junction channels. The single-channel records themselves appear disorderly. The open and closed states are noisy, the current amplitudes are non-uniform, and the baselines meander. Perhaps gap junction channels behave differently than other ion channels; however, if the biophysical properties of gap junction channels have another standard, that distinction deserves notice. The section on MIP channels contains one article. MIPs are the major intrinsic proteins in ocular lens fiber membranes, and they are an oddity. One data figure shows that MIPs can form channels in bilayers, but the focus of this chapter is not on biophysics but on molecular structure, regulation, and expression. MIPs become functional when cells change shape. They are members of the CHIP family, ubiquitous ion channels that are found in tissues as diverse as the mammalian kidney and nitrogen-fixing plant roots, where they serve as water channels. Because of their ubiquity and their broad role in fundamental processes, the MIP family could have easily occupied more than the present 14 pages. Treatment of the calmodulin-regulated channels is even more scanty. Channels in one-celled organisms receive more attention. Although not much information exists on what the channels in microbes actually do, the authors argue that function will follow patch clamp. They missed a chance to point out that in 1969 the bacterium *Aerobacter cloacae* provided the molecules for the first single channel records.

Section II of the *Handbook*, which forms 20% of the total, examines the engaging new area of ion channels in intracellular membranes. Ca-release channels (ryanodine receptors and IP_3 receptors) set the initial focus. Single-channel records are sparse in section II of the *Handbook*, and the best data come from reconstitution experiments. That will change as the field develops. For example, the nuclear envelope contains IP_3 receptors, and patch clamping the outer membrane of the nucleus allows the investigation of IP_3 channels in a native membrane. For now, the mitochondrial membranes occupy center stage. The articles on mitochondrial channels commence with a historical summary and an overview of techniques, and they close with ATP-sensitive mitochondrial channels. Like the nucleus, the mitochondrion has a double membrane structure. Thus the experimental preparation and the interpretation of data must reckon with an inner and an outer membrane, a complication that is worth the effort. The physiological role of mitochondrial channels, as with other channels featured in the *Handbook*, remains uncertain. The first chapter in this section, however, contains a useful table of ideas about what mitochondrial channels do, with references as current as 1992.

The final pages of the *Handbook* treat the structure and regulation of the fusion pore. Like the gap junction, the fusion pore joins two membrane-bound compartments. In the case of fusion, however, channel formation is transitory. An engaging connection between fusion pores and the cytoskeleton emerges in this article. This discussion of the link between the skeleton of the cell and channels in the membrane is noticeably absent in other parts of the *Handbook*, where in large part membrane-bound channels appear separate from the structure of the cell, a position that is no longer tenable. The authors of this last article attack fusion channels with multimedia fervor–electron microscopy, biochemistry, voltammetry (to monitor neurotransmitter release), and electrical engineering (to separate capacitance from conductance). Of particular interest are the virus-induced pores, an exotic new field of biophysics that is changing our concept of the mechanisms that underlie viral infection. As a bonus, this last chapter includes the best cartoon and the only color plate in the *Handbook*.

Virtually no equations appear in the *Handbook*; even a subchapter on "mathematical models" contains none. This omission seems intentional, and it aims the book toward readers that eschew analytic and computational biophysics. The title of the work suggests that it is directed toward researchers who seek encyclopedic details about channels. In this regard, however, the *Handbook* falls short. This leaves a substantial readership for existing works on the biophysics and biology of ion channels with which Peracchia's book will have to compete. At $120.00, about the price of a subscription to *Nature*, the *Handbook* will have an uphill struggle.