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## Preface

Just over 60 years ago, Hodgkin and Huxley first proposed the ionic basis of the action potential in neurons. Their insightful—and foresighted—work, based on experiments performed in squid giant axons, laid the groundwork for a new research field: ion channel biophysics. The elegance and importance of their work earned them a Nobel Prize 11 years after their groundbreaking work was first published and set the stage for other ion channel biophysicists to follow in their footsteps: Sakmann and Neher (1991) and MacKinnon (2003). Many others, however, substantively contributed to a rich research field, achievements, and advances which are celebrated each year at the Annual Meeting of the Biophysical Society. The study of ion channel biophysics has far-reaching implications in medicine, animal behavior, and evolution. Ion channels are targets for a vast and impressive array of naturally occurring and artificial compounds, including toxins and pharmaceutical agents. Their presence in the membrane of all cells makes them particularly vulnerable (in the case of toxins) and attractively accessible (in the case of drugs, some of which are modeled after toxins).

Voltage-gated sodium channels, the focus of this Handbook, are—in a sense—the first in a physiological lineage of ion channels, and the classic opening line of many publications about sodium channels exemplifies their importance; sodium channels are the basis of the rising phase of action potentials in nerve and muscle. That simple understatement characterizes the critical importance of sodium channels in the electrical activity of neurons and muscle cells. Sodium channels are responsible for the generation and propagation of action potentials along the cell membrane and are, therefore, the lynchpin in the processes of information transmission within the nervous system and muscle contraction.

Mutations in voltage-gated sodium channels impart changes in their structure and function. Some of these changes underlie diseases that span the spectrum from relatively benign to fatal. For clinical reasons, then, the study of mutations in sodium channels hold great potential for understanding the molecular basis of disease. Many mutations impart changes in the biophysical properties of sodium channels, particularly those associated with gating, and are thus of great interest in terms of understanding the structure/function relationship of channels. Indeed, site-directed mutagenesis has been, for nearly a quarter century, since Stuhmer et al. (1989),

the technique of choice to understand the structural basis of sodium channel function. The involvement of sodium channel mutations in disease is the subject of Chapters “The Voltage Sensor Module in Sodium Channels,” “Slow Inactivation of  $\text{Na}^+$  Channels,” “The Role of Non-Pore-Forming  $\beta$  Subunits in Physiology and Pathophysiology of Voltage-Gated Sodium Channels,” “Altered Sodium Channel Gating as Molecular Basis for Pain: Contribution of Activation, Inactivation, and Resurgent Currents,” Regulation/Modulation of Sensory Neuron Sodium Channels,” and “The Role of Late  $I_{\text{Na}}$  in Development of Cardiac Arrhythmias” of this Handbook.

By virtue of their critical importance in cellular excitability and their vulnerable position in the cell membrane, including an extensive exposure to the extracellular milieu, sodium channels are attractive targets for toxins, venoms, and drugs. In addition, sodium channel activity is modulated by a host of intracellular messengers. Studies of the interactions between sodium channels and agents that bind to them have revealed a wealth of information about their structure and function, and many biophysical properties of sodium channels have been revealed by these interactions. We have also learned much about evolution, predator–prey interactions, and discovered many agents to treat a wide range of diseases of excitability. The interaction between sodium channels and both naturally occurring and manufactured agents continues to be a vibrant and important line of research with implications for the treatment of diseases underlying the highest morbidity and mortality: cancer and heart disease. Chapters “Proton Modulation of Cardiac  $I_{\text{Na}}$ : A Potential Arrhythmogenic Trigger,” “Probing Gating Mechanisms of Sodium Channels Using Pore Blockers,” “Animal Toxins Influence Voltage-Gated Sodium Channel Function,” “Ubiquitylation of Voltage-Gated Sodium Channels,” and “Pharmacological Insights and Quirks of Bacterial Sodium Channels” in this Handbook deal with various aspects of sodium channel modulation by intrinsic and extrinsic agents.

Bacterial sodium channels have finally provided a way to visualize the structure of voltage-gated sodium channels through crystallography. This relatively recent breakthrough has allowed researchers in the field to “put it all together” through homology modeling. Soon, someone will crystallize a mammalian sodium channel and bring us one step closer to an even more complete understanding of how structure and function relate to one another, how drugs and toxins interact with the channel, and how changes in channel structure result in debilitating diseases. The authors and editor of this volume of the Handbook of Pharmacology hope that the chapters contained herein will inspire present and future sodium channel devotees to pursue the unanswered questions and resolve the structure and function of this complicated, fascinating, and physiologically pivotal protein.



<http://www.springer.com/978-3-642-41587-6>

Voltage Gated Sodium Channels

Ruben, P.C. (Ed.)

2014, VIII, 295 p. 58 illus., 36 illus. in color., Hardcover

ISBN: 978-3-642-41587-6