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REVIEW

Thomas M. Weiger · Anton Hermann · Irwin B. Levitan

Modulation of calcium-activated potassium channels

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Abstract Potassium currents play a critical role in action potential repolarization, setting of the resting membrane potential, control of neuronal firing rates, and regulation of neurotransmitter release. The diversity of the potassium channels that generate these currents is nothing less than staggering. This diversity is generated by multiple genes (as many as 100 and perhaps more in some creatures) encoding the pore-forming channel α subunits, alternative splicing of channel gene transcripts, formation of heteromultimeric channels, participation of auxiliary (non-pore-forming) β and other subunits, and modulation of channel properties by post-translational modifications and other mechanisms. Prominent among the potassium channels are several families of calcium activated potassium channels, which are highly selective for potassium ions as their charge carrier, and require intracellular calcium for channel gating. The modulation of one of these families, that of the large conductance calcium activated and voltage-dependent potassium channels, has been especially widely studied. In this review we discuss a few selected examples of the modulation of these channels, to illustrate some of the molecular mechanisms and physiological consequences of ion channel modulation.

Keywords Calcium-activated potassium channel · BK channel · Slo · Modulation

Abbreviations *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid · *ATP* adenosine triphosphate · *ATPγS* adenosine 5'-O-(3-thiotriphosphate) · *BK* maxi calcium activated potassium channel · *cAMP* adenosine 3',5'-cyclic monophosphate · *cGMP* guanosine 3',5'-cyclic monophosphate · *DHS-I* dehydrosoysaponin I · *dSlo*: *Drosophila* Slowpoke · *DTT* dithiothreitol · EC_{50}: half maximal effective concentration · *GC*: guanylate cyclase · *hSlo*: human Slowpoke · *IK* intermediate conductance calcium activated potassium channel · *IP3* inositol triphosphate · K_v voltage-dependent potassium channel · *NMDA N*-methyl-D-asparate · *NO* nitric oxide · *NOS* nitric oxide synthase · *SK* small conductance calcium activated potassium channel · *Slo* Slowpoke · *Slob* Slo binding protein · *Slip* Slo interacting protein · *TEA* tetraethylammonium

T.M. Weiger (✉) · A. Hermann
Department of Molecular Neurobiology
and Cellular Physiology,
University of Salzburg, Institute of Zoology,
Hellbrunnerstrasse 34, 5020 Salzburg, Austria
E-mail: thomas.weiger@sbg.ac.at
Fax: +43-662-63895679

I.B. Levitan
Department of Neuroscience,
University of Pennsylvania School of Medicine,
Philadelphia, PA 19104, USA

Introduction

Ion channels are a ubiquitous class of specialized membrane proteins that form hydrophilic pores, through which ions move down their electrochemical gradients across the membrane. The current carried by ions flowing through plasma membrane ion channels underlies a number of fundamental physiological phenomena, including for example sensory transduction, muscle contraction, action potential generation and propagation, and synaptic transmission. Ion channels are dynamic proteins that can switch rapidly between different conformational states, a phenomenon known as channel gating. A channel that is in a conformation that permits ion flow is said to be "open", whereas "closed" channels are in a conformation that does not allow ions to flow. There is an equilibrium between these open and closed states, that determines the amount of current that flows across the membrane as a function of time. This equilibrium can be influenced by such factors as the membrane voltage, the binding of extracellular ligands such as neurotransmitters or intracellular messengers including calcium and cyclic nucleotides to the channel protein, or covalent modification of the channel

by protein phosphorylation or other mechanisms. Such modulation of the gating of ion channels can sometimes last for a very long time, and certainly is critical for long-term plastic changes in the electrical excitability of neurons and other cells.

Among the voltage-dependent ion channels, those that are selective for potassium ions are remarkable for their diversity. Some 100 distinct genes encoding potassium channels have been described, in organisms ranging from bacteria to humans. Potassium channels were probably the first ion channels to evolve, most likely to participate (at least originally) in osmoregulation and cell volume control (Hille 2001). We will focus in this review on a potassium channel subfamily whose gating is regulated by the binding of intracellular calcium, the so-called calcium activated potassium channels.

Calcium-activated potassium channels

Calcium-activated potassium channels can be found in a variety of tissues and cells including nerve, muscle, pituitary or chromaffin cells among others (Latorre and Miller 1983; Vergara et al. 1998; Latorre et al. 1989). They are found in both vertebrates and invertebrates, and in fact the first description of calcium activated potassium conductance in excitable cells was in molluscan neurons (reviewed by Meech 1978; Hermann and Hartung 1983). There are several categories of calcium activated potassium channels that are defined by their single channel conductances. These include the small conductance (SK) and intermediate conductance (IK) channels that we will not discuss here. Instead, we will restrict ourselves in this brief review to the ubiquitous large conductance calcium activated potassium channels, with single channel conductances in the range of 200–300 pS, whose gating is regulated not only by calcium but also by membrane voltage. These channels are often known as "maxi" or "BK" (for big K) channels, and more recently have been referred to as "Slo" channels because they are encoded by the Slowpoke gene family (see below). Their dual regulation by voltage and calcium allows BK channels to act as molecular integrators of the state of intracellular messenger systems and the electrical properties of the plasma membrane. They play a particularly important role in neuronal signaling. For example, calcium-activated potassium channels are enriched in synaptic terminals and axons (Knaus et al.1996), where they facilitate membrane repolarization during an action potential and thereby participate in the regulation of neurotransmitter release (Gho and Ganetzky 1992; Bielefeldt and Jackson 1994). In addition, genetic and molecular approaches have demonstrated that BK channels are key determinants of certain behaviors (Brenner et al. 2000a).

The first BK channel to be cloned was from the fruit fly *Drosophila* (Atkinson et al. 1991; Adelman et al. 1992); for a review of insect ion channels including BK channels see Wicher et al. (2001). A *Drosophila* mutant called Slowpoke, whose behavioral phenotype is reflected in its name, was found to be defective in calcium activated potassium current in nerve and muscle. The Slowpoke (Slo) gene was cloned by a positional cloning approach, and was found to share certain structural characteristics (Fig. 1) with the Shaker family of voltage-dependent potassium channels that had been cloned previously. Genes homologous to this *Drosophila* Slowpoke (dSlo) were later identified in a variety of other species, including humans (Butler et al. 1993; Dworetzky et al. 1994; Tseng-Crank et al. 1994; Wei et al. 1996).

BK channels appear to be encoded by only a single gene (*Slo1* locus in the human genome; 10q22.3). Recently, however, two other genes, *Slo2* and *Slo3*, were shown to encode structurally similar channels (Schreiber et al. 1998; Yuan et al. 2000). In addition, RNA splicing at several different sites can give rise to multiple distinct ion channels from the *Slo1* gene (Butler et al. 1993; Tseng-Crank et al. 1994). Some of the splice variants differ from each other in their biophysical properties (Lagrutta et al. 1994; Tseng-Crank et al. 1994), thereby allowing fine-tuning of BK currents to the needs of a particular cell. For example, alternative splicing seems to play a particularly critical role in the tonotopic organization of the cochlea (Jones et al. 1999; Ramanathan et al. 1999).

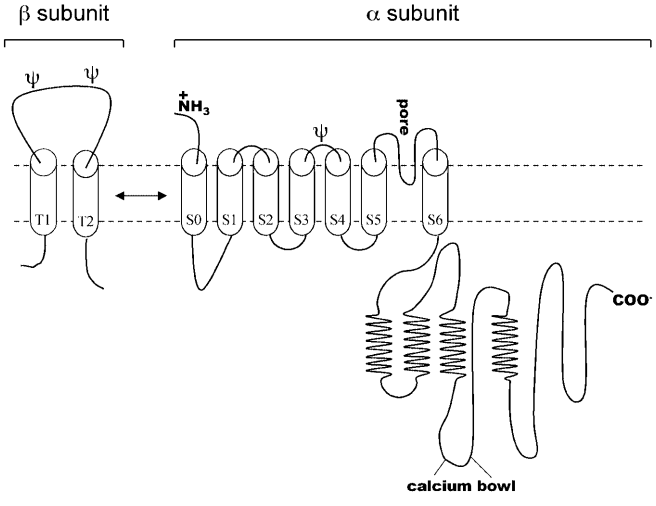

Fig. 1. Putative structures of maxi calcium-activated potassium channel (BK) subunits. The pore-forming α subunits of the Slowpoke family of BK channels are large proteins (~1,200 amino acids) that resemble other voltage-dependent potassium channels in having six membrane-spanning domains (S1–S6), with a pore region between S5 and S6. An additional membrane-spanning domain (S0) places the amino terminal outside the plasma membrane. Most notable is the extended carboxyl terminal tail domain, comprising about two-thirds of the α subunit protein sequence. It includes a negatively charged region (the so-called calcium bowl) that has been implicated in calcium binding, and is the site of interaction with several channel modulatory proteins including protein kinases. The auxiliary β subunits are small proteins (~200 amino acids) with two membrane-spanning domains (T1 and T2). ψ, potential sites for N-linked glycosylation. Modified from Vergara et al. (1998)

BK channels consist basically of two parts (Fig. 1). One part is a core membrane-spanning region (segments S1-S6) resembling the α subunit of voltage-dependent potassium (K_v) channels. In contrast to K_v channels, however, there is also a large carboxyl terminal tail domain that plays a role in calcium sensing and acts as a partner for protein-protein interactions (Wei et al. 1994; Schreiber and Salkoff 1997; Schopperle et al. 1998; Xia et al. 1998; Fig. 1). In addition, BK channels contain a unique *N*-terminal segment (S0) that is an additional membrane spanning domain, and hence the amino terminus resides outside the cell (Meera et al. 1997).

Gating of BK channels – or how they are regulated by calcium and voltage

Under physiological conditions BK channels are activated by voltage and an increase in free intracellular calcium. Activation of the channel varies over a wide range of calcium concentration from 10 nmol l^{-1} to 10 μmol l^{-1} (Marty 1989; Latorre et al. 1989; Soria and Cena 1998), and open probability changes in a voltage-dependent manner e-fold for every 10–15 mV of depolarization (Moczydlowski and Latorre 1983; Blatz and Magleby 1984). However, the gating is considerably more complex than was at first thought. Under low- or zero-calcium conditions the channel behaves like a purely voltage-dependent channel. (Talukder and Aldrich 2000; Horrigan et al. 1999). The conclusion drawn from these observations is that the voltage-sensing mechanism is independent of the binding of calcium to the channel during the activation process, and that calcium is not absolutely required to activate BK channels. However, calcium shifts many of the voltage-dependent parameters of BK channels to more negative voltages, and thereby allows the channel to function under physiological conditions (Barrett et al. 1982; Cox et al.1997).

Modulation of BK channels

In addition to this complex pattern of gating by voltage and calcium, the activity of BK channels can be modulated by a wide variety of molecules and molecular mechanisms (see Table 1). Other ion channels, including most or perhaps all other flavors of potassium channel, are also subject to modulation by similar mechanisms. We focus here on BK channels because they have been especially widely studied in this regard, and because their modulation is representative of modulatory phenomena that have been seen with other kinds of channels. A few selected examples of modulatory molecules and mechanisms, discussed below, serve to illustrate the general themes of BK channel modulation.

Table 1. BK channel modulatory molecules and mechanisms. Some of the molecules and molecular mechanisms that can influence the properties of BK channels are listed here. A few selected examples are discussed in the text

Molecules	
Blockers:	Polypeptide blockers including charybdotoxin, iberiotoxin, limbatotoxin Indole alkaloids including paspalitrem A, paspalitrem C, aflatrem, penitrem A, papalinine, paxilline, verruculogen, paspalicine, paspalinine Non-specific blockers including tetraethylammonium (TEA), barium, quinidine, sapecin B, clotrimazole, ruthenium red
Openers:	Maxi K diol, indole analogs (e.g., CGS 7184), benzimidazolone analogs (e.g., NS1619, NS004), substituted diphenylurea (e.g., NS 1608), phloretin, niflumic acid, flufenamic acid, NPPB [5-nitro-2-(3-phenylpropylamino) benzoic acid], Evans blue, estradiol (requires β subunit), DHS-I (requires β subunit)
Second messengers:	Adenosine 3',5'-cyclic monophosphate (cAMP), cGMP, calcium, ceramide, inositol triphosphate (IP_3)
Proteins:	Auxiliary subunits including β1 through β4, Slob, Slo interacting protein (Slip)
Other molecules:	Ethanol, fatty acids, diamines, polyamines, NO
Mechanisms	Voltage, pH, redox state, surface electrostatics, phosphorylation, nitrosylation

Modulation of BK channels by pH

A change in pH from the physiological range of about 7.0 to more acidic values (6.0) decreases BK channel activity. Mean channel open time decreases, and closing times between openings are increased. The half-maximal activation voltage is shifted to the right, i.e., the channel needs a greater depolarization to be activated. (Laurido et al. 1991; Andersen et al. 1995; Church et al. 1998). Changes in pH are only effective from the cytoplasmic side but not from the extracellular side of the channel (Church et al. 1998).

Modulation of BK channels by redox potential

The reducing agent dithiothreitol (DTT) increases human Slowpoke (hSlo) channel activity without changing the unitary current (DiChiara and Reinhart 1997). The half-maximal activation voltage is shifted to the left, making the channel more sensitive to depolarization. DTT also prevents a ''run down'' phenomenon over time in excised patches, which apparently results from

exposure to an oxidizing environment after patch excision. Oxidizing agents were shown to have the opposite effect to DTT. For example, H_2O_2 causes a decrease in open probability over time and does not prevent run down of the channel. Several cysteine residues within the channel protein appear to be the main targets for these effects (DiChiara and Reinhart 1997). In contrast, oxidation of methionine residues enhances specific voltage-dependent opening transitions and slows deactivation, thereby effectively activating the channel (Tang et al. 2001). The physiological significance of these complex oxidation-reduction effects remains unclear, although it is interesting that nitric oxide (see below) can confer a redox-related BK channel modulation that influences the shape and duration of action potentials.

BK channel pharmacology

A number of creatures have evolved potent toxins that target potassium channels in general, and BK channels in particular. Many of these toxins block the channel pore, and have proven exceptionally useful in elucidating features of channel structure. We will not discuss these here, but will mention briefly some naturally-occurring and synthetic compounds that can act as BK channel openers. By increasing potassium current and thereby hyperpolarizing the cell, such compounds can prevent or reverse the cytotoxic cell damage that often results from hyperexcitability, and hence they are of potential therapeutic interest. BK channel openers might be a very promising target to control a number of diseases like asthma and other chronic lung diseases (for review see Rogers 1996), as well as the neuronal damage that results from stroke and trauma. Although most of the currently available compounds have side effects that render them unsuitable for clinical use, rational drug design holds promise for the discovery of therapeutically useful channel openers.

A number of benzimidazolone analogs are claimed to be BK channels openers (Kaczorowski and Garcia 1999). For instance, NS 1619 has been reported to be a specific BK channel opener (Olesen et al. 1994), although another group has challenged the conclusion that this drug is specific for BK channels (Patel et al. 1998). Riluzole a drug used for the management of amyotrophic lateral sclerosis (Neatherlin 1998), opens BK channels in a direct, dose-dependent manner without affecting single channel current amplitude. This may explain its inhibitory action on neurotransmission (Wu and Li 1999). A recent report shows that monochloramine, a membrane-permeant oxidant generated during colitis by a large amount of ambient luminal NH_3 in the colon, opens BK channels by a direct action on the channel (Prasad et al. 1999). Nitric oxide (NO), a gas produced in many cells of the body (see below), as well as the herb dehydrosoysaponin I (DHS-I), also open BK channels. Interestingly, at low concentrations, DHS-I can increase BK channel activity only in the presence of an auxiliary β subunit (see below). Although the list of BK channel openers continues to expand, our present understanding about their mechanism of action remains limited, and thus it may be some time before they will be introduced in routine clinical use.

Polyamines modulate BK channels from the intracellular side

Polyamines (putrescine, spermidine, spermine) are ubiquitously present in all prokaryotic and eukaryotic cells. They consist of a class of simple aliphatic molecules with two, three or four positive charges under physiological conditions (Tabor and Tabor 1984; Pegg 1986). Polyamines are known to be involved in many biological phenomena including cell proliferation, differentiation, apoptosis and ion channel modulation. After excessive electrical stimulation or induced epileptic seizures their levels in brain increase (Pajunen et al. 1978; Baudry et al. 1986), raising the question of their involvement in the modulation of neuronal electrical activity. We know now that polyamines modulate a wide range of ion channels, including inwardly rectifying potassium channels, K_{ATP} channels, *N*-methyl-D-asparate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, calcium channels and finally BK channels (Herman et al. 1993; Drouin and Hermann 1994; Ficker et al. 1994; Weiger and Hermann 1994; Fakler et al. 1995; Gomez and Hellstrand 1995; Williams et al. 1995, 1996; Kashiwagi et al. 1996; Biedermann et al. 1998; Niu and Meech 1998). Spermine, apparently due to its four positive charges, was found to be the most active molecule in modulating the activity of the diverse channels listed above.

Drouin and Hermann (1994) reported that spermine, when applied from the internal side of the cell membrane, caused a reduction of calcium activated potassium current in neurons of *Aplysia californica*. Polyamines do not affect channel activity when applied from outside. These results were confirmed by single channel studies in GH3 pituitary tumor (Weiger and Hermann 1994). Although only micromolar concentrations of polyamines can induce rectification in inwardly rectifying potassium channels, millimolar concentrations are required to affect BK channels. Spermine decreases not only BK channel open probability, but also single channel current amplitude. The latter phenomenon results from a fast block, during which the blocker moves so rapidly in and out of the channel pore that the recording system clips the signal like a lowpass filter. This blocking effect is greater at more depolarized voltages.

The fact that polyamines are only effective when applied from the inside of the cell membrane raised the question of whether related molecules might block from the outside. A number of diamines similar in structure to polyamines were tested (Weiger et al.

1998); 1,12 diaminododecane, a molecule with the same length as spermine but lacking the two middle amino groups, turns out to be a very potent blocker of BK channels when applied from the outside. Molecular modeling revealed that the size of the water shells surrounding these molecules could account for their different behaviors.

Nitric oxide modulates BK channel activity

NO, a radical gas, acts as a multifunctional intra- and intercellular messenger in diverse physiological and pathological processes in a great variety of animals and tissues (Jacklet 1997; Marechal and Gailly 1999; Bredt 1999; Moroz 2000; Liaudet et al. 2000; Prast and Philippu 2001). NO is produced from the amino acid L-arginine and converted to L-citrulline by calcium/calmodulin activated nitric oxide synthase (NOS) and various cofactors. Important features of NO in its biological action are its high membrane permeability and its short half-life of a few seconds. Major targets of NO are other radicals, metal containing proteins (ferrous heme in enzymes, i.e., in guanylate cyclase, GC), thiols (sulfhydryl groups in proteins, L-cysteine), or oxygen. NO acts on ion channels either by direct S-nitrosylation of the channel protein, or by activation of the cyclic guanosine monophosphate (cGMP) protein pathway, or both, which eventually results in conformational changes of the channel leading to changes in current flow. For the nitrosylation process, hydrophobic pockets within proteins may target NO (or its higher oxide N_2O_3) to cysteine moieties (Nedospasov et al. 2000). In general, reducing agents appear to mimic the effects of NO (increase channel activity) while oxidizing agents have the opposite effect (decrease channel activity). NO was shown to activate BK channels by cGMP-dependent (Robertson et al. 1993; Archer et al. 1994; Carrier et al. 1997; Lu et al. 1998; Nara et al. 2000) and cGMP-independent (Bolotina et al. 1994; Shin et al. 1997; Abderrahmane et al. 1998; Mistry and Garland 1998; Lang et al. 2000) mechanisms, and to enhance BK channel activity independently of voltage and calcium (Ahern et al. 1999). The latter result raises the possibility of NO activating BK channels independently of nerve stimulation. On the other hand, NO has also been reported to depress BK currents (Erdemli and Krnjevic 1995; Zsombok et al. 2000), leading to increased neuronal excitability. Another gaseous messenger, CO, has been shown to increase BK channel activity in a cGMP-independent manner in smooth muscle (Wang et al. 1997; Kaide et al. 2001). Finally, it is interesting to note that sildenafil, the active compound in Viagra, may influence synaptic transmission by modulating the activity of presynaptic BK channels (Medina et al. 2000).

What is the biological significance of the action of NO on BK channels? An increase of potassium current by NO, as reported in most cases, is likely to suppress nerve or muscle excitability, thereby decreasing action potential duration and firing rate. Since calcium activated potassium channels are often concentrated in neuronal cell bodies and nerve terminals (Knaus et al. 1996), NO may modify membrane excitability at strategically important sites.

Phosphorylation of BK channels: a mechanism for dynamic modulation

Protein phosphorylation by a number of different protein kinases is a ubiquitous mechanism for modulating the physiological activity of proteins (Cohen 1988). Phosphorylation of ion channels is a widespread modulatory mechanism that has been thoroughly investigated (for reviews see Kaczmarek 1988; Shearman et al. 1989; Levitan 1994, 1999; Catterall 2000). It is clear, from measurements carried out on purified BK channels, or on BK channels reconstituted in phospholipid bilayers, that the phosphorylatable modulatory site is either part of the ion channel protein itself or is located on some regulatory component that is intimately associated with the ion channel protein (Ewald et al.1985; Reinhart et al. 1991). In some cases, BK channel modulation has been shown to be associated with dephosphorylation by phosphoprotein phosphatases (White et al. 1991; Shipston and Armstrong 1996; Hall and Armstrong 2000; Shipston et al. 1999; Smith and Ashford 2000). There are multiple phosphorylation sites in BK channels, that may be phosphorylated by different protein kinases. The channel activity may be increased or decreased by phosphorylation, depending on the particular protein kinase involved and the specific site or combination of sites that is phosphorylated. A general theme is that most and perhaps all ion channels are modulated by protein phosphorylation/dephosphorylation, but the precise molecular mechanism and the physiological outcome may differ from channel to channel, and even for the same channel under different conditions.

At least one type of BK channel reconstituted from rat brain in an artificial bilayer was shown to be modulated by the application of adenosine triphosphate (ATP) or adenosine 5'-O-(3-thiotriphosphate) (ATPγS) in the absence of any exogenous protein kinase, indicating phosphorylation by a protein kinase activity that remains closely associated with the channel (Chung et al. 1991). Subsequent experiments have indeed demonstrated the direct binding of several different protein kinases directly to BK channels (Wang et al. 1999). As we shall discuss below, not only protein kinases but a variety of other signaling proteins have been shown to bind directly to different kinds of ion channel proteins. An emerging concept is that many ion channels exist in the membrane simply as one component of a dynamic signaling protein complex, that includes the ion channel protein itself together with one or more other proteins that contribute to the regulation of channel activity.

Alcohol excites BK channels

During the last decade it has become clear that ethanol acts on ion channels not only by disturbing the lipid phase of the membrane, but also interacts with and modulates some channels directly. BK channels are among those channels modulated directly by ethanol. By recording single channel currents it was shown that ethanol at pharmacological concentrations activates BK channels, with an EC_{50} of 24–65 mmol l^{-1} (equivalent to 1.1–3.0 promille) (Jakab et al. 1997; Dopico et al. 1996, 1998, 1999). Experiments with cloned channels in oocytes (Dopico et al.1998) indicate that an auxiliary subunit is not required for the action of ethanol. By opening BK channels, ethanol will hyperpolarize the cell thereby suppressing the calcium triggered release of hormones or neurotransmitters. For a recent review on ethanol and BK channels see Dopico et al. (1999).

The BK channel is not a lonely channel: auxiliary proteins that bind to the channel modulate its properties

The early picture of an ion channel sitting on its own in the plasma membrane has changed dramatically over the last several years. It is now clear that ion channels can bind tightly to a number of partner proteins, that in turn modulate the channel's properties. The amino terminal as well as the long carboxyl tail domain of BK channels have been found to be attractive sites for binding partners. For example, two novel proteins that bind to and modulate dSlo have been identified by a yeast two-hybrid screen, using either part (Xia et al. 1998) or all (Schopperle et al. 1998) of the tail domain as the "bait". One of these proteins, named Slob (for slo-binding), activates dSlo channel activity by shifting its voltage dependence of activation to the left (Schopperle et al. 1998). In addition, the binding of another protein named 14–3-3 to Slob changes the picture completely, by shifting the voltage dependence of activation to the right, thereby making it more difficult to open the channel (Zhou et al. 1999). The interaction of 14–3-3 with Slob is regulated by the phosphorylation of two specific serine residues in Slob, by the type II calcium/calmodulin-dependent protein kinase, and hence the modulation of channel activity by these binding partners is itself under dynamic control (Zhou et al. 1999).

Although the pore-forming α subunits of calcium-activated potassium channels can form functional channels when expressed alone, they may often be associated with auxiliary subunits in native tissue. For example, purified BK channels from smooth muscle tissue consist of an α subunit and a 25-kDa protein that was termed a β subunit (Garcia-Calvo et al. 1994). When this first discovered $\beta 1$ subunit is coexpressed with the α subunit, it shifts the voltage dependence of activation to the left, thereby making the channel more sensitive to voltage (Knaus et al. 1994). $\beta 1$ can also influence modulation of the channel by protein kinases, and alter toxin binding to the channel protein (McManus et al. 1995; Dworetzky et al. 1996; Tseng-Crank et al. 1996). Although the α subunits of BK channels are known to form functional tetramers, there is as yet no information available about the α-β stoichiometry in native cells. In addition, it is not yet known whether the β subunits are constitutively associated with the α subunits, or whether their interaction is subject to dynamic regulation.

β subunits of the $\beta 1$ type have now been cloned from many sources. They consist of roughly 200 amino acids with two transmembrane regions and a large extracellular loop (Fig. 1). All $\beta 1$ subunits possess four conserved cysteines in the extracellular loop, as well as two N-linked glycosylation sites. They are expressed predominantly in peripheral tissues, to a very limited extent in brain, and not at all in endothelial cells (Tseng-Crank et al. 1996; Papassotiriou et al. 2000). In contrast to other BK channel binding proteins, β subunits are functionally coupled to the amino terminal of the channel protein (Wallner et al. 1996). More recently another β subunit type that confers rapid inactivation on BK channels has been identified (Wallner et al. 1999; Xia et al. 1999). This $\beta 2$ subunit exhibits 45% amino acid identity with $\beta 1$, and has a similar membrane topology. It is expressed mainly in chromaffin cells and some hippocampal neurons. Another related β subunit, $\beta 3$, is highly enriched in testis (Brenner et al. 2000b).

Using a biochemical approach, Wanner et al. (1999) purified a 25-kDa protein tightly bound to BK channels isolated from brain, providing the first evidence for a brain specific β subunit. In 2000 four groups independently cloned and characterized a nervous system specific $\beta 4$ subunit from mouse and human (Brenner et al. 2000b; Weiger et al. 2000; Meera et al. 2000; Behrens et al. 2000). $\beta 4$ is only very distantly related in amino acid sequence to the other β subunits, but its predicted membrane topology is similar, with two membrane-spanning domains and a large extracellular loop. $\beta 4$ binds tightly to the α subunit of BK channels, and colocalizes strikingly with the α subunit in brain (Weiger et al. 2000). $\beta 4$ modulates the voltage dependence of channel activation, and protects the channel from its interaction with classical BK channel blockers like charybdotoxin or iberiotoxin by slowing the association rate dramatically (Brenner et al. 2000b; Weiger et al. 2000; Meera et al. 2000; Behrens et al. 2000). It is interesting that, in an earlier functional study of BK channels from rat brain, both toxin-sensitive and toxin-insensitive varieties of BK channel were reported (Reinhart et al. 1989).

Conclusions

From the data reviewed here, it is evident that calcium-activated potassium channels are key integrators in many biological systems. Their activity can be modu-

lated over a very wide range by multiple and highly diverse mechanisms. The challenge for the future is to understand the roles these multiple mechanisms play in the physiological regulation of cellular excitability.

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