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PREFACE

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In 1981, the ion channel community marveled at single-channel recordings of calcium-dependent potassium currents showing an exceptionally high unitary conductance, which later earned them the designation of “Big Potassium,” or BK, channels. This discovery was made possible by the recently developed patch-clamp method and was achieved quasi-simultaneously in two laboratories on each side of the Atlantic: in chromaffin cells by Dr. Alain Marty at the Max Planck Institute for Biophysical Chemistry and in muscle cells by Drs. Barry Pallotta, Karl Magleby, and John Barrett at the University of Florida School of Medicine. The following 35 years of research has continued to mesmerize BK channel aficionados by revealing the structural details that underlie the unique dual gating of BK channels by voltage and calcium, as well as the diversity and complexity of mechanisms exploited by BK channels to adjust their activity to a variety of cellular contexts. Not surprisingly, these superlative features have turned out to be critical determinants of tissue function throughout the body, most notably in smooth muscle and in the nervous system. This volume of *International Review of Neurobiology* is meant to provide an integrated perspective on our current understanding of the structure, function, and regulation of BK channels, with levels of analysis ranging from the submolecular conformational changes that drive channel pore opening to the systemic implications of BK channel dysfunction in diseases such as epilepsy.

In Chapter 1, Drs. Antonios Pantazis and Riccardo Olcese discuss the structural principles that govern BK channel activation by membrane potential and calcium, and they explain how BK channels represent both a model and a rebel in the ion channel realm. The following three chapters provide an overview of the mechanisms regulating BK channel biophysical properties, subcellular localization, and pharmacological sensitivity. Chapter 2 by Drs. Qin Li and Jiusheng Yan addresses the influence of auxiliary β and γ subunits, Chapter 3 by Drs. Michael Shipston and Lijun Tian details the role of alternative splicing and posttranslational modifications, and Chapter 4 by Drs. Hongkyun Kim and Kelly Oh reviews the functional impact of BK channels’ interaction with a dense network of proteins. While BK channels are primarily located at the plasma membrane, they are also present in intracellular organelles and Chapter 5 by Drs. Boxing Li and Tian-Ming Gao describes the properties and function of mitochondrial and nuclear BK channels.

The activity of BK channels can be modulated by a multitude of small molecules. In Chapter 6, Drs. Toshinori Hoshi and Stefan Heinemann propose a classification of BK channel modulators according to their molecular mode of action, and they analyze the effects of several endogenous messengers and synthetic compounds in this framework. Chapter 7 by Drs. Alex Dopico, Anna Bukiya, Guruprasad Kuntamallappanavar, and Jianxi Liu focuses

on the effects of ethanol on BK channel activity and their relevance for alcohol-driven behaviors.

The following four chapters analyze the role of BK channels in the physiology of different types of excitable cells located in the central nervous system, pituitary gland, inner ear, and blood vessels, respectively. In Chapter 8, Drs. Candice Contet, Scott Goulding, Dika Kuljis, and Alison Barth describe the complex influence of BK channels on neuronal excitability, along with their role in suppressing neurotransmitter release. They also review the numerous neurological disorders that are associated with an imbalance in BK channel activity. In Chapter 9, Drs. Peter Duncan and Michael Shipston contrast the facilitatory influence of BK channels on the bursting activity of anterior pituitary cells with their inhibitory influence on hormone secretion by posterior lobe neuroendocrine terminals. In Chapter 10, Drs. Sonja Pyott and Keith Duncan explain the evolutionary dichotomy that differentiates the role of BK channels in electrical tuning of nonmammalian vs mammalian hair cells. In Chapter 11, Drs. Gayathri Krishnamoorthy-Natarajan and Masayo Koide review the critical contribution of BK channels to vasodilation and neurovascular coupling. Finally, Chapter 12 by Drs. Gregory Kaczorowski and Maria Garcia discusses the therapeutic potential of BK channel modulators and provides a unique insider's perspective on the failures and successes of medicinal chemistry efforts targeted at BK channels.

Collectively, these chapters offer a fascinating journey along the varied and interconnected trails of BK channel research, where every reader will hopefully find vantage points of interest.

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