Preface

The present volume of our series “Methods and Principles in Medicinal Chemistry” is dedicated to “Voltage-gated Ion Channels” and their impact as targets for drug design.

Ion channels are ubiquitously distributed throughout cellular life; they represent integral membrane proteins that both produce and transduce the electrical signals crucial to the maintenance and function of cells. Ion channels gate or regulate the ion flow between the cytoplasmic compartment and the extracellular space and between subcellular compartments. They open and close in response to changes in membrane potential, changes in ion concentrations on either side of the membrane, and agonist binding to the channel or closely associated regulatory proteins. Under pathological conditions ion channels contribute to or drive a variety of disease processes from achalasia and arrhythmias to xerostomia and vertigo.

Ion channels can be classified in several distinct ways. The most common classification refers to the ions for which they are selective. Their primary mode of stimulus allows a classification into ligand- and voltage-gated channels. Alternatively, they can be classified by their electrophysiological properties and by their pharmacological sensitivity to toxins and synthetic drugs. Increasingly, they are classified according to their sequences, demonstrating that ion channels exist as super-families with considerable structural homology between the members, despite very different electrophysiological and pharmacological properties.

Whereas our initial understanding of ion channel structure and function was largely due to electrophysiological data, our knowledge was remarkably advanced by the work of Roderick MacKinnon and his coworkers on the three-dimensional structures of potassium channels. We are now at a stage where it becomes increasingly possible to start the integration of structural and functional data to provide a detailed understanding of both channel function and how drugs interact with and modulate such channel function.

A main characteristic of ion channels is their remarkable sensitivity to chemical modulation. Ion channels are excellent targets for drug design because: a) they are loci for integrated cellular communication: many inputs control the level of cellular membrane potential and thus the degree of excitation or inhibition; b) they are highly efficient molecular machines that enable the selective permeation of certain ions; c) there exists a multiplicity of channel types and subtypes; d) each
channel type and subtype typically has a multiplicity of discrete ligand binding sites that are allosterically coupled to the gating and permeation machinery of the channel; and e) the binding characteristics of the ligand can be modulated, both quantitatively and qualitatively, by factors such as membrane potential or channel phosphorylation.

The present volume comprises eight sections, the first four of which deal with basic background information. An introduction by the volume editors is followed by in-depth overviews dedicated to STRUCTURE AND FUNCTION OF ION CHANNELS (by William A. Catterall), DRUG INTERACTIONS AT ION CHANNELS (by Bruce Bean and Stefan McDonough) and to ASSAY TECHNOLOGIES (by Derek Leishman and Gareth Waldron).

The fifth section refers to CALCIUM CHANNELS. Clinton Doering and Gerald Zamponi give a general overview on calcium channels, whereas the most important calcium channel subtypes including T-type channels (by Thomas Connolly and James Barrow), L-type channels (by David J. Triggle) as well as N-type channels (by Terry Snutch) are separately treated in follow-up chapters.

SODIUM CHANNELS represent the focus of the next section. An overview on this ion channel class by Doug Krafte, Ken McCormack and Mark Chapman is followed by a chapter on sodium channel subtype selectivity from Tito Gonzales.

A quite comprehensive section is dedicated to POTASSIUM CHANNELS starting with an overview by Murali Gopalakrishnan. Then five different potassium channel subtypes and their relevant modulators are described in adequate detail. They comprise Kv1.3 channels (reviewed by George Chandy, Heike Wulff, Christine Beeton; and Michael Pennington), Kv1.5 channels (by Stefan Peukert and Heinz Goegelein), Ca\(^{2+}\)-activated K\(^+\) channels (by Sean C. Turner and Char-Chang Shieh), K\(_{ATP}\) channels (by William Carroll), and finally KCNQ channels (by Grant McNaughton Smith and Alan Wickenden).

The last section is dedicated to GENETIC AND ACQUIRED CHANNELOPATHIES. Introductory remarks to this important aspect of ion channel research are given by Dennis Wray. Structural and ligand-based models for HERG and their application in medicinal chemistry are then debated by Yi Li, Giovanni Cianchetta, and Roy Vaz. The concluding chapter of this volume, written by Armando Lagrutta and Joseph Salata, treats relevant safety issues in ion channel drug development.

The series editors believe that this book is unique in its topic and presentation and adds a fascinating facet to the series. We are indebted to all authors for their well-elaborated contributions and we would like to thank the volume editors David Triggle, Murali Gopalakrishnan, David Rampe, and Wei Zheng for their enthusiasm to organize this volume. We also want to express our gratitude to Renate Doetzer and Frank Weinreich from Wiley-VCH for their valuable contributions to this project.

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