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**Introduction – On Ion Channels**

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Ion channels are membrane proteins that are pore forming to permit ion transit according to concentration and electrochemical gradients. They are ubiquitously distributed throughout cellular life and indeed some form of ion moving (and other solute moving) device must have developed very early in cellular evolution and certainly must have evolved simultaneously with the development of the cell membrane.

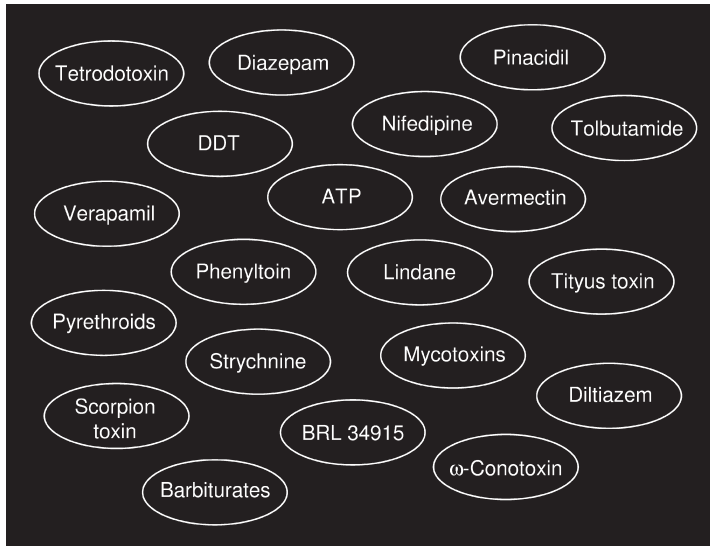
Ion channels are also one of the mechanisms by which cells respond to informational inputs. Under physiological conditions these channels permit an orderly movement of ions across cell membranes and contribute both to cellular signaling processes and to the maintenance of cellular homeostasis. Under pathological conditions ion channels contribute to or drive various diseases processes from achalasia and arrhythmias to xerostomia and vertigo.

Ion channels are allosteric proteins that undergo significant conformational transitions in response to various informational inputs, including mechanical tension, voltage gradients and endogenous and exogenous chemical signals. The latter inputs are of particular interest to the clinician, pharmacologist and the pharmaceutical industry since they represent opportunities, both real and potential, for drug intervention. However, as usual, Nature, the supreme medicinal chemist, long ago seized this opportunity and a remarkable number of toxins from venomous species are directed against both ligand- and voltage-gated ion channels. Indeed, one of the principal characteristics of ion channels is their remarkable sensitivity to chemical modulation.

The chemical species depicted in Fig. 1.1 provide adequate testimony to this point. Currently, there exists ion channel therapeutics for anesthesia, anxiety, epilepsy, hypertension, insomnia and pain and excellent opportunities for ion channel therapeutic modulation in, for example, affective disorders, allergic disorders, autoimmune diseases, contraception, incontinence, and stroke.

Ion channels are excellent targets for drug design because they are:

1. Loci for integrated cellular communication: many inputs control the level of cellular membrane potential and thus the degree of excitation or inhibition.



**Fig. 1.1** Drugs and toxins that act at ion channels.

2. Highly efficient molecular machines that permeate ions selectively at rates that can approach diffusion-controlled.
3. There exists a multiplicity of channel types and subtypes.
4. Each channel type and subtype typically has a multiplicity of discrete ligand binding sites that are coupled allosterically to the gating and permeation machinery of the channel.
5. The binding characteristics of the ligand can be modulated, both quantitatively and qualitatively, by factors such as membrane potential or channel phosphorylation.

There are thus provided opportunities for multiple modes of interaction that can in principle generate a common pharmacological and therapeutic endpoint. Figure 1.2 depicts drug interaction at the L-type voltage-gated calcium channels, site of interaction several of cardiovascular drugs: three separate sites are indicated, but there are probably at least eight such sites, all linked allosterically to the guts of the calcium channel. Figure 1.3 provides a second example of multiple drug interaction where a neuroprotective strategy might be to prevent cellular depolarization and block calcium entry into neurons: this can be achieved through various discrete strategies from blockade of voltage-gated calcium channels to activation of ATP-dependent potassium channels. Parenthetically, Fig. 1.2 also presents a dilemma common to a number of therapeutic strategies, namely that for some diseases (in this case neuroprotection during ischemic stroke) various pathologic mechanisms are operative and modulation of only one may not be an effective strategy.

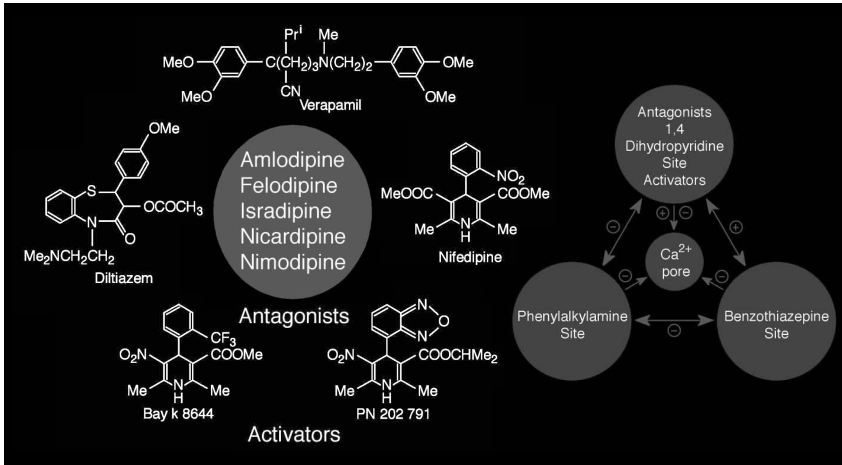


Fig. 1.2 Drug interactions at the L-type voltage-gated calcium channel.

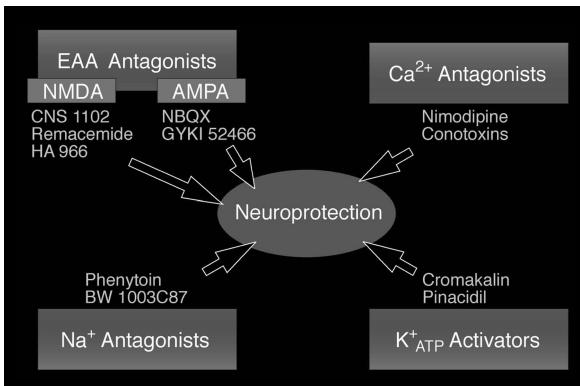
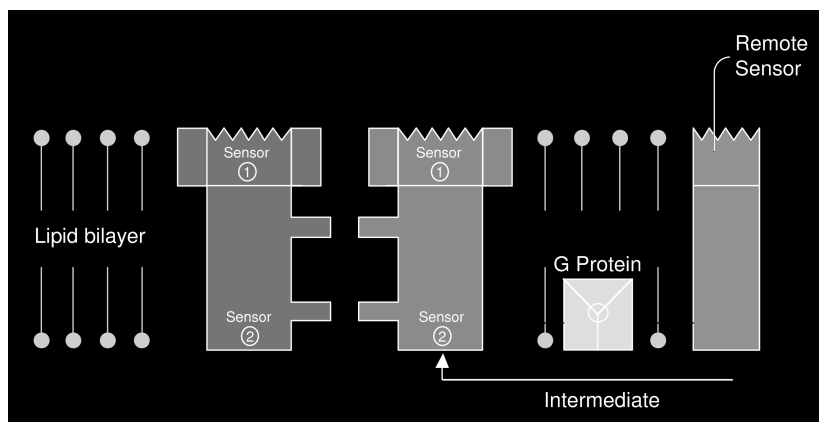


Fig. 1.3 Neuroprotective strategies implemented by drugs acting on diverse ion channels.

Until very recently our understanding of ion channel structure and function has been derived largely from electrophysiological data, leading to the representation depicted in Fig. 1.4. Despite the cartoon-like characteristics of Fig. 1.4, the electrophysiology underlying it has been astonishingly successful in explaining channel function and how drugs interact with channels. The past decade has seen major advances in our knowledge of channel structure and function, starting with the remarkable work of Roderick Mackinnon and his colleagues and their success in providing solid-state structures of the potassium channels. We are now at a stage where it becomes increasingly possible to start the integration of structural and functional data to provide for a detailed understanding of both channel function and of how drugs interact with and modulate such channel function.



**Fig. 1.4** Two-dimensional representation of an ion channel, depicting the major structural features.

It is thus believed that this book will appear at an appropriate time in our understanding of ion channels. All four editors have worked extensively for several years on the medicinal chemistry and pharmacology of ion channels and recognize that for a successful approach to the development of new drugs active at ion channels it is increasingly necessary to follow an integrated approach. A medicinal chemistry approach in the absence of an understanding of ion channel function and behavior and without recognizing what assay technologies are telling us is not likely to be successful. Far greater integration of chemical, biochemical, biophysical, pharmacological and structural approaches are necessary. Additionally, there are drug discovery programs where it is necessary that certain types of channel-modulating behavior not be found, notably activity at HERG channels. This has resulted in the expenditure of millions of research dollars annually and supports a growing “cottage industry” of small companies specializing in ion channel safety assays. Thus, even non-ion channel programs need to be aware of at least some aspects of ion channel structure and function.

This book is organized to optimize such an interdisciplinary approach. Although the primary emphasis is on drugs active at voltage-gated calcium, potassium and sodium channels the chemical pharmacology of these drugs is set against a background of channel classification, function and structure. Accordingly, the initial chapters deal with, respectively, channel structure and function, state-dependent interactions of drugs with channels and the assay technologies for drug screening. These three initial chapters provide the necessary background for the more detailed understanding of drug actions at calcium, potassium and sodium channels. These channels are discussed in three separate sections, each of which starts with an overview of the respective channel class. The volume concludes with a three-chapter section on ion channel diseases or “Channelopathies” and discussions of channel safety, with particular reference to HERG.

The next decade is almost certain to see continuing major advances in our knowledge of channel structure as more ion channels provide three-dimensional views. The challenge will be to link that structural knowledge to the definition of channel function and to our knowledge of drug action at those channels. That should lead to therapeutic advances for arrhythmias, neurodegenerative disorders, pain and stroke, all of which are unmet or underserved medical needs and where ion channels are significant contributors to the underlying pathologies.

We thank all of our contributors to this volume. They have all put aside other activities to contribute their specific knowledge and expertise and the success of the book will be entirely due to them.

