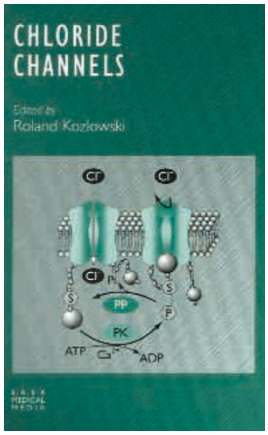
Negative thinking: anion channels



Chloride Channels
edited by Roland Kozlowski
Isis Medical Media Limited Feb 2000
£60.00, $99.50

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Ion channels are 'tunnel' proteins that allow the passive flow of mostly inorganic ions across otherwise extremely hydrophobic membranes. This flow can occur at extraordinary high flux rates, despite an often very high specificity regarding the ion species that is allowed to pass. When asked about ion channels, most biologists will probably think at first of the voltage-dependent K^+, Na^+ and Ca^{2+} channels, or maybe of the excitatory postsynaptic Na^+/K^+ (and Ca^{2+}) permeable, neurotransmitter-activated channels. All of these are cation-selective channels. Indeed, not many years ago, the only anion-specific channels that had been studied extensively with electrophysiological, biochemical, and molecular-biological methods were the inhibitory postsynaptic GABA and glycine receptors, which are structurally very similar to the very well-studied cationic nicotinic acetylcholine receptors. Other species of chloride channel, of which one or the other is present in practically all cell types, are sometimes referred to as the 'poor cousins' of cation channels because much less is known about them, despite their now widely recognized physiological importance.

In recent years, however, the situation has started to change. The interest is partly a result of the spectacular success of the cloning of the CFTR chloride channel, the protein that is defective in cystic fibrosis, and to the impressive progress in the elucidation of the primary structures and functional properties of the members of the large gene-family of ClC chloride channels. It is also due to the application of high-resolution electrophysiological methods – patch clamping – to cells that were previously inaccessible to such studies. In fact, the field of chloride-channel research is now so broad that it was impossible to cover all currently studied and important topics even in a conference solely dedicated to them ('Chloride Channels' Conference, Oxford, October 1999), the proceedings of which are collected in the homonymous book.

The physiological importance of chloride channels is dramatically shown by their involvement in various hereditary diseases, an aspect that is dealt with in several chapters. However, the main focus of the conference and the proceedings, and one of the most debated topics today, is the so-called swelling-activated chloride channel, an ubiquitous channel that is thought to be of great importance for all cell types, even though its precise physiological function is far from being understood. Its principal role may be to allow cells to lose salt after swelling, in order to recover their original volume. This channel is discussed in six of the fourteen chapters. Two main questions have been awaiting an answer for a rather long time now — what is (or are) the molecular correlate(s) of the channel and what is the mechanism that leads to its activation? Several very good chapters deal with the (possible) physiological function, the pharmacology, and the (possible) mechanisms of its activation that relate to the latter problem. For example, a very interesting dependence of the activation of the swelling-activated chloride channel on the intracellular ionic strength and a correlation with the activity of certain protein tyrosine kinases have been recently found. On the other hand, there is a large disagreement regarding the molecular identity of the swelling-activated chloride channel, and the different viewpoints are represented by the various authors. Unfortunately, the situation is probably quite confusing for those not directly involved in the field (and also for those within the field). There are now many candidate genes, some of which have been discounted by most experts, whereas others, like the ClC-3 channel, are still debated. This highly disputed issue will hopefully be resolved in the near future. As a result, some chapters of the present volume may be of only limited value as a reference.

Similar disagreements exist also for another important class of chloride channels, the calcium-activated chloride channels. The recent physiological, biophysical and molecular studies of this important type of chloride channel are, however, quite underrepresented in the book, apart from a very interesting description of its possible importance for smooth-muscle contraction.

Likewise, other types of chloride channel described in physiological contexts, but for which the molecular counterparts have not yet been identified, such as the hyperpolarization-activated chloride channels present in epithelial cells of the choroid plexus, are virtually unmentioned in this book. From the extensive fields of research on CFTR and GABA/glycine receptors, only a few specific (although very interesting and important) topics are included.

Chloride Channels is certainly not exhaustive. Nevertheless, the book provides an extremely rich source of references and a very well-elaborated index. It therefore represents an excellent entry point for anybody interested in specific aspects of these still rather poorly understood membrane-transport proteins. □

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