PREFACE

Ion channels are pore-forming membrane proteins expressed in almost all cell types. These proteins trigger electrical signaling throughout the body by gating the flow of ions across the cell membrane. Two characteristic features of ion channels distinguish them from other types of ion transporter proteins. First, this is the very high rate of ion transport through the channel compared to other transporter proteins (often 10^6 ions per second or greater) and second, ions pass through channels down their electrochemical gradient without the participation of metabolic energy.

The sequencing of the human genome has identified more than 400 putative ion channels. However, only a fraction of these theoretically identified channels have been cloned and functionally characterized. The widespread tissue distribution of ion channels, along with the multiple physiological consequences of their opening and closing, makes targeting of ion channels very promising targets for development of therapeutics. The potential validation of ion channels as drug targets provides an enormous market opportunity for their reemergence as key targets in drug discovery. However, to realize the great potential of this target class, an understanding of the validation of these targets as well as development of suitable screening technologies that reflect the complexity of ion channel structure and function remains key drivers for exploitation of this opportunity.

In spite of some important drugs targeting ion channels which are today in clinical use, as a class, ion channels remain underexploited in drug discovery. Furthermore, many existing drugs are poorly selective with significant toxicities or suboptimal efficacy. This thematic volume of the *Advances in Protein Chemistry and Structural Biology* is dedicated to ion channels as therapeutic targets and more specifically as promising treatment targets in neurological and psychiatric disorders. Chapter 1 in this volume summarizes current advances about the protein biogenesis process of the Cys-loop receptors. Operating on individual biogenesis steps influences the receptor cell surface level; thus, manipulating the proteostasis network components can regulate the function of the receptors, representing an emerging therapeutic strategy for corresponding channelopathies. Chapter 2 proposes for the first time a novel conceptual framework binding together transient receptor potential (TRP) channels, voltage-gated sodium channels (Nav),

and voltage-gated calcium channels (Cav). Authors propose a "flow-excitation model" that takes into account the inputs mediated by TRP and other similar channels, the outputs invariably provided by Cav channels, and the regenerative transmission of signals in the neural networks, for which Nav channels are responsible. This framework is used to examine the function, structure, and pharmacology of these channel classes both at cellular and whole-body physiological level. Building on that basis, the pathologies arising from the direct or indirect malfunction of the channels are discussed. The numerous pharmacological interventions affecting these channels are also described. Part of those are well-established treatments, like treatment of hypertension or some forms of epilepsy, but many others are deeply problematic due to poor drug specificity, ion channel diversity, and widespread expression of the channels in tissues other than those actually targeted.

Chapter 3 reviews the potential role of ion channels in membrane physiology and brain homeostasis where ion channels and their associated factors have been characterized with their functional consequences in neurological diseases. Furthermore, mechanistic role of perturbed ion channels identified in various neurodegenerative disorders is discussed. Finally, ion channel modulators have been investigated for their therapeutic intervention in treating common neurodegenerative disorders. Chapter 4 is dedicated to acid-sensing ion channels (ASICs) which are important pharmacological targets being involved in a variety of pathophysiological processes affecting both the peripheral nervous system (e.g., peripheral pain, diabetic neuropathy) and the central nervous system (e.g., stroke, epilepsy, migraine, anxiety, fear, depression, neurodegenerative diseases). This review discusses the role played by ASICs in different pathologies and the pharmacological agents acting on ASICs that might represent promising drugs. Perspectives and limitations in the use of ASICs antagonists and modulators as pharmaceutical agents are also discussed.

Chapter 5 focuses on the glutamatergic system and its associated receptors that are implicated in the pathophysiology of major depressive disorder. The *N*-methyl-D-aspartate (NMDA), a glutamate receptor, is a binding and/or modulation site for both classical antidepressants and new fast-acting antidepressants. Thus, this review presents evidences describing the effect of antidepressants that modulate NMDA receptors and the mechanisms that contribute to the antidepressant response. Chapter 6 continues on the glutamatergic system. Glutamate is the major neurotransmitter that mediates

excitatory synaptic transmission in the brain through activation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptors. These receptors have therefore been identified as a target for the development of therapeutic treatments for neurological disorders including epilepsy, neurodegenerative diseases, autism, and drug addiction. Their therapeutic potential has since declined due to inconsistent results in clinical trials. However, recent advances in basic biomedical research significantly contribute to our knowledge of AMPA receptor structure, binding sites, and interactions with auxiliary proteins. In particular, the large complex of postsynaptic proteins that interact with AMPA receptor subunits has been shown to control AMPA receptor insertion, location, pharmacology, synaptic transmission, and plasticity. Thus, these proteins are now being considered as alternative therapeutic target sites for modulating AMPA receptors in neurological disorders.

Chapter 7 is an experimental example of the role of the intercellular gap junction inwardly rectifying K^+ (Kir) channels and two-pore domain K^+ (K_2P) channels in brain homeostasis maintained by astrocytes. Authors combined functional and molecular analyses to clarify how low pH affects K^+ channel function in astrocytes freshly isolated from the developing mouse hippocampus. No evidence has been found for the presence of ASIC and transient receptor potential vanilloid receptors in hippocampal astrocytes. However, the assembly of astrocytic K^+ channels allows tolerating short, transient acidification, and glial Kir4.1 and K_2P channels can be considered promising new targets in brain diseases accompanied by pH shifts. Chapter 8 in this volume discusses the ion channels modification by small ubiquitin-like modifier (SUMO) proteins and their role in neurological channelopathies, especially the determinants of the channels' regulation. SUMO proteins covalently conjugate lysine residues in a large number of target proteins and modify their functions. SUMO modification (SUMOylation) has emerged as an important regulatory mechanism for protein stability, function, subcellular localization, and protein–protein interactions. It is until recently that the physiological impacts of SUMOylation on the regulation of neuronal K^+ channels have been investigated. It is now clear that this ion channel modification is a key determinant in the function of K^+ channels, and SUMOylation is implicated in a wide range of channelopathies, including epilepsy and sudden death.

Nonetheless, ion channels remain a relatively underexploited family of proteins for therapeutic interventions. A number of recent advances in both

technology and biomedical knowledge suggest that these proteins are promising targets for future therapeutic development. Therefore, the aim of this volume is to promote further research in the structure, function, and regulation of different families of ion channels which would result in designing new efficient targeted drugs with significantly fewer adverse effects.

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