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MINI-REVIEW

Metabolic Control of K^+ Channels: An Overview

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Why is there such a tremendous diversity of K^+ channels? What role does each of them play? How is their activity regulated? Do they all share a common basic structure? All these are questions that investigators playing with these ubiquitous membrane integral points ask themselves each day. A partial and vague answer to some of these questions is that potassium channels may be considered the guardians of the cellular electrical homeostasis and, therefore, there must be many of them and all of them must be finely tuned.

Arbitrarily, we can group K^+ channels in five different types (Rudy, 1988; Moczydlowski *et al.*, 1988): (a) Voltage-dependent K^+ channels which in turn can be subdivided into channels showing fast inactivation ("A" channels) and delayed rectifiers of the Hodgkin and Huxley (1952) type (Hille, 1984); (b) calcium-activated K^+ channels that are usually classified into two different classes of high (maxi, BK) and small (SK) conductance, although as we will see below they can also be classified according to their sensitivity to specific toxins (Blatz and Magleby, 1987; Latorre *et al.*, 1989); (c) inward rectifiers that give origin to a current that activates with hyperpolarizing voltages in contrast to the "A" and delayed rectifier channels that activated with depolarizing voltages (Rogawski, 1985; Rudy, 1988); (d) potassium channels coupled to receptors, as in the case of those coupled to muscarinic receptors in the heart muscle; and (e) adenosine triphosphate-dependent channels (Noma, 1983). The dissection of the different K^+ channels has been carried out using pharmacological and, more recently, genetic tools. They have been classified according to the type of activation (or inactivation)

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kinetics, channel conductance, and sensitivity to different toxins and blockers. This review series is mainly concerned with one aspect of K^+ channel activity: its modulation by the cell metabolic machinery. However, given the very important role that toxins and molecular biology play in the elucidation of K^+ channel function and structure, this series of mini-reviews also includes these two topics.

Most of what we know about Ca^{2+}-activated K^+, K(Ca), channels comes from single-channel studies done in the large unitary (maxi) conductance channel, and the first two reviews are mostly dedicated to this channel. Quoting Meech (1978), . . . "Perhaps the most important function of a calcium-mediated potassium activation system is to provide a link between cell metabolism and membrane conductance." In this series, McManus discusses the manner by means of which internal Ca^{2+} modulates the activity of the maxi K(Ca) channel. A comparison of this type of channel with a family of small conductance K(Ca) channels sensitive to the bee venom apamin indicates that, in general, small K(Ca) channel are more sensitive to Ca^{2+} than maxi K(Ca) channels. The large conductance of the maxi K(Ca) channels has been the delight of biophysicists working on ion conduction and channel gating and has allowed them to know, with exquisite kinetic detail, how Ca^{2+} regulates channel activity. It has become clear that several calcium ions intervene in the opening reaction, giving rise to a complex kinetic scheme containing many closed states and at least three open states. McManus introduces us, in an almost painless way, to this complicated topic, showing in passing how to take advantage of the information contained in the transitions between the open and close conformation of a single channel molecule. Extracellular signals are able to modulate the activity of some K(Ca) channels. However, it was a common belief that in most cases changes in channel activity were mediated by an increase in the cytoplasmic Ca^{2+} promoted by second messengers such as cAMP or IP_3. Through a series of examples, Toro and Stefani show that this is not the case, and a picture emerges in which K(Ca) channels appear to have a complex metabolic regulation and to be rich in internal and external receptors for nucleotides and hormones. Moreover, Toro and Stefani discuss in detail the unexpected result obtained in Stefani's laboratory that, once incorporated into a planar bilayer, the maxi K(Ca) channel can be up-regulated by intracellular GTP and extracellular norepinephrine. This and other results (which the reader can fully appreciate in Toro and Stefani's review) have led Stefani's group to propose that a GTP-dependent protein directly gate maxi K(Ca) channels in planar bilayers. This result is both surprising and very interesting since we expected the triad receptor–effector–channel to be loosely coupled (see review by Brown *et al.*). After incorporation into the planar membrane, this triad is at infinite dilution in the bilayer lipids, and therefore their components, if they are loosely coupled, should fly apart.

Regulation of K^+ channels by GTP-dependent proteins is discussed in detail by Brown *et al.* The hypothesis that the α-subunit of G-proteins directly couples receptors to K^+ channels is tested using the experimental evidence available. In particular, Brown *et al.* discuss the most important experiments that led to the conclusion that the α-subunit of G_k and G_i proteins, and not the subunit complex, are responsible for the activation of the muscarinic K^+ channel. This mechanism appears to be a general one used by a series of K^+ channels in different cells and tissues. Potassium channels are also modulated by phosphorylation, and this is not unexpected given their great diversity. In the following review, Perozzo and Bezanilla offer an elegant biophysical explanation for the up-regulation mediated by phosphorylation of the squid axon delayed rectifier. Although the metabolic machinery that leads to channel phosphorylation in the squid giant axon has not yet been elucidated, this preparation offers the advantage that measurements of single-channel, macroscopic, and gating currents can be performed and their characteristics studied in much detail. The studies of Perozo and Bezanilla on the effect of phosphorylation on the squid K^+ current have led to the proposal that phosphorylation modulates this current by introducing a fixed charge (the phosphate group donated by the ATP molecule?) in the neighborhood of the voltage sensor. Therefore, the phosphorylation reaction would induce an electrostatic potential which shifts the voltage-dependent parameters, as found experimentally by Perozo and Bezanilla.

As ubiquitous as the K(Ca) channels are a class of K^+ whose activity depends on the intracellular concentration of ATP (K_{ATP} channels). At physiological ATP concentrations these channels have a very low probability of opening, but this is dramatically increased in the absence of this nucleotide. In particular, these channels are present in skeletal muscle fibers, and their characteristics are discussed and compared with those shown by K_{ATP} channels present in other tissues in the review by Davies *et al.* Since the intracellular concentration of ATP is in general well buffered, Davis *et al.* discuss the attractive hypothesis that other factors such as hormones, the ADP/ATP ratio, and the pH, rather than changes in ATP concentration, are responsible for the control of channel activity. In skeletal muscle these channels are responsible for the increase in K^+ conductance induced by metabolic exhaustion but, as discussed in the review of Davis *et al.*, it is probably that they are involved in the electrical activity of the exercising muscle. There is a large body of evidence that the K_{ATP} channel directly binds ATP with Hill numbers that vary between 1 in skeletal muscle to 4 in heart muscle. Similarly, patch clamp and reconstitution studies have shown that second messengers (cyclic nucleotides) are able to regulate directly channel activity, independent of protein phosphorylation. Some of these cases are discussed in the review of Latorre *et al.* These channels play an important role in the processes of visual and olfactory transduction both in vertebrates and

invertebrates. Cyclic nucleotide-activated channels in these tissues are not strictly K^+ channels since they let K^+ and Na^+ pass almost equally well through them. However, Latorre *et al.* discuss the case of a highly K^+ selective cAMP-activated channel present in *Drosophila* muscle that shares several of the cyclic nucleotide binding properties shown by the other cyclic nucleotide-activated channels. This channel is persistently activated in the larval muscle of *dunce*, a *Drosophila* with a problem in learning and retention and which has abnormally high levels of intracellular cAMP.

Dissection of macroscopic potassium currents has for many years been difficult due to the lack of specific blockers or toxins showing high affinity for these integral membrane proteins. This situation radically changed with the discovery of a series of scorpion toxins able to inhibit at nanomolar concentrations several different K^+ channels. Garcia *et al.* in their review show us that toxins against K^+ channels can be found, beside scorpions, in snakes as well as bees and guide us through their molecular characteristics, selectivity, and mode of action. All these toxins open new avenues toward the elucidation of physiological roles and the purification of this important family of channels.

Finally, MacKinnon illustrates with specific examples the power of molecular biology in helping us to understand some biophysical properties of K^+ channels. The primary structure of several K^+ channels has been elucidated and, at variance with other voltage-gated channels, like Na^+ and Ca^+ channels, the peptide forming the K^+ is much smaller, having a molecular weight similar to one of the four homologous internal domains of Na^+ channels. First, MacKinnon discusses the experimental evidence that supports the notion that there are four subunits forming a K^+ channel. Second, he gives us a walk inside a K^+ channel ion conduction system, pointing out those residues important for normal ion movement. Third, he shows the molecular nature of the inactivation gate in a K^+ channel—the so-called "A" channel.

Though space limitations do not permit me to give the reader a full account of all the accomplishments in this exciting field, I hope that the efforts of the contributors to this mini series may be rewarded by attracting others toward ion channel research.

Acknowledgments

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