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Potassium Channels

Basic Aspects, Functional Roles, and Medical Significance

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OUR knowledge of the physiology of ion channels has increased tremendously during the past 15 years, largely because of two major technical advances: (1) single-channel recording techniques, which have permitted the measurement of currents from individual ion channels in a variety of tissues, and (2) molecular cloning, which provides sequence information about the structural composition of the proteins comprising ion channels. Together, these techniques and the availability of cloned receptors have significantly advanced our understanding of the manifold function of ion channels that selectively allow the movement of potassium ions (K^+) across the cell membrane and that are essential for regulating excitability of tissues. This review will explore for anesthesiologists, who routinely regulate the perioperative functioning of excitable tissues such as the heart and nervous system, how this new information may influence the clinical practice of anesthesia.

Electrophysiologists have known for many years that there were specialized membrane structures that allow the selective movement of sodium and potassium across the membrane. The first detailed analysis of this process appeared in Hodgkin and Huxley's classic investigations into the components of the squid giant axon action potential in the late 1940s and early 1950s. These studies recognized the importance of the movement of K^+ out of the cell to produce rapid repolarization of the cell membrane after a depolarizing spike. They also identified a "leakage" current, a component of which was a result of the passage of K^+, that draws the membrane potential toward the equilibrium potential for K^+ (~ -90 mV in most cells). The discovery of compounds such as the organic cation tetraethylammonium (TEA^+) and barium ions that block K^+ currents in neural and cardiac tissues further characterized these currents.[1]

A dramatic advance occurred in the mid-1980s when molecular cloning techniques isolated a DNA sequence specifying a potassium channel (K channel) from the common fruit fly, *Drosophila melanogaster*. Interestingly, these scientists had begun by searching for the molecular basis of an unusual response to volatile anesthetics: exposure of certain mutant fruit flies to anesthetizing concentrations of diethyl ether led to spasms of leg movement, *i.e.*, the *Shaker* phenotype. A mutation within a single protein proved to be the basis of the phenotype. Ultimately this protein was determined to be a subunit of a voltage-activated, K^+-selective channel.[2] Since that initial discovery, the pace of cloning has continued. There are now more than 50 different identified K channels, organized into four main families (to be discussed). It is estimated that there are more to be discovered.[3]

Beyond the increase in specific information about K channels at the cellular and molecular levels, there is an emerging awareness of the potential for pharmacologic and potentially therapeutic manipulation of K channels. This review will survey the field of K channels, describe their structures, explain their crucial role in the physiologic function of excitable tissues, and discuss the emerging understanding of their clinical influence.

Molecular Structure of K Channels

Molecular biological techniques have been successful in producing detailed information about the amino acid

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sequences that comprise ion channel proteins. Cloning the DNA sequence that codes for a new ion channel usually proceeds either from knowledge of its protein sequence or by following its specific electrophysiologic function in a functional assay to identify the specific gene. Electrophysiologists have been instrumental in this process by first identifying a specific current in a particular cell of which a new cloned sequence may be the source.

Once a full-length clone has been identified, one of the main endeavors that follows is to understand how the discovered sequence relates to other known channels and which sequences give rise to specific functions. What has emerged from this analysis of cloned K channels is a picture of both interrelatedness and diversity.

Motifs or Structural Domains Found in Voltage-gated K Channels

Cloning of the *Shaker* channel provided the first opportunity to analyze the primary amino acid sequence of a K channel. At the same time, other investigators were cloning voltage-gated sodium (Na) and calcium (Ca) channels,[4,5] and it immediately became clear that the fundamental structures of all these channels were closely related. Voltage-gated Na or Ca channel proteins are comprised of a large continuous sequence that codes for four repeated elements, each of which are homologous to one *Shaker* protein (fig. 1A). A single one of these structural elements is believed to span the membrane six times (fig. 1B). It is now firmly established that four *Shaker* proteins are needed to assemble a functional voltage-gated K channel (K_V),[6] thus producing a structure similar to voltage-gated Na and Ca channels, one that has been broken up into subunits.

The genes coding for voltage-gated K channels are present not only in *Drosophila* but also in mammals, and they are recognizable as K channels by possessing a conserved signature amino acid sequence. This structure, called the "H5" or "pore" domain, is found in all K channels cloned to date and is thought to create the lining of the ion-conducting pathway. Experiments making specific mutations in this pore-forming sequence have established that it is essential for the potassium selectivity of the channel and for binding the K channel blocker TEA^+.[7] Therefore, finding this signature sequence identifies a new clone as a K channel.

Another conserved feature is found in the fourth membrane spanning segment (S4). Found in all voltage-gated ion channels, including Na and Ca channels, S4 domains contain positively charged amino acid residues, allowing

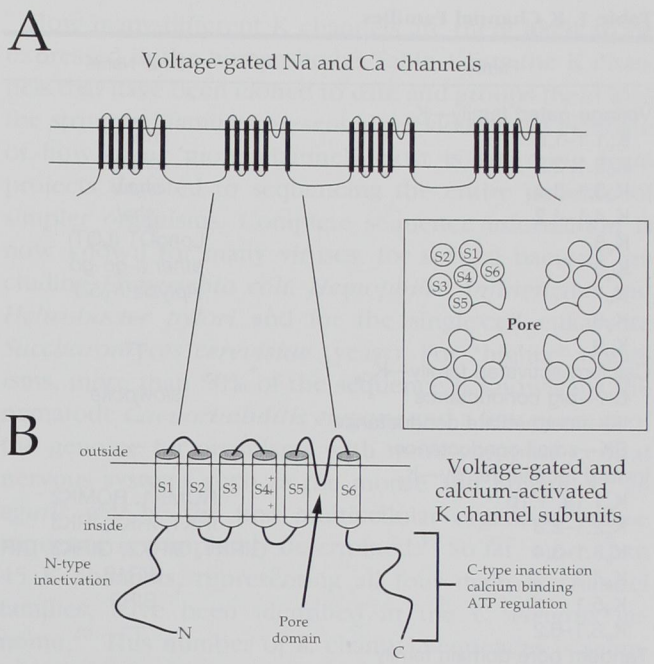

Fig. 1. Conserved structure of K channels. The primary amino acid sequences of voltage-gated Na and Ca channels (*A*) display a repeated domain structure homologous to individual voltage-gated K channel subunits (*B*). The cylindrical segments of the amino acid chain represent alpha-helical transmembrane components of the channel protein structure. The pore or H5 domain is a highly conserved feature in all K channels that occur between two conserved transmembrane segments (S5 and S6). Voltage-gated subunits also have four other membrane-spanning domains that sense changes in membrane potential (primarily the charged residues in S4). Amino (N)- and carboxy (C)-termini contribute to inactivation and modulation by small molecules (Ca^{++} and ATP). Inset: view from above the plane of the membrane (extracellular side) depicting how four K channel subunits may be arranged to form a central pore and how the six transmembrane segments of each subunit are packed. Structural model as per Durell and Guy.[103]

them to participate in "sensing" changes in membrane potential. The charged amino acids change orientation during membrane depolarization to open the ion-conducting pathway. The movement of these charged residues can even be measured as tiny gating currents.

Since the cloning of *Shaker*, more genes coding for a diversity of voltage-gated K channel subunits have been isolated. They have been grouped into four subfamilies based on similarity of their amino acids sequences and on whether they will coassemble with other subunits (table 1). For example, all of the members of the *shaker* subfamily have more than 60% of their primary amino acid sequence identical with other *shaker* subunits; although compared with members of the *shab* subfamily, *shaker* members are only about 40% homologous. Furthermore, *shaker* subunits cannot combine with *shab*

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Table 1. K Channel Families

Family	Other Name
Voltage-gated family—K_V	
K_V1.1–1.8	*shaker*
K_V2.1–2.2	*shab*
K_V3.1–3.4	*shaw*
K_V4.1–4.2	*shal*
K_V5	LongQT (LQT)
K_V6	*ether a-go-go*
K_V7	*Aplysia* K_V*5.1*
K_V8	—
K_V9	—
Calcium-activated family—K_{Ca}	
BK—big conductance	*slowpoke*
IK—intermediate conductance	—
SK—small conductance	—
Inward rectifier family—K_{ir}	
K_{ir}1.1a, 1.1b	ROMK1, ROMK2
K_{ir}2.1–2.3	IRK1, IRK2, IRK3
K_{ir}3.1–3.4	GIRK1, GIRK2, GIRK3, CIR
K_{ir}4.1	BIR10
K_{ir}5.1	BIR9
K_{ir}6.1–6.2	—
Tandem pore domain family	
TWIK-1	—
TREK-1	—
TASK	—
TRAAK	—

Left column lists cloned channels or identified currents that are members of each of the four structural classes of K channels. Right column gives alternative names either for the *Drosophila* channel or that may have appeared in the literature before the standardization of nomenclature. The tandem pore domain family has been identified too recently for standardization.

ROMK = rat outer medullary (kidney) K channel; IRK = inward rectifier K channel; GIRK = G protein-coupled inward rectifier; CIR = cardiac inward rectifier; BIR = β cell inward rectifier; TWIK = tandem pore weak inward rectifier K channel; TREK = TWIK-1 related K channel; TASK = TWIK-1 related acid-sensitive K channel; TRAAK = TWIK-1 related arachidonic acid stimulated K channel.

subunits (nor with *shaw* or *shal* subfamily members) to produce functional ion channels.

In recent years, investigators have also discovered other protein sequences without homology to voltage-gated subunits, yet can be shown to coassemble with them and modulate their function. When authentic K channels are purified from mammalian brain, large molecular complexes (molecular weight, approximately 400 kd) are isolated. These macromolecular complexes were shown to comprise eight individual proteins, representing four copies of two distinct protein types.[8] Four voltage-gated K channel subunits (α subunits) were found to be associated with four copies of a new protein termed β subunits. Subsequent cloning of the genes for β1, β2, and β3 subunits revealed novel sequences for these hydrophilic proteins without homology to other K channels. Coexpression of β1 with *Shaker* subfamily α subunits appears to alter their function by accelerating the inactivation of the K^+ current.

Other K Channel Families

Ca^{++}-activated K Channels (K_{Ca}) Are Structurally Similar to Voltage-gated K Channels. Electrophysiologists in the 1960s identified K currents in several tissues that not only were voltage-activated but whose open probability was also governed by intracellular Ca^{++} concentrations. These currents are found in neurons, muscle, and secretory cells in vertebrates and are potently inhibited by charybdotoxin, a toxin isolated from scorpion venom. The loss of this Ca^{++}-activated current in *Drosophila* muscle gives rise to the *slowpoke* phenotype.[9] When the gene coding for this channel was cloned, its structure was found to have many elements in common with the *Shaker*-type subunits, including the H5 and S4 domains; but in addition, this sequence also coded for a long extension at the carboxy-terminal end of the protein that is presumed to function in sensing Ca^{++} levels or for modulation by other small molecules (fig. 1B). The relationship of these channels to each other has become clearer with the new information coming from genome sequencing projects (to be discussed).

Inward Rectifying K Channels. Another K channel family, the inward rectifiers (K_{ir}), can be thought of as a "functional fragment" of a voltage-gated type channel (fig. 2A, left). Here, the conserved pore domain links two transmembrane sequences.[10] These membrane-spanning sequences are the only ones present in an inward rectifier sequence and are homologous to the S5 and S6 transmembrane segments of *Shaker*. Inward rectifiers have unique electrophysiologic properties (to be discussed) that make them essential in many tissues for stabilizing the membrane potential.

A model of how an inward rectifier K channel assembles within the cell membrane is shown in figure 2B. The transmembrane segments (M1 and M2) are responsible for maintaining integration of the protein within the hydrophobic environment of the lipid membrane, whereas the H5 region is thought to form a funnel or "inverted tepee" -type structure[11] and mediates passage of K^+ ions selectively. Inward rectifier K channels are subject to blockade from the inside by magnesium (Mg^{++}) ions and by polyamine compounds, such as spermine and spermidine, which causes the channel to act like a one-way street, letting K^+ ions into the cell freely but limiting exit (see discussion of *Rectification*).

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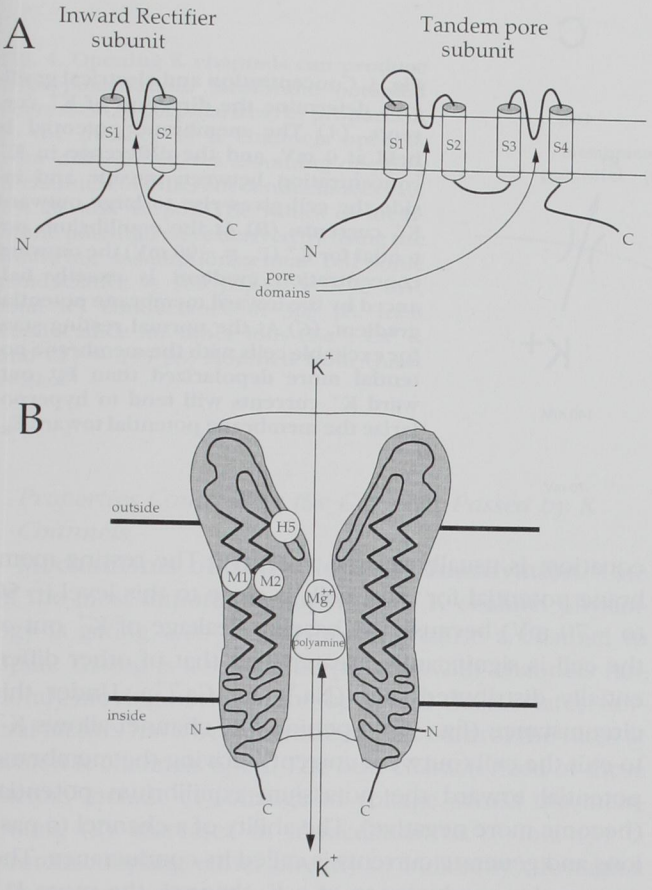

Fig. 2. Transmembrane topology of inward rectifier (*left*) and tandem pore domain (*right*) K channels. At bottom is shown a cut-away section of a model of an inward rectifier K channel displaying the putative relation of the pore-lining (H5) domain with adjoining transmembrane segments. Magnesium ions and polyamines block outward K currents from the intracellular side of the ion channel.

Tandem Pore Domain K Channels. The most recent addition to the families of K channels has been a group whose existence has only emerged in the past 3 years. The prototypic K channel of this type was found first in common baker's yeast (TOK1) and was immediately recognized as being unique because it contained two pore or H5 sequences in tandem in its primary amino acid sequence.[12] A model of how tandem pore K channels are aligned with respect to the plasma membrane is shown on the right of figure 2A. Since TOK1 was first described, four mammalian (TWIK-1, TREK-1, TASK, and TRAAK) and one *Drosophila* (ORK1) tandem pore K channels have been isolated.[13–18] It appears that these channels are responsible for baseline or leak currents and that they may be the most numerous of all K channels.

How many different K channels are there likely to be expressed in the human body? Table 1 lists the K channels that have been cloned to date and groups them into the structural families presented previously. An estimate of how many more channels exist is emerging from projects devoted to sequencing the entire genome of simpler organisms. Complete sequence information is now known for many viruses, for several bacteria, including *Escherichia coli*, *Hemophilus influenzae*, and *Helicobacter pylori* and for the single-cell eukaryote *Saccharomyces cerevisiae* (yeast). For "higher" organisms, more than 50% of the sequence is known for the nematode *Caenorhabditis elegans* and a few percent of the genome for organisms with more complex central nervous systems such as the mouse and human. *C. elegans* will be the first multicellular organism whose sequence is completely determined.[19] So far, more than 45 K channels, representing all four main K channel families, have been identified in the *C. elegans* genome.[20] This number of K channel sequences is seemingly disproportionate as the *C. elegans* nervous system is so simple (308 neurons total). The tandem pore domain group is the largest, with more than half of the K channels identified as being of this type. Because there are many nematode genes that have direct homologues in higher organisms,[21–23] there are expectations that the full panoply of *C. elegans* K channels, if not more, will also be represented in more complex nervous systems. To understand their roles in the function of excitable tissues, we next turn to consider their basic electrophysiologic behavior.

Electrophysiologic Basis of K Channel Function

Basic Mechanisms

The way in which K channels help stabilize the excitability of tissues relies on several key electrophysiologic concepts. Briefly, the resting membrane potential for a given cell is a function of the differential distribution of the most abundant common ions (Na^+, K^+ and Cl^-) between the inside and the outside of the cell. This differential distribution is maintained primarily by energy-consuming ion transporters such as Na^+/K^+ ATPase.

A living cell exists with a high concentration of potassium on the inside and a low concentration on the outside. Potassium moves rapidly and selectively across the membrane through ion channels, with the net movement of ions being determined by two forces, the *con-*

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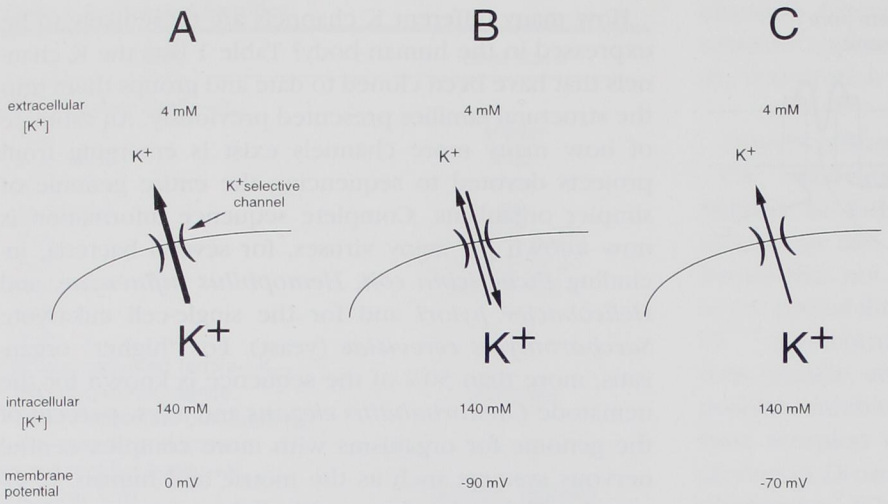

Fig. 3. Concentration and electrical gradients determine the direction of K^+ currents. (*A*) The membrane potential is held at 0 mV, and the difference in K^+ concentration between outside and inside the cell gives rise to large outward K^+ currents. (*B*) At the equilibrium potential for K^+ ($E_K = -90$ mV) the outward concentration gradient is exactly balanced by the inward membrane potential gradient. (*C*) At the normal resting state for excitable cells with the membrane potential more depolarized than E_K, outward K^+ currents will tend to hyperpolarize the membrane potential toward E_K.

centration gradient and the *electrical* gradient. We can examine the influence of these gradients by artificially changing the cell's membrane potential, as is done experimentally with a whole cell voltage clamp apparatus. If the electrical force was eliminated by holding the membrane potential at zero and then a K^+ selective ion channel was opened (fig. 3A) so that K^+ could pass into or out of the cell equally well, potassium would diffuse out of the cell following its concentration gradient, from a high intracellular K^+ concentration to low extracellular K^+ concentration. This flow of current normally causes a change in membrane potential, but the voltage clamp apparatus compensates for this flow of ion by injecting current of opposite polarity (positive or negative ions as need be), holding the membrane potential at the set level.

However, in a normal cell with no voltage clamp applied, the outward flow of K^+ would cause a relative deficiency of positive charges at the inside of the cell membrane, generating a negative potential across the membrane. Potassium ions would continue to pass through the K^+ selective channels until the inside of the cell membrane became so negative that the electrostatic attraction for positively charged K^+ ion was equal to the force moving the ion down its concentration gradient (fig. 3B). At this point we have reached the equilibrium potential for potassium (E_K)—the balance point for the concentration and electrical forces—where no net movement of K^+ occurs in either direction through open K^+ selective ion channels.

Given the 20- to 40-fold difference in K^+ concentration that exists between the two sides of the membrane, the equilibrium potential for K^+, calculated from the Nernst equation, is usually around -90 mV. The resting membrane potential for most cells is close to this level (-50 to -70 mV) because the baseline leakage of K^+ out of the cell is significantly greater than that of other differentially distributed ions (Na^+ and Ca^{++}). Under this circumstance (fig. 3C), opening a K channel allows K^+ to exit the cell (outward current), driving the membrane potential toward the potassium equilibrium potential (become more negative). The ability of a channel to pass ions and generate currents is called its conductance. The greater the conductance of a K channel, the more K^+ ions can pass through the channel per unit time. Conductance, the reciprocal of resistance, is measured in siemens, and the small conductances of ion channels are measured in picosiemens (pS). As an example, a 1-pS conductor to which a 100-mV electrical potential is applied passes approximately 625 ions in 1 ms.

The efficiency of potassium channel opening as a regulator of membrane potential is striking. Based on some reasonable assumptions about a particular cell, the number of K channels of a given conductance that need to be opened to generate significant hyperpolarization can be estimated (fig. 4). Beginning from a resting potential of -55 mV, which is for example the resting potential of an atrial cell of the heart, opening as few as 20 K channels can produce hyperpolarization of 10–20 mV. By taking the membrane potential away from the threshold needed for action potential activation or the opening of Ca^{++} channels, hyperpolarization tends to decrease excitability. Any drug or modulator that increases the opening a particular K channel can greatly reduce excitability of the tissue expressing that channel.

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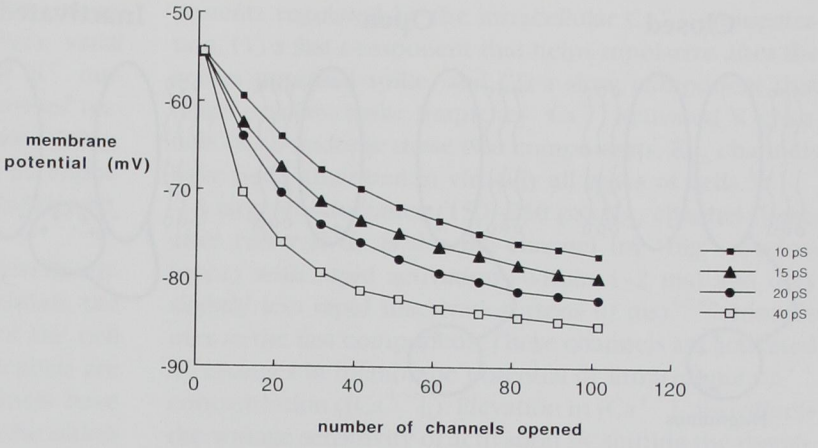

Fig. 4. Opening K channels can produce hyperpolarization. Membrane potential decreases (hyperpolarizes) in proportion to the number of K channels opened. Four different curves assuming opening K channels of different conductances (10, 15, 20, and 40 pS). The values of membrane potential were derived by using the following assumptions: total cell ionic conductance = 500 pS, E_K = −90 mV, total K^+ conductance of 305 pS, total conductance for other ions (Na^+, Ca^{++}, and Cl^-) = 195 pS. Modified from Quast *et al.*[104]

Properties Controlling the Currents Passed by K Channels

Mechanisms of Activation and Inactivation. One of the most important properties of K channel physiology is gating, *i.e.*, the factors that cause a channel to open. Gating is a stochastic process with channels randomly moving between the open and closed states. Several factors have been identified that control the rates at which K channels open. The best characterized of these factors include (1) change in voltage across the membrane, (2) increases in intracellular Ca^{++} ion, (3) G protein-coupling either directly or indirectly (through a change in intracellular second messenger), and (4) change in intracellular ATP concentration. The opening of some K channels, known as background or leak channels, is not strongly regulated by these factors, and so their ability to conduct K^+ is determined by their rectification properties, *i.e.*, the property of electrical systems to pass current in one direction better than the other.

The molecular basis of activation is best characterized for the voltage-gated channels. On depolarization of the cell membrane, the original *Shaker* channel produces a rapidly activating and rapidly inactivating K^+ current, *i.e.*, the channel is completely open within 1 ms and closes again within 10 ms. Each type of voltage-gated K channel has a particular threshold voltage at which the frequency of channel opening rapidly increases. Precisely defined regions of these proteins mediate these functions. All voltage-gated K channels share a particular membrane-spanning domain (S4) that has a series of positively charged amino acid residues (typically arginine) lying along one face of the alpha-helical structure. A change in the membrane potential, sensed by this molecular structure, causes movement of these charges within the structure of the protein. This molecular rearrangement is thought to induce a conformational change transmitted to the ion-conducting pathway, allowing potassium ions to pass through the membrane. Relatives of the *Shaker* channel reach full opening more slowly, over a period of 2–300 ms. They also may differ in the threshold at which opening occurs. Associated β subunits are also important in determining the activation threshold. All of the structural determinants producing this diversity of K channel behavior are not completely known.

The mechanisms that cause inactivation of voltage-gated K channels are distinct from those that produce activation. Two types of inactivation, which differ in terms of the speed of onset, have been described. Rapid inactivation (N-type inactivation), as with *Shaker* K channels, occurs through the interaction of the amino (N)-terminal end of the ion channel protein with the ion-conducting pore. The N-terminus assumes the structure of a ball at the end of a tether (fig. 5). A surface of charged amino acid side chains is believed to assemble along one face of the ball. The tethered ball serves to block the open state of the channel from the cytoplasmic side; the physical occlusion of the pore prevents any further ion flux.[24] With the charged surface of the inactivation particle wedged into the inner side of the ion-conducting pore, they are subject to the electrical field of the membrane. As the membrane recharges, the ball moves away from the pore opening, and the blockade is relieved. Slow inactivation (C-type inactivation) occurs through features found in the carboxyl terminus and may involve protein rearrangement, leading to narrowing of the mouth of the pore.[25]

Rectification. Rectification is an important property of K channels, one that is crucial for understanding how they influence the electrophysiologic behavior of cells.

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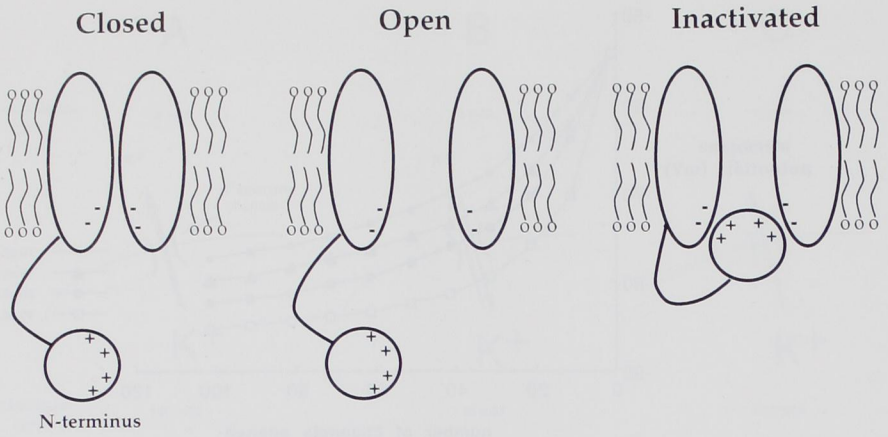

Fig. 5. Inactivation of voltage-gated K channels. Channels undergo a conformational change induced by membrane depolarization to open the ion-conducting pathway. The open probability increases steeply over a narrow range of membrane potentials that is characteristic for each K channel subtype. After activation, some types of voltage-gated K channels rapidly inactivate. N-type inactivation occurs through the interaction of the amino (N)-terminus of the channel with the channel pore. A "ball-and-chain" model best describes how N-type inactivation occurs. N-type inactivation must be relieved before currents can flow through an open channel again.

Most simply, rectification describes the ability of an ion-conducting pore to pass ions through the cell membrane more easily in one direction than the other. For K channels, inward rectification means that at any given driving force caused by voltage, the inward flow of K^+ ions is greater than the outward flow with the opposite driving force. This effect is shown most effectively in terms of the current–voltage (I-V) relation for a given type of K channel. The relationship between the current passed through a channel over a range of transmembrane potentials can be recorded in a membrane patch as the membrane potential is changed continuously over a large range of potentials. Currents that are not markedly time- or voltage-dependent can be studied effectively in this way, giving a signature I-V curve.

Figure 6A shows the I-V curves obtained for inward rectifier K channels in myocardial tissues. The data represent single channel currents recorded from these channels with three different external K^+ concentrations. As predicted by the Nernst equation, the reversal potential (the point at which the curves cross the *x* axis) becomes less negative as the K^+ concentration increases. At potentials below the reversal potential, the curves display a steeply linear relationship, indicating strong inward rectification. Above a membrane potential of around −40mV, inward rectifiers are blocked from the inside in a voltage-dependent manner by positively charged substances (Mg^{++} and polyamines), and little or no outward K^+ current can be passed. In the range of membrane potential near the action potential threshold, between the reversal potential and -40mV, inward rectifiers are able to pass small outward currents.

These outward currents (known as the region of negative slope conductance) are extremely important for understanding how action potentials are generated. In-

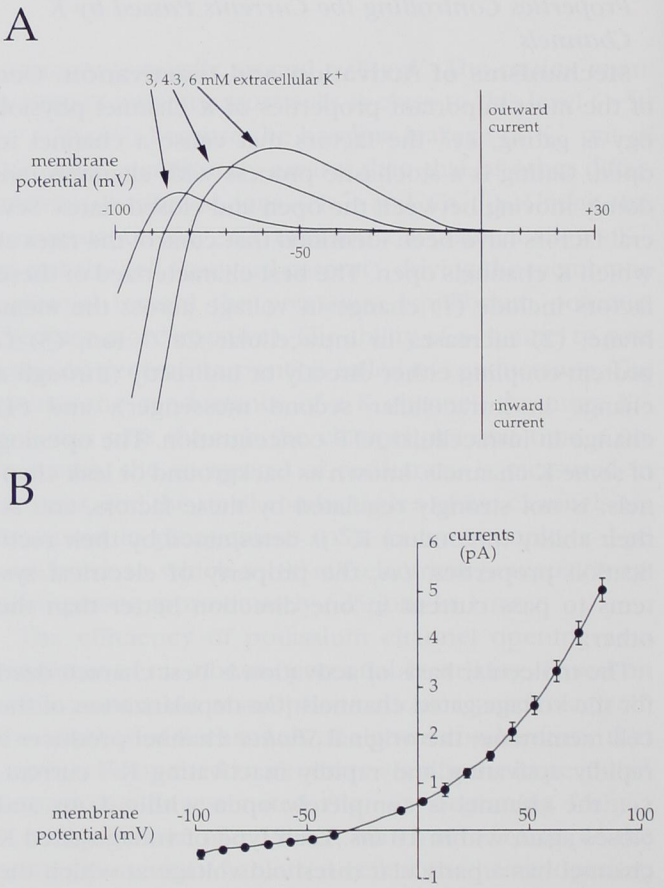

Fig. 6. Rectification. Current (pA = picoamperes) *versus* voltage (mV = millivolts) relation for inwardly (*A*) or outwardly (*B*) rectifying K channels. Data represent single K channel current for the strong inward rectifier in heart (modified from Lynch[105]) and strong outward rectifier TASK.[16] TASK currents were recorded from outside-out patches 150 mM K^+ in the recording pipette and 150 mM NaCl in the bath. TASK currents are fit with a third degree polynomial function indicating outward rectification greater than that predicted from the Goldman-Hodgkin-Katz equation.

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ward rectifiers pass currents only in a narrow range, around the resting membrane potential, where small depolarizations are resisted by the outward K^+ currents.[26] If a depolarization is large enough, inward rectifiers become blocked, allowing action potential firing. Thus, channels with these characteristics play an important role in setting the membrane potential and regulating overall excitability.[27]

In contrast, outward rectifiers display a different current–voltage relation (fig. 6B). At positive potentials, the currents representing movement of K^+ out of the cell are large, whereas those seen at negative potentials are negligible. Thus outwardly rectifying K channels have greatest influence during the positive phase of the action potential, tending to repolarize the membrane back toward the normally negative resting potential by passing large outward currents. Pure outwardly rectifying K channels have been described in a variety of tissues, including guinea pig ventricular myocytes, rat dorsal root ganglia, and molluscan neurons.[28–30] These currents should not be confused with K channels that have been called delayed rectifiers; these are voltage-gated K channels that show a delayed onset of activation and represent an extreme example of outward rectification caused by the channel opening with depolarization. The example of an outward rectifier shown in figure 6B is the tandem pore domain K channel, TASK. It is known that the messenger RNA coding for this protein is found in heart tissue, and it is reasonable to speculate that currents observed during the plateau phase of ventricular myocyte depolarization may be caused by the action of this channel.

Rectification therefore may be the result of a unidirectional channel blockade by endogenous compounds such as Mg^{++} ions or polyamines, but it may also result from the specific ion channel protein structure, although little has been defined in terms of structural determinants that give rise to rectification. Progress in understanding this aspect of K channel function will require greater resolution of the three-dimensional structure of individual K channels to illuminate portions that can both sense the voltage field and restrict ion flow.

Intracellular Regulation by Small Molecules—Ca^{++} and ATP. The opening of some voltage-gated K channels is also sensitive to changes in the intracellular Ca^{++} concentration. For example, action potential spikes in vertebrate neurons may activate voltage-dependent Ca channels that rapidly increase the intracellular Ca^{++} concentration. In many cells an afterhyperpolarization follows that can be broken down into two components regulated by the intracellular Ca^{++} concentration: (1) a fast component that helps repolarize after the action potential spike, and (2) a slow component that helps regulate spike frequency. Ca^{++}-activated K channels (K_{Ca}) underlie these two components. K_{Ca} channels have been identified in virtually all types of cells.[31]

A large conductance (150–250 pS) K_{Ca} channel (hereafter referred to as the BK channel for "big" conductance) with rapid activation (within 1–2 ms) and only slightly less rapid inactivation (tens of ms)[32,33] contributes to the fast component. These channels are activated by changes in membrane potential or intracellular Ca^{++} concentration ($[Ca^{++}]_i$). Elevation in $[Ca^{++}]_i$ also affects the voltage sensitivity of activation by shifting the threshold to more negative membrane potentials.[34] The apparent role of BK channels is to activate quickly and, by passing large outward K^+ currents, rapidly calm excitable tissues that have been depolarized or that have elevated $[Ca^{++}]_i$.

The slow component of the afterhyperpolarization represents the action of a smaller conductance (10–14 pS) Ca^{++}-activated K channel, the SK channel for "small" conductance.[32,34] In contrast to the BK channel, this recently cloned sequence found in the mammalian brain and heart activates slowly (10–1,000 ms) and decays in seconds. Thus, this channel appears to be the second line of defense for an excitable cell against overexcitability. This mechanism can be seen as a way to restrain Ca^{++} entry (by preventing depolarization and activation of voltage-gated Ca channels), thereby limiting potentially damaging increases in intracellular Ca^{++}. A third type of K_{Ca} channel with intermediate conductance (IK; 18–50 pS) has also been described in some tissues.[35]

Because BK and SK channels are activated by changes in $[Ca^{++}]_i$, why do they differ in their rates of activation? Evidence has accumulated recently that this difference may be understood by realizing that changes in $[Ca^{++}]_i$ do not occur uniformly throughout the cell. BK channels may be localized near voltage-gated Ca^{++} channels that cause rapid elevation in $[Ca^{++}]_i$ termed calcium sparks.[36] In contrast, SK channels may be compartmentalized to areas of the cell where changes in $[Ca^{++}]_i$ occur less rapidly.

Another ubiquitous group of K channels, found in the heart, pancreas, smooth muscle, and central nervous system, are sensitive to changes in intracellular ATP (K_{ATP} channels, recently reviewed by Kersten *et al.*[37]). They sense the metabolic state of the cell, inhibited by ATP when energy supply is abundant and activated

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when energy stores deplete. Recent molecular biology advances have shed light on the composition of functional K_{ATP} channels, which appear to be a complex of a K_{ir} channel with another large modulatory protein, the sulphonylurea receptor (to be discussed).

By having the regulation of K channels linked to these small molecules, the excitability of cells is tied to their functional state. This linkage is important for overall cellular efficiency. For example, when energy stores are low (reduced ATP levels), activation of K_{ATP} channels hyperpolarizes the membrane potential toward the potassium equilibrium potential, thereby reducing the energy-intensive work of ion pumps restoring ion gradients after action potential discharges. Similarly, an increase in $[Ca^{++}]_i$, which can stimulate a variety of intracellular energy-consuming processes, causes a concomitant activation of K_{Ca} channels acting as a negative feedback mechanism to reduce cellular electrical activity. By virtue of this linkage to common small molecules then, K channels have profound influence on the functioning of highly metabolically active tissues, such as neurons or cardiac muscle.

Summary of the Electrophysiologic Properties of Different Types of K Channels

The discussion of activation, inactivation, rectification, and modulation leads to a better understanding of how each type of K channel operates. Voltage-gated K channels primarily of the *Shaker* type, but also the calcium-activated K channels, open in an all-or-none fashion when the membrane potential to which they are subject reaches the threshold for activation. Variation in threshold and in the rates of activation and inactivation produces great diversity of function. In addition, K_{Ca} channels become more active when Ca concentrations inside the cell increase. Inward rectifiers and tandem pore domain K channels are responsible for baseline or "leakage" currents. Their open probabilities are more constant, and the size of the currents they pass is determined by the nature of their individual current–voltage relationship. As such, inward rectifiers are important components of K currents at negative membrane potentials, near E_K, whereas outwardly rectifying baseline currents have predominant effects during action potential depolarizations. The diversity in electrophysiologic function shown by K channels then gives rise to their essential role for precisely shaping the electrical activity of excitable tissues.

Clinical Significance of Normal and Abnormal K Channel Activity

As information has accumulated about the structure and function of K channels, the roles of these channels in regulating the activity of excitable tissue in healthy and disease states emerge. Certain K channels in the pancreas are essential for regulating insulin secretion, whereas other types in the heart maintain the normal heart rhythm. The disordered function of these cardiac K channels can be the basis of malignant dysrhythmia and may cause sudden death. K channels in the central nervous system play important roles as the end effector of many G-protein–coupled receptor systems and have been linked to some rare genetic diseases.

Physiologic Roles of K Channels

The primary effect of potassium channels activity is to reduce the excitability of the tissues in which they are found. As discussed previously, potassium channels play a major role in setting the resting membrane potential. When they open, K channels tend to draw the membrane potential closer to the K^+ equilibrium potential. By so doing, they move voltage-gated Na and Ca channels farther from the membrane potential at which their open probability increases sharply, inhibiting action potential propagation.

Of equal importance is the role K channels play in dissipating excitatory influences. Any increase in the leak of positive charges (Na^+ or Ca^{++}) into the cell will increase the tendency to membrane depolarization. Having a variety of K channels gated by different mechanisms helps dampen these small depolarizations.

Another important role for K channels is to determine the duration and frequency of action potentials. At the top of figure 7 is shown a typical action potential tracing that could be recorded from a cardiac myocyte, and at the bottom, the K currents that occur at various phases of this action potential are shown. Na and Ca channels also play important roles in the rapid depolarization and repolarization of the membrane that defines action potential, but we will focus on the currents contributed by K channels. The opening of each type of K channel is determined by different forces: voltage-gated currents occur with depolarization and act to repolarize, whereas baseline K channels, such as the inward rectifiers, only pass currents when the membrane potential is near E_K. Contrast this with the action potential spikes seen in neuronal tissue (fig. 8). Action potential breadth is narrower in part because of greater K^+ efflux triggered by

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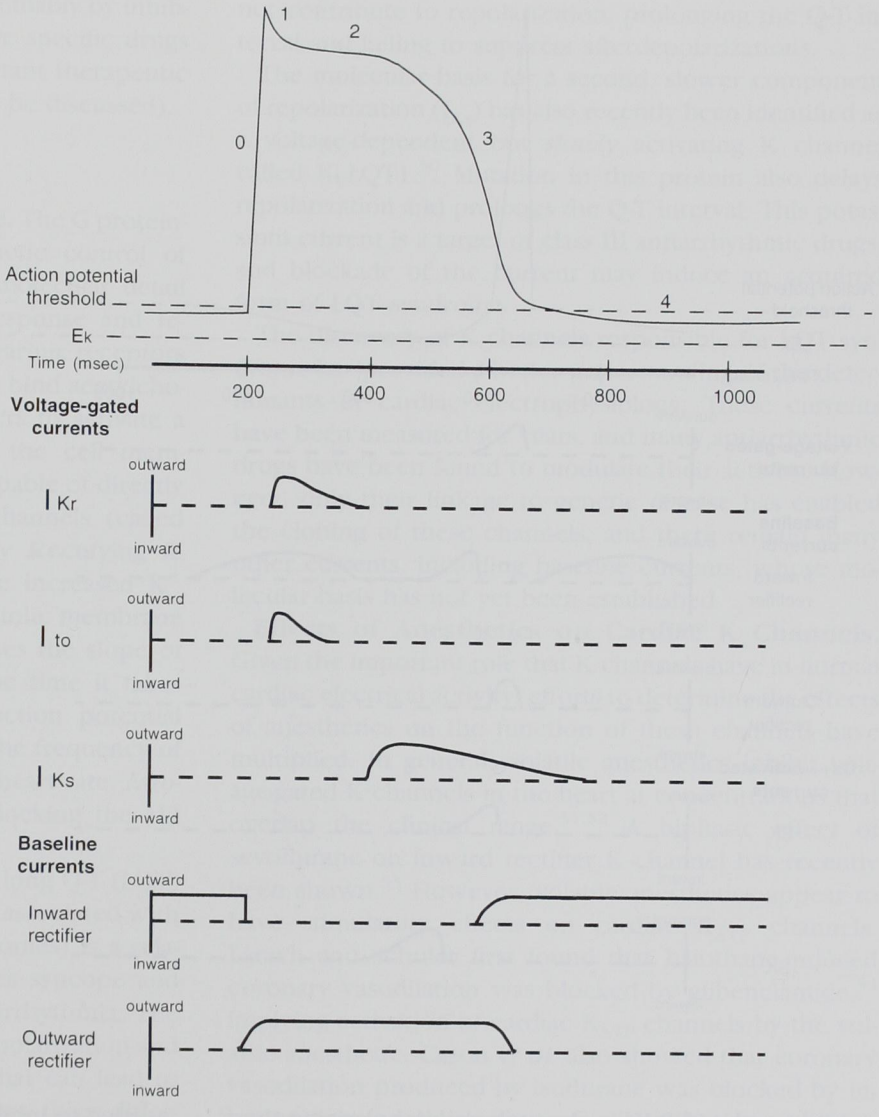

Fig. 7. Idealized cardiac myocyte action potential tracing. Below are shown K^+ currents that have been described in these cells at various phases of the action potential cycle. I_{Kr} = rapidly activated K^+ current; I_{to} = transient outward K^+ current; I_{Ks} = slowly activated K^+ current. Modified from the Task Force of the Working Group on Arrhythmias of the European Society of Cardiology.[106]

voltage change and changes in intracellular Ca^{++}. After-hyperpolarization caused by the activity of SK channels determines how frequently a train of action potentials can occur (interspike interval).

K Channels in the Pancreas—The Sulphonylurea Receptor

The clinically used sulphonylureas—glibenclamide (glyburide) and previously, tolbutamide—are important oral hypoglycemic agents taken by patients with type II diabetes. The binding site for these drugs is a large membrane protein, termed the sulphonylurea receptor (SUR), which forms a functional complex with an inwardly rectifying K channel ($K_{ir}6.2$).[38,39] The resulting complex forms an active K channel that is inhibited by μM concentrations of intracellular ATP. At least two subtypes of SUR have been cloned so far. In pancreatic β cells, SUR_1 combines with $K_{ir}6.2$ to form a complex that appears to have a central role in the regulation of insulin secretion.[38] In a fasting state, declining blood glucose concentration produces a decrease in intracellular ATP levels. The SUR-K_{ATP} channels in the β cell are thought to be spontaneously open, causing hyperpolarization.[40] Because insulin secretion depends on the activation of voltage-gated Ca channels and insulin exocytosis,[41] this action blocks insulin secretion and additional hypoglycemia. Insulin secretion is induced when abundant glucose causes an increase in intracellular ATP,

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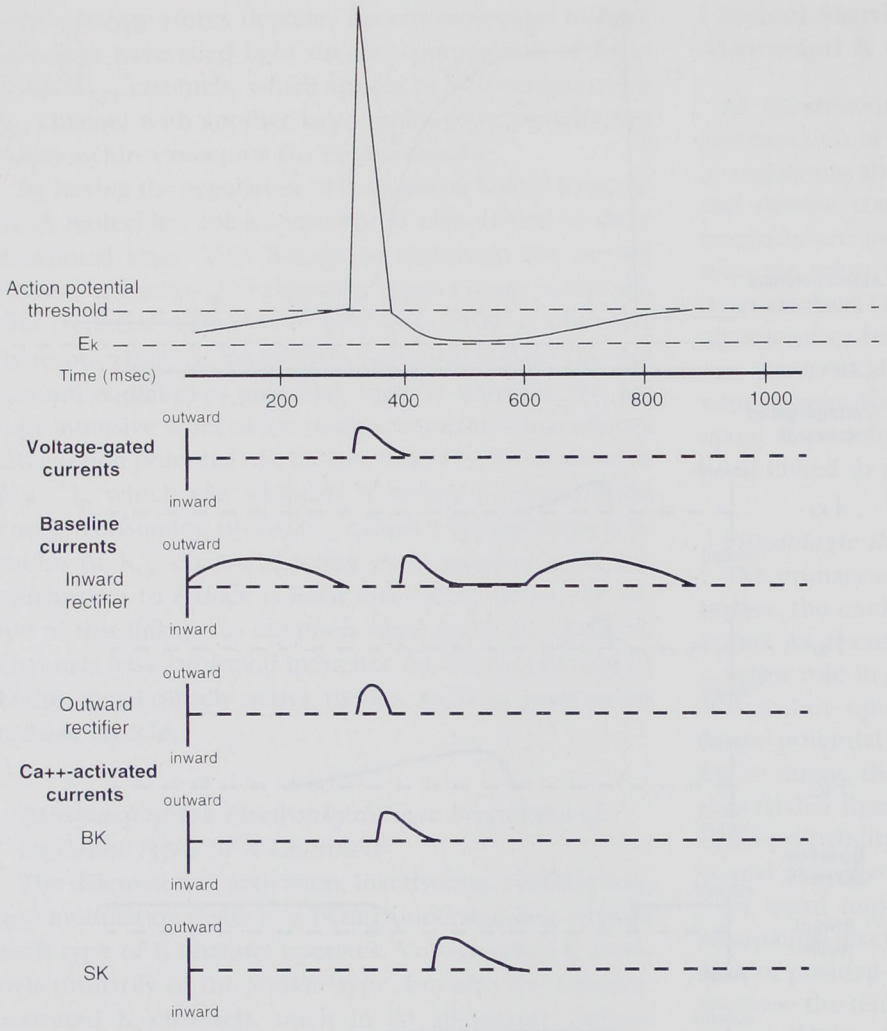

Fig. 8. Idealized neuronal action potential tracing. Below are shown typical currents active during various phases of the action potential.

inhibiting the SUR-K_{ATP} channels and depolarizing the β cell to activate voltage-gated Ca channels. Binding sulphonylurea drugs to the SUR-K_{ATP} channel complex also closes the K_{ATP} channel to bring about more insulin secretion.[35] Inherited mutations in the SUR_1 gene, leading to disordered and inappropriate insulin secretion, have recently been shown to be the cause of familial persistent hyperinsulinemic hypoglycemia of infancy.[42]

The SUR_{2a} combines with $K_{ir}6.2$ to form cardiac K_{ATP} channels, whereas SUR_{2b} combines with $K_{ir}6.2$ to form the channel in smooth muscle. The functional role of SUR-K_{ATP} complexes in other tissues remains unclear, but recent evidence has implicated cardiac K_{ATP} channels as cardioprotective (for a recent review, see reference 37). In heart muscle, vascular smooth muscle, and the brain, ATP levels are far higher than concentrations needed to inhibit K_{ATP} channels nearly completely. During ischemia or anoxia, intracellular ATP may decrease enough to relieve K_{ATP} inhibition and decrease tissue excitability by hyperpolarization. The fact that the SUR is so closely associated with K_{ATP} in many tissues implies an important mode of K_{ATP} channel modulation and maybe even endogenous sulphonylureas-like substances. Whether there are K_{ATP} channels that operate independently, *i.e.*, that are not functionally associated with a SUR, is not known.

During the past 10 years a new class of pharmacologic agents has emerged that act like ligands to increase the activity of K_{ATP} channels. This diverse group of compounds has been termed K channel openers (KCOs). The first compound of this class, cromakalim, has been found to have limited clinical use because of unwanted

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side effects such as hyperglycemia, presumably by inhibiting normal insulin secretion. But more specific drugs have the potential for becoming important therapeutic agents for a variety of disease states (to be discussed).

K Channels in Cardiac Function

Muscarinic Inhibition of Heart Rate. The G protein-mediated mechanism for parasympathetic control of heart rate has been described in full molecular detail from receptor to electrophysiologic response and requires a K channel at the final step. Muscarinic receptors (M_2 subtype)[43] on atrial pacemaker cells bind acetylcholine released from parasympathetic fibers to activate a pertussis toxin-sensitive G protein in the cell membrane.[44,45] The activated G protein is capable of directly opening inwardly rectifying type K channels (called "GIRKs" for ***G*** protein-linked ***I***nwardly ***R***ectifying ***K*** channels) in the cell membrane.[46] The increased K^+ conductance increases the maximal diastolic membrane potential of the atrial cells and decreases the slope of spontaneous depolarization, slowing the time it takes these pacemaker cells to reach the action potential thresholds. These two effects decrease the frequency of pacemaker cell discharge and slow the heart rate. Atropine antagonizes this mechanism by blocking the M2 muscarinic receptor.

Long Q-T Syndrome. The congenital long Q-T (LQT) syndrome (Romano-Ward syndrome or if associated with deafness, Jervell or Lange-Nielsen syndromes) is a relatively rare inherited disorder that causes syncope and sudden death as a result of ventricular arrhythmia. The increased Q-T interval reflects delayed repolarization and can cause an early afterdepolarization that can lead to *torsade de pointes*. During the past 3 years, three different ion channels genes, two of which are K channels, have been found responsible for the disease.

HERG (human *ether-a-go-go*-related gene—K_v6) is a voltage-dependent human K channel, closely related to the *ether-a-go-go Drosophila* gene and the molecular mediator of a *rapidly* activating, *rapidly* inactivating outward current (I_{Kr}) contributing to action potential repolarization.[47] The kinetics of inactivation of HERG are unique. They display strong inward rectification and produce large outward currents only if they are reactivated quickly after repolarization has occurred. Thus they appear to be specifically involved in suppressing the generation of premature afterbeats.[48] Six different heritable mutations of this gene that greatly reduce the (I_{Kr}) current have been identified.[49] Mutant channels do not contribute to repolarization, prolonging the Q-T interval and failing to suppress afterdepolarizations.

The molecular basis for a second, slower component of repolarization (I_{Ks}) has also recently been identified as a voltage-dependent but *slowly* activating K channel called K_VLQT1.[50] Mutation in this protein also delays repolarization and prolongs the Q-T interval. This potassium current is a target of class III antiarrhythmic drugs, and blockade of the current may induce an acquired form of LQT syndrome.

The discovery of K channels responsible for LQT syndrome has provided a better understanding of the determinants of cardiac electrophysiology. These currents have been measured for years, and many antiarrhythmic drugs have been found to modulate their activity. However, only their linkage to genetic disease has enabled the cloning of these channels, and there remain many other currents, including baseline currents, whose molecular basis has not yet been established.

Effects of Anesthetics on Cardiac K Channels. Given the important role that K channels have in normal cardiac electrical activity, efforts to determine the effects of anesthetics on the function of these channels have multiplied. In general, volatile anesthetics inhibit voltage-gated K channels in the heart at concentrations that overlap the clinical range.[51,52] A biphasic effect of sevoflurane on inward rectifier K channel has recently been shown.[53] However, volatile anesthetics appear to have stimulatory effects on cardiac K_{ATP} channels. Larach and Schuler first found that halothane-induced coronary vasodilation was blocked by glibenclamide,[54] implying activation of cardiac K_{ATP} channels by the volatile anesthetic. Cason *et al.* also showed that coronary vasodilation produced by isoflurane was blocked by intracoronary administration of glibenclamide, whereas the vasodilation produced by sodium nitroprusside was unaffected by glibenclamide.[55] These results suggest specific activation of cardiac K_{ATP} channels by volatile anesthetics, resulting in myocardial preservation during ischemia.[56–58] However, Han *et al.*, using patch clamp techniques on rabbit ventricular myocytes, found that the direct application of 2–3% isoflurane produced approximately 50% inhibition of K_{ATP} channel activity.[59] Thus, the effect of the volatile anesthetic may be indirect, through activation of G protein-coupled pathways involving adenosine A1 receptors.[60]

The actions of intravenous anesthetic agents on cardiac K currents have also been studied. Etomidate, propofol, and midazolam, which have some negative inotropic properties, were studied to determine their

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effects on cardiac Ca^{++} and K^+ currents.[61] At clinical concentrations, these agents produce much greater inhibition of Ca^{++} currents than K^+ currents, suggesting they induce myocardial depression by altering intracellular Ca^{++} influx. However, in an *in vitro* study, sodium thiopental was shown to inhibit inward rectifier K^+ currents, thereby possibly contributing to the arrhythmogenicity of other agents, such as halothane, epinephrine, and CO_2.[62]

Local anesthetics, especially bupivacaine, exert strong, potentially lethal effects on the heart. Although the mechanism of local anesthetic cardiotoxicity is primarily mediated by slow recovery of blockade of cardiac Na channels, effects of local anesthetics on K channels in the heart may contribute to cardiotoxicity. For example, lemakalim, a K channel opener of cardiac K_{ATP} channels, can effectively antagonize bupivacaine-induced depression of cardiac conduction,[63] suggesting that hyperpolarization may help reverse Na channel blockade. Conversely, ropivacaine and bupivacaine can produce open channel blockade of cardiac voltage-gated[64,65] and baseline K channels,[16] preventing repolarization and the reestablishment of sufficiently negative resting membrane potentials to relieve Na channel inactivation. A dual effect on Na and K channels then might interact synergistically to intensify local anesthetic cardiotoxicity. Such a mechanism has also been suggested for the mechanism of local anesthetic conduction blockade in neural tissues.[66] Bupivacaine inhibits the transient outward K^+ current but not inward rectifier currents in rat ventricular myocytes, which could prolong the action potential, delay repolarization, and make the myocardium more susceptible to reentrant dysrhythmia.[67]

K Channels in the Lung

The presence of K_{ATP} channels within the lung is clear because KCOs are capable of relaxing bronchial smooth muscle. Application of cromakalim to uncontracted bronchial smooth muscle can prevent histamine-induced bronchoconstriction but does not produce much relaxation alone.[68] However, KCOs are able to relieve hyperreactive airway obstruction in a guinea pig model of asthma. This discrepancy may be explained by recognizing the role of hyperreactivity in bronchospastic airways, which may specifically be mediated by K_{ATP} channels.[69] Inhibiting airway neural transmission by attenuating nonadrenergic, noncholinergic transmission also may contribute to the apparent efficacy of KCOs as antiasthmatic drugs.[70–72] The development of drugs that are selective pulmonary KCOs could provide another approach to the management of severe bronchospasm.

Potassium channels are also involved in the mechanism of hypoxic pulmonary vasoconstriction. The ability to sense changes in oxygen tension occurs in type 1 cells of the carotid body and in smooth muscle cells in the pulmonary vasculature and appears to be mediated by hypoxia-induced inhibition of an outward potassium current.[73] This inhibition results in depolarization of the membrane, causing activation of voltage-gated Ca channels, smooth muscle contraction, and vasoconstriction.[74]

K Channels in the Central Nervous System

Information in the central nervous system (CNS) is encoded in the repetitive firing of neuronal synapses. The frequency of firing and the variation in firing pattern determine the nature of the information, *i.e.*, information processing is not merely a binary operation but a rich layering of subtle variations in activity. Furthermore, neurons are connected to many other neurons, both excitatory and inhibitory, that cooperate to modulate the output of a given nerve. Therefore, modification of neuronal firing rate would be expected to affect information processing in the CNS. As described previously, K channels are essential for inducing hyperpolarization, for limiting spike duration, and for determining spike frequency. It is conceivable that altering these features of neuronal function through K channel modulation may potently affect CNS function. In addition, scientists have begun to discover some disease states caused by K channel dysfunction. For example, the rare familial syndrome episodic ataxia has been linked to point mutation in the $K_V1.1$ gene.[75] The *weaver* mouse is from a strain of mice that displays abnormal development of the cerebellum, caused by a single mutation in the inward rectifier K channel (GIRK2).[76]

G Protein-coupled K Channels in the CNS. In the same way that cardiac muscarinic receptors activate cardiac GIRK channels, many other receptors for neurotransmitters and neuropeptides are known to activate, either directly or indirectly, K channels of the inwardly rectifying type (table 2). Opioids exert their analgesic effects by binding to opiate receptors, which leads to opening of K channels and neuronal hyperpolarization.[77]

The distribution of these receptors determines the neuronal response evoked by their activating neurotransmitters. Because they activate intracellular effectors and second messengers, G protein-coupled responses tend

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Table 2. G Protein Coupled Receptors That Activate K Channels[107]

Muscarinic (m1,m2)
α2 adrenergic
μ, δ, κ opioid
Dopaminergic (D2)
Adenosine (A1)
Serotonin 1A
Metabotropic glutamate
Angiotensin II
Endothelin-1
Melatonin
$GABA_B$
Somatostatin

$GABA_B$ = γ-aminobutyric acid receptor (B subtype).

to be slow in onset and relatively prolonged compared with responses produced by ligand-gated ion channels. But when G protein-coupled receptors can interact with ion channels, the responses they produce may be as rapid and as fleeting. This combination of rapid yet prolonged response suggests that these systems are capable of producing profound neuromodulation.

Effects of General Anesthetics Mediated *via* CNS K Channels? An important goal of basic research into the mechanism of anesthetic action remains the identification of one or more molecular sites within the CNS where general anesthetics act to produce CNS depression. At present, the leading candidate for such a site remains the $GABA_A$ receptor system (reviewed by Tanelian *et al.*[78]), and a large body of evidence has accumulated in recent years pointing toward these receptors as primary determinants of anesthetic action.[79,80] However, our understanding of the function of the CNS remains sufficiently incomplete that other mechanisms of CNS depression remain to be examined. As this review has shown, K channels are fundamentally important for governing the excitability of the tissues in which they are expressed, and so it is plausible to hypothesize that modulation of K channel activity could be involved in the global CNS depression produced by general anesthetics. Sporadic studies have appeared in the literature that have found anesthetic activation of K channels in several different neuronal preparations.

Nicoll and Madison found that diethyl ether and halothane produce hyperpolarization of rat hippocampal neurons as a result of an increase in the permeability of the cell membrane to K^+.[81] Berg-Johnsen and Langmoen found that 1.5–5% isoflurane hyperpolarized rat and human cortical and hippocampal neurons, again as a result of an increase in potassium conductance.[82,83] Southan and Wann reported small hyperpolarizing shifts in the resting membrane potential of hippocampal neurons by 1–5% enflurane.[84] El-Beheiry and Puil also found neocortical neuronal hyperpolarization by 2–3% isoflurane.[85] Both of these latter two studies found a reduction in the afterhyperpolarization, suggesting inhibition of K_{Ca}. Invertebrate neurons have also been found to have K channels that can be activated by volatile anesthetics, first in a single neuron of the European pond snail, *Lymnaea stagnalis,*[86] and in several neurons within the abdominal and pleural ganglia of the marine mollusc *Aplysia californica.*[87]

One of the best-documented examples of anesthetic mechanisms coupled to K channel function has been shown with the α_2-adrenergic system. In rats with implanted locus ceruleus cannulas, Nacif-Coelho *et al.* determined that the K channel blockers charybdotoxin (K_{Ca}), dendrotoxin (K_V), and quinine (K_{Ca} and K_V) reduced the hypnotic effect of dexmedetomidine.[88] This study offers evidence that K channels of these families may be specifically involved in anesthetic states.

These few reports showing activation of CNS K channels stand in contrast to many other studies that have found inhibition of various K_V and K_{Ca} currents by volatile anesthetics, intravenous anesthetics, and ethanol.[52,89–99] The problem in extrapolating from the isolated effects on one K channel type to neurophysiologic effects *in vivo* is that there are more than one channel type in a given cell, making it harder to distinguish the individual contribution of modulated channels. Drugs that selectively affect K channel function could help with this problem,[100] and the development of such agents will aid research into the role of K channels and could lead to new therapeutics.

Therapeutic Potential of Drugs that Modulate K Channel Function

Although great progress has been made in defining and understanding K channels during the past decade, there is still much to be learned. The most exciting area may be in efforts to modulate the activity of specific K channels to bring about therapeutic effect. From a theoretical standpoint, enhancing K channel activity could play major roles, for example, in the management of seizure disorders, hypertension, and myocardial, cerebrovascular, and peripheral vascular ischemia. Other clinical situations such as sepsis, transplant immunology, and vasospasm may also be amenable to management involving K channel modulation.

Diazoxide and minoxidil are KCOs currently approved

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for use that open K_{ATP} channels in the vasculature to produce vasodilation and reduce increased blood pressure.[31] The clinical usefulness of both drugs has been limited by side effects, such as fluid retention and hyperglycemia. Nicorandil is a hybrid compound with KCO-like effect to produce arterial dilation and organic nitrate venodilator effects.[101] As such it has excellent antianginal activity by increasing coronary blood flow and compares favorably with nitroglycerin, atenolol, and nifedipine in prevention of angina and in improvement of exercise capacity in patients with stable angina.[102] Compounds that operate as KCOs on bladder smooth muscle may soon be marketed to control incontinence.

Potassium channel openers represent a new class of compounds that have some current clinical use. At present these are only compounds that have effect on K_{ATP} channels, although there are some experimental agents that directly open K_{Ca} as well. This new direction in the pharmacology of ion channels has great potential, primarily because the number and diversity of K channels is so large. As the biology of K channels is better understood, rational targets for drug development will emerge.

Conclusion

The study of K channels is a burgeoning field. These channels are ubiquitous. They appear to be more diverse in structure and function than any other types of ion channel. K channels are instrumental in governing excitable tissue. They shape the action potential, set the membrane potential, and determine firing rates. There already are some drugs in clinical use that target K channels, and more are being sought to improve our ability to regulate excitability. Such agents could be useful in ameliorating diseases such as epilepsy, asthma, and chronic pain, and in enhancing neural and myocardial protection. The revolution in molecular biology should certainly help us move quickly toward such clinical advances.

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