Preface

Since the cloning of the first ion channel (the voltage-gated Na^+ channel from the electric eel *Electrophorus electroplax*) over 25 years ago at least 250 structurally distinct ion channel subunits have been identified. Each ion channel allows the rapid passive passage of ions (cations or anions) along electrochemical gradients across poorly permeable lipid bilayers (cell surface or intracellular compartments) at a rate (millisecond time frame) that is at least three orders of magnitude faster than that afforded by pumps or carrier proteins and over ten times faster than diffusion. This unique property allows ion channels to contribute to a wide variety of cellular processes, including electrical excitability, maintenance of membrane potential, hormone/neurotransmitter release, regulation of cell volume, apoptosis and activation of second messenger signalling cascades and of other ion channels, that are central to virtually all physiological processes.

Classically, the ion channel superfamily has been broadly subdivided into: (1) ligand-gated ion channels (LGIC) which comprise channels that are activated by Ca^{2+}, nucleotides and neurotransmitters, and (2) voltage-gated ion channels (VGIC) that are activated by changes in membrane potential. However, this classification is simplistic in that there are (a) many subdivisions that can be made within these two broad classes and (b) there are examples of ion channels that are activated by both ligand and voltage as well as other modalities such as light or mechanical stretch. Not surprisingly, molecular biological approaches have revealed extensive structural diversity within the ion channel superfamily with, for example, primary subunits possessing from between one or two (e.g., intracellular chloride channels or P_{2X} receptors) to 24 (e.g., voltage-gated Ca^{2+} channels) transmembrane domains. Despite the fact that sequencing of the human/rodent genomes is now complete there remain functionally defined conductances for which the molecular identity of the ion channel mediators has not been elucidated. However, for those where the molecular identity and amino acid sequence is available, experimental approaches, such as site-directed mutagenesis in combination with homology modelling and X-ray structural analysis, have identified molecular determinants of aspects of ion channel function such as voltage-dependence, activation, inactivation, deactivation, desensitisation, conductance, ionic selectivity, rectification and ligand-mediated activation/inhibition/modulation. In addition, intracellular regulatory sequence motifs have been discovered on numerous ion channels that enable cytoplasmic factors such as cyclic nucleotides, kinases and phosphatases to modulate their activity both positively and negatively. A further level of complexity is afforded by the fact that most ion channels exist as heteroligomeric assemblies of subunits that are also frequently associated with auxillary proteins that can have a significant impact on their biophysical and pharmacological properties. Furthermore, it is now recognized that ion channels can exhibit enzymatic activity. Thus, the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel hydrolyzes nucleotide triphosphates.

Looking beyond the characteristics of individual ion channels in isolation there is now a wealth of data on their tissue and subcellular localisation as well as their physiological function at the cellular, organ, and whole animal (including human) levels. By combining this knowledge with that of the biophysical properties of the channels it has been possible to begin to reconcile the aetiology and phenotype of several muscular and neurological diseases (including movement disorders, migraine, and epilepsy) that are caused by inherited mutations in the genes of specific ion channels. The list of these so-called 'channelopathies' is expanding rapidly, as is the phenotypic range associated with mutations within each individual channel (e.g., periodic paralysis, myotonias, malignant hyperthermia). Thus, mutations in different ion channels can result in remarkably similar phenotypes, whereas distinct mutations within the same gene can cause quite distinct disease phenotypes. Furthermore, alterations in ion channel function resulting from autoimmunity as well as acquired disorders of RNA processing can act as risk factors for, or directly precipitate, disease. It should also be noted, however, that there are many central and peripheral diseases that are not directly linked to ion channel mutations that are effectively treated by drugs that specifically modify ion channel activity.

Given that (1) ion channels are central to physiological processes as diverse as diuresis and cognition and (2) the experimental technologies to investigate ion channel function are now well established and widely available, it is certain that these transmembrane proteins will continue to be the focus of intensive interest in both academic and industrial research groups alike. This book was compiled in response to this widespread interest and both as an aid for education in the ion channel field and to facilitate research, in that it reviews the basic principles of ion channel function and provides detailed overviews of the structural, biophysical, physiological and pharmacological aspects of individual ion channels across the ion channel super family.