Molecular Diversity of K^+ Channels

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ABSTRACT: K^+ channel principal subunits are by far the largest and most diverse of the ion channels. This diversity originates partly from the large number of genes coding for K^+ channel principal subunits, but also from other processes such as alternative splicing, generating multiple mRNA transcripts from a single gene, heteromeric assembly of different principal subunits, as well as possible RNA editing and post-translational modifications. In this chapter, we attempt to give an overview (mostly in tabular format) of the different genes coding for K^+ channel principal and accessory subunits and their genealogical relationships. We discuss the possible correlation of different principal subunits with native K^+ channels, the biophysical and pharmacological properties of channels formed when principal subunits are expressed in heterologous expression systems, and their patterns of tissue expression. In addition, we devote a section to describing how diversity of K^+ channels can be conferred by heteromultimer formation, accessory subunits, alternative splicing, RNA editing and posttranslational modifications. We trust that this collection of facts will be of use to those attempting to compare the properties of new subunits to the properties of others already known or to those interested in a comparison between native channels and cloned candidates.

The first molecular components of K^+ channels were identified only about a decade ago by molecular cloning methods.[1–5] However, the number of cloned and characterized components has grown so much that reviewing the molecular biology of K^+ channels has become a daunting, if not impossible, task in a chapter of these dimensions. Several excellent reviews, discussing specific aspects of this subject have appeared in recent years.[6–16] The present chapter presents a review as comprehensive as possible of all the K^+ channel subunits known to date, aimed mainly at scientists who might be interested in finding possible molecular correlates for their functional findings. We limited the scope by focusing primarily on mammalian K^+ channel principal and auxiliary subunits. Most of the data are presented in tabular format. It is possible that our tables have missing and even erroneous data. We wish to apologize to our colleagues for these errors and omissions and will appreciate receiving comments. Given space limitations we have not included specific references from which the data in the tables were extracted. To alleviate this constraint, we intend to publicize a web page[e] on which this information will be accessible along with additional data that similarly had to be omitted because of space considerations.

The availability of K^+ channel cDNAs has allowed enormous progress in the understanding of the structure and molecular mechanisms of function of K^+ channels. Important

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[e]http://k-channels.med.nyu.edu/

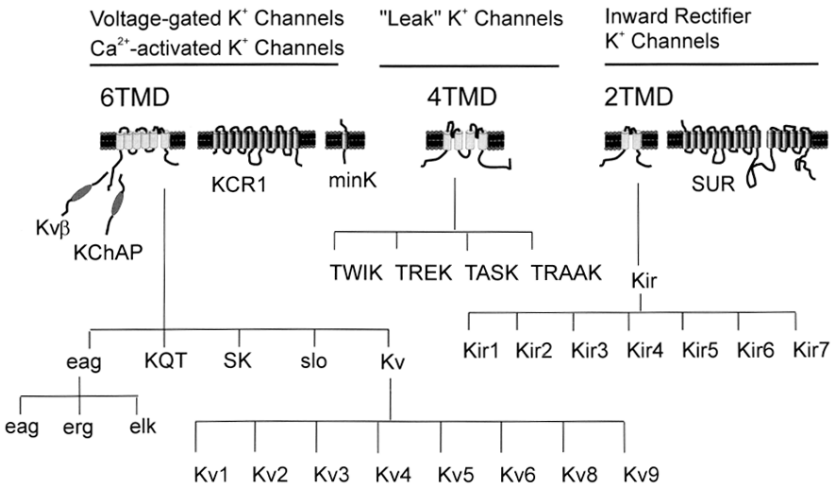

FIGURE 1. Schematic representation of the three groups of K^+ channel principal subunits. They are classified into three groups in terms of their predicted membrane topology—those that have six transmembrane domains (TMDs), those with four transmembrane domains and those with only two transmembrane domains. Each group of principal subunits is divided into discrete families on the basis of sequence similarity (see FIGS. 2 and 3). Each family can be further subdivided into several subfamilies, which often contain several closely related subfamily members. A functional classification places the voltage- and Ca^{2+}-regulated K^+ channels in the 6TMD group, the "leak" K^+ channels in the 4TMD group, and the inward rectifier K^+ (Kir) channels in the 2TMD group. Also shown in the figure are some of the auxiliary subunits that have been shown to alter expression levels and/or kinetics of K^+ channel principal subunits when expressed in heterologous expression systems. For clarity, they are grouped together with the principal subunits with which they have been shown to interact (see text for more details).

new insights into the mechanisms of ionic selectivity, voltage- and calcium-dependent gating, inactivation and blockade of these channels have been obtained. These efforts recently culminated with the crystallization and high-resolution structural analysis of a K^+ channel[17]—the first natural membrane channel for which high-resolution real structural information is now available. This work provided strong evidence in favor of a tetrameric K^+ channel structure. This structure was first suggested based on the similarities between six transmembrane K^+ channel subunits and each of the four internally homologous repeats of Na^+ and Ca^{2+} channels[18] and was supported experimentally.[17,19,20] In this structure, four independent subunits or homologous repeats of one or two subunits form the infrastructure of a channel with a fourfold symmetry around a central pore. We can expect that this breakthrough will bring a deeper and accelerated understanding of the structure and function of K^+ channels.

Less progress has been made in understanding the physiological significance of the enormous molecular diversity of K^+ channel protein subunits (TABLE 1[f]). Over 100 different proteins, subunits of distinct types of K^+ channels, have been identified to date, and the list is rapidly growing (FIG. 1). In addition to the pore-forming or principal subunits (often

[f] All tables appear at the end of the paper.

called α subunits), which determine the infrastructure of the channel, many K^+ channels (like Na^+ and Ca^{2+} channels) contain auxiliary proteins that can modify the properties of the channels, often significantly. Most of the known principal K^+ channel subunits express in heterologous expression systems as functional homomultimeric channel complexes. However, some principal subunits do not form functional homomultimeric channels, but must coassemble with other (similar) subunits for expression of functional channels (e.g., G-protein–activated K^+ channels; GIRKs). These subunits may be called coassembly principal subunits. All known principal subunits of K^+ channels show a certain amount of sequence and structural similarity, and they might all be related through evolution. There is sufficient primary sequence similarity between the different principal subunits that members of new families of K^+ channel proteins have been discovered by degenerate PCR or by screening databases of "expressed sequence tags" (ESTs) and sequences deposited by various genome projects. It remains possible, however, that some unknown K^+ channels may have principal subunits that are unrelated to those known today.

Auxiliary subunits (sometimes referred to as β subunits) have primary sequences not resembling principal subunits. They interact with channel complexes containing principal subunits and may alter their electrophysiological or biophysical properties, expression levels, or expression patterns. In addition, many K^+ channel molecular complexes interact with additional proteins such as regulatory enzymes and elements of the cytoskeleton (see chapters by Morgan Sheng and John Adelman, this volume). We term these *associated proteins*, with the understanding that the distinction between auxiliary subunits and associated proteins may not be simple on occasions. Since K^+ channels are thought to be multimers of principal subunits, which may form heteromeric channels with closely related principal subunits in various combinations, the number of possible distinct K^+ channels based on these different combinations may be in the order of hundreds, if not thousands (see DIVERSITY CONFERRED BY HETEROMULTIMER FORMATION..., below). However, it is not known how much of this potential diversity is actually used in native cells. A major task of future research is to identify physiological roles of the cloned proteins, starting with the identification of native channels containing specific types of cloned subunits. This is particularly important because most of the cloning work has been done in the absence of prior isolation of native proteins. Therefore, the exact relationship between the molecular components identified by cloning and native channels is, in most cases, not known and must be a priority for future research.

CLASSIFICATION OF K^+ CHANNEL PRINCIPAL SUBUNITS

There are several types of K^+ channels, including voltage-gated and Ca^{2+}-activated K^+ channels, inward rectifiers, "leak" K^+ channels, and Na^+-activated K^+ channels.[21,22] Principal subunits of at least the first four types have already been identified, and they are divided into three groups based on structural properties (FIG. 1). The first group, consisting of six transmembrane domain (TMD) proteins, are components of voltage-gated (Kv) and Ca^{2+}-activated K^+ channels. The second group, consisting of proteins with two TMDs, are components of inward rectifier K^+ (Kir) channels. The third group, known as two-pore subunits, are components of "leak" K^+ channels. Each of these groups is further divided into families, which in turn are divided into subfamilies, with several closely related members within most of these subfamilies.

The first major group of K^+ channel principal subunits to be identified contain six transmembrane domains (TMDs) (S1-S6), with a conserved P (pore or H5) domain. Functionally, they form voltage- and/or Ca^{2+}-activated K^+ channels when expressed in heterologous expression systems. This group contains the Kv family (with eight subfamilies: Kv1–Kv6 and Kv8–Kv9) as well as members of the KQT, eag, SK, and slo families of principal subunits.

The second major group of pore-forming subunits are components of inward-rectifying K^+ (Kir) channels and the first members were first identified by expression cloning.[23–25] Kir principal subunits have a predicted membrane topology of two TMDs (M1–M2) and a pore domain, analogous to S5-P-S6 of the 6TMD K^+ channel subunits. There are currently seven subfamilies (Kir1–Kir7), most of which form K^+ channels with various degrees of inward rectification when expressed in heterologous expression systems.

A third group of mammalian K^+ channel principal subunits was recently described and contains four putative TMDs (M1–M4) and two P domains (P1 and P2).[12,26] Structurally, these principal subunits have a predicted membrane topology as if they consisted of two spliced Kir subunits. Whereas the 6TMD and 2TMD principal subunits are thought to assemble as tetrameric proteins to form functional channels (see above), the 4TMD subunits are thought to dimerize, thereby retaining the fourfold symmetry around the central pore.[12,27] There are currently four members in this novel family of K^+ channel principal subunits (FIG. 1 and TABLE 1), but it is possible that more members might be cloned in the near future (see later). Functionally, these principal subunits express K^+ selective channels that do not appear to gate in a manner as observed with channels formed by Kir principal subunits. Since the current responds to changes in extracellular K^+ concentration in a manner described by the Goldman-Hodgkin-Katz equation, these channels are also referred to as "leak" K^+ channels.[12] Recent reports [28] indicate that at least some of these channels can be extensively modulated (e.g., by arachidonic acid or pH; TABLE 1).

The P domain of K^+ channel principal subunits is critically important for channel function. Approaches using both mutagenesis [29,30] and X-ray crystallography[17] suggest a role for this domain in the formation of the K^+ selective pore of the channel. The consensus pore sequence[g] calculated from a simultaneous alignment of the P domains of K^+ channel principal subunits that are shown in TABLE 1 is: [TS]-[MLQ]-T-T-[IV]-G-Y-G[31] and appears to be hallmark of K^+ channel principal subunits.

Mammalian K^+ Channel Principal and Auxiliary Subunits

TABLE 1 lists published sequences of mammalian (mostly from human, rat, and mouse) K^+ channel principal and auxiliary subunits cloned to date. As far as possible, we used standard nomenclature[32,33] to describe the various genes. In addition to Genbank or Swissprot accession numbers and trivial (author-assigned) names of known alternatively spliced variants, we also give the gene name as defined by the Human Genome Organization (HUGO) Nomenclature Committee,[h] chromosomal localization, and possible (or confirmed) associated diseases related to allelic variants. These data for principal subunits

[g] The consensus pore sequence was calculated from a simultaneous alignment of the pore regions of K^+ channel principal subunits using MEME (http://www.sdsc.edu/MEME). A residue was included if it had a probability of occurrence larger than 0.2.

[h] http://www.gene.ucl.ac.uk/nomenclature/

have been subdivided by functional classification, as described above. The auxiliary subunits are listed in terms of the main principal subunits with which they are thought to interact.

Genealogical Analysis of Genes Coding for Principal K^+ Channel Subunits

We performed a genealogical analysis of the K^+ channel principal subunits shown in TABLE 1 with the aim of examining relatedness between the various genes. For this analysis, we divided the K^+ channel principal subunits on the basis of their predicted transmembrane topology. FIGURE 2 is a phylogenetic tree of six TMD voltage-gated and Ca^{2+}-activated K^+ channels generated by parsimony analysis, and FIGURE 3 shows a similar analysis for the two TMD principal subunits representing Kir principal subunits.

For the six-TMD group, a strong primary node (bootstrap value of 99% in FIG. 2) exists that includes the members of all of the Kv subfamilies (Kv1–Kv6 and Kv8–Kv9). The question may arise whether the KQT family should be considered as part of the Kv family. However, the KQT family has a much weaker sequence identity to Kv genes (19–25%) than is found between members of the Kv subfamilies (33–50%) (TABLE 2A). It is therefore likely that the divergence of the KQT and the Kv gene families preceded the divergence of the different Kv subfamily members. Thus, for the purposes of this review, the KQT family will be regarded as a discrete family. The analysis shows that members of eag, erg, and elk subfamilies showed clustering with a strong node (bootstrap value of 100%), suggesting that they all originated from a single ancestral gene.

Interestingly, although there are large structural differences (e.g., the length of the C-terminus) between SK and slo, these families (which are all principal subunits of Ca^{2+}-activated K^+ channels) grouped together with a strong bootstrap value (73%; FIG. 2). Thus, within the regions used to perform the parsimony analysis (which included most of the six transmembrane domains), characters exist that diagnosed SK and Slo as close relatives.

It is often difficult to determine whether a gene belongs to a certain subfamily. For the purposes of this review, we used identity scores as the only criterion to subdivide genes into different subfamilies. Other criteria may exist, such as the presence of regulatory sequences (e.g., ATP-binding sequences, etc.), similar electrophysiological or pharmacological phenotypes in expressed channels, or similar regulation by metabolic pathways. Concentrating only on similarity of the primary sequences, it is interesting to note that an identity score of >55%[i] exists among members of individual Kv, eag, KQT, and slo subfamilies (TABLE 2A). In fact, this threshold value of ~55% holds true within each of the 6TMD K^+ channel *subfamilies* except for the SK genes. Within the SK gene family, SK4 appears to diverge from other SK family members (TABLE 2B), suggesting that SK4 might represent a member of a new emerging subfamily of SK genes.

Within the 2TMD family, members of the Kir2, Kir3, Kir5 (the latter having only a single member), and Kir6 subfamilies each fall into their own expected groups (FIG. 3). The classification of the remainder of the genes (members of Kir1, Kir4, and Kir7 subfamilies)

[i] Note that this number was derived from multiple sequence alignments where portions of unstable sequences were removed for the generation of trees. When whole sequences are aligned, this number may be smaller. The threshold value of 55% identity can be extracted from the percent identity table for the 2TMD potassium channels as well as the 6TMD channels; i.e., in both identity tables, genes that have identity values of less than 55% belong to different subfamilies.

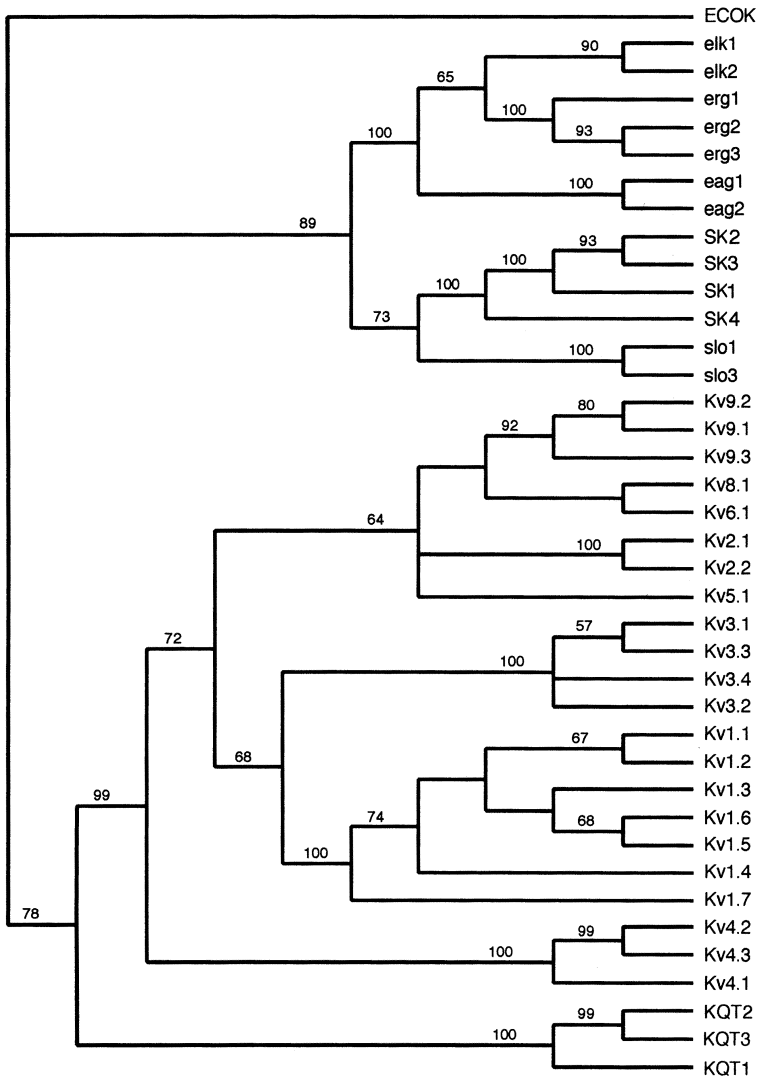

FIGURE 2. Strict consensus phylogenetic tree of 6TMD voltage-gated and calcium-activated K^+ channels generated by parsimony. The parsimony tree is generated by heuristic search using PAUP 3.1.1.[138] Ten random addition searches with TBR branch swapping were performed. The *E. coli* K^+ channel homologue ECOKCH (accession #L12044) was used as an outgroup). ClustalX was used to generate all alignments of amino acid sequences. By varying the alignment-parameters, we were able to identify regions that lack alignment stability. We proceeded to remove alignment ambiguous regions by implementing a "culling" procedure.[139] In this analysis, only regions that span the six transmembrane domains were used. All characters were equally weighted in the analysis. Bootstrap values generated using PAUP 3.1.1[138] are shown on the tree when available, and they represent a measure of node robustness. Sequences of eag2, elk1, and elk2 used in this analysis are from B. Ganetzky (see this volume).

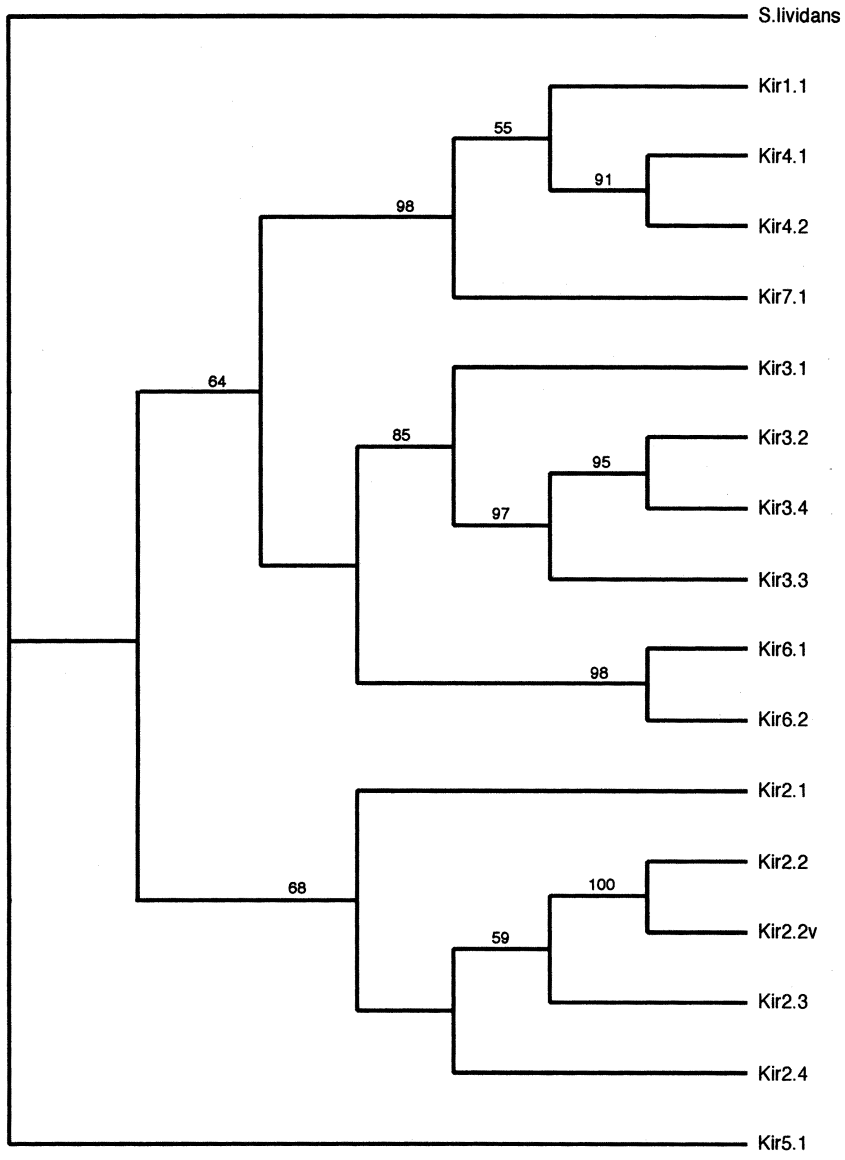

FIGURE 3. One of two most parsimonious trees of 2TMD inward rectifier K^+ channels that are generated by heuristic search. For methods used, please refer to the legend of FIG. 2. The *S. lividans* skc1 K^+ channel principal subunit (accession Z37969) was used as an outgroup. Except for small portions of the NH_2 and COOH terminals, most of the amino acid sequences were used in this analysis. To measure node robustness, we generated bootstrap values (shown on tree when available) using PAUP 3.1.1.

deserves comment. Following the cloning of Kir1.1 and its splice variants (TABLE 1), the primary sequences of closely related genes were published. Ambiguity arose in the naming of these genes. Whereas BIR10[34] was proposed to be named Kir4.1,[33] others have been referring to this gene as Kir1.2[35] because of its apparent sequence similarity to Kir1.1. Similarly, there has been equal ambiguity in the naming of Kir1.3/Kir4.2.[36,37] More recently, a member of a potentially new subfamily was cloned and was called Kir7.1,[38] but was also named Kir1.4 by others (Genbank accession number AB013890). As seen in TABLE 2C, a threshold identity value of >55% also exists among members of individual Kir subfamilies, except for the subfamily that includes Kir1.1, Kir1.2/Kir4.1, Kir1.3/Kir4.2, and Kir1.4/Kir7.1. When examining this particular subfamily (Kir1/Kir4/Kir7), an identity score as low as 36% is found, suggesting that (at least some of) these genes might indeed belong to different subfamilies. A more detailed analysis of identity scores of these genes (TABLE 2D) shows that Kir1.4/Kir7.1 is only 36–39% identical to the other three genes. Similarly, while Kir1.2/Kir4.1 and Kir1.3/Kir4.2 are 62% identical to each other, they are only 47% identical to Kir1.1. Thus, the possibility that discrete Kir4 and Kir7 subfamilies exist (as originally proposed)[33,38] must be considered. These considerations led us to adopt this nomenclature for the remainder of this chapter. Although our analysis supports the idea that members of the Kir1, Kir4, and Kir7 subfamilies are not sufficiently similar in terms of their primary sequences to be grouped as a single subfamily, the analysis shown in FIGURE 3 illustrates that these genes are more closely related to each other than to other Kir subfamily members.

In mammals, the 4TMD gene family is currently the smallest among the three main groups of K^+ channels, with only four representatives published to date. Among them, TRAAK and TREK are more closely related to each other than to either of the other two genes, TWIK and TASK, as indicated by alignment and phylogenetic analysis (data not shown). A more detailed description of 4TMD principal subunits in *C. elegans* appears elsewhere in this volume (see chapter by Salkoff).

CORRELATION OF K^+ CHANNEL PRINCIPAL SUBUNITS WITH NATIVE CHANNELS

The molecular diversity of K^+ channel-forming proteins (TABLE 1) is far greater than that found for native K^+ currents,[21] which adds additional complexity when one attempts to correlate the molecular candidate with a particular native current expressed in a specific tissue. In order to infer a relationship between heterologously expressed and native K^+ channels, there are several criteria that may be used.

1. A close resemblance between the biophysical properties of native channels and those of channels expressed in heterologous expression systems may signify a possible relationship. Further support for such a relationship will be provided if they are similarly affected by pharmacological compounds, toxins, and other interventions. In order to assist in these comparisons, we compiled the data presented in TABLE 4.
2. The tissue expression of mRNA (and protein) of the candidate principal subunits should correspond with the tissues in which the native current is expressed. Data in TABLE 5 should assist in this comparison.

3. The functional consequences of processes such as heteromultimeric assembly by different principal subunits, their regulation by auxiliary subunits, and posttranslational modification should be considered. We present examples where these processes have been shown to influence channel properties. Because of the amount of detail involved, this information is supplied mainly in textual format (DIVERSITY CONFERRED BY HETEROMULTIMER FORMATION..., below).
4. Strong support for a causal relationship between native and candidate cloned K^+ channel principal subunits can be obtained from experiments involving deletion or overexpression of the target channel principal subunits (transgenic animals or overexpression of wild-type, antisense, or dominant negative constructs in isolated cells). Since this is a relatively new area of investigation, there are only a few examples where these methodologies have been applied (see TABLE 3).

It is important to note, however, that these criteria do not exclusively define a relationship between cloned and native proteins. For example, negative results might well be caused by unknown events occurring at the molecular level, such as interactions of K^+ channel principal subunits with other cytosolic or membrane-bound proteins or their regulation by unknown endogenous compounds and peptides or poorly understood posttranslational modifications.

FUNCTIONAL PROPERTIES OF K^+ CHANNELS IN HETEROLOGOUS EXPRESSION SYSTEMS

We have listed the functional and pharmacological properties of the currents expressed by K^+ channel principal subunits in heterologous expression systems in TABLE 4. Where possible, we report data obtained from expression studies using mammalian cells under patch-clamp conditions. Otherwise, we report data obtained from the *Xenopus* expression system. In cases in which there is close agreement between several reports on the same protein, we report an averaged value. When large discrepancies exist in published values to make it impossible to find a consensus value, we give a range of values. In come cases, we favored reports in which a more extensive functional analysis was performed.

In using these tables it is important to remember that experimental variables can have important effects on published parameters. In addition, a native channel composed of a particular subunit may have properties different than those in heterologous expression systems due to factors such as those listed in DIVERSITY CONFERRED BY HETEROMULTIMER FORMATION..., below, or other factors that are sometimes difficult to predict. We would like to mention three such examples of problems encountered using heterologous expression systems: First, it has been observed that Kir3.1 expresses G-protein–activated K^+ channels in *Xenopus* oocytes, but not in mammalian cultured cells. It is now clear that this is due to the presence of an intrinsic Kir3.4 subunit (called XIR) in *Xenopus* oocytes[39] (see chapter by Wickman in this volume) that is not found in mammalian cells and is required for expression of G-protein–activated K^+ channels. Second, artifacts can be caused by the unusually large amounts of channels expressed in heterologous expression systems. The flow of large currents may lead to effects such as K^+ accumulation in the extracellular spaces, which in turn can modify the behavior of expressed channels. Last, some channels can be very sensitive to particular elements in the extracellular or intracellular solution, such as

blockade of several voltage-gated K^+ channels by Mg^{2+}. Care should therefore be exercised when comparing the electrophysiological phenotype of native K^+ currents with those presented in TABLE 4.

TISSUE EXPRESSION OF K^+ CHANNEL SUBUNITS

Studies on the cell- and tissue-specific expression of K^+ channel genes vary widely. Some genes such as Kv3 (see chapter by Rudy *et al*., this volume), Kir3 (see chapter by Kevin Wickman *et al*., this volume), and several Kv1's[16] have been studied in great detail in several laboratories. Others have been studied to a much lesser extent. We attempted to give a representative overview of expression patterns of known K^+ channel genes in TABLE 5. However, the nature of available information will be reflected in our compilation.

Different laboratories use different methods to analyze expression levels of various K^+ channel transcripts. Some of these methods are more quantitative in nature (Northern blot analysis and RNAse protection assays) but have a limited spatial resolution. In contrast, *in situ* hybridization techniques can have excellent spatial resolution, but quantification is more difficult. RT-PCR is very sensitive, and results obtained with this technique are difficult to quantify. Given this sensitivity, it is often difficult to interpret a result when no attempt at quantification is made. Antibodies have now been raised to a number of K^+ channel proteins, and they can be great tools for the analysis of protein products, but problems of specificity can arise. We present a table on the tissue and brain distribution of K^+ channel gene products (TABLE 5). However, caution should be exercised in using this table. For example, results for some genes may come from many studies using different methods, whereas for others data may have been derived from a single study. Great care should be taken when making a quantitative comparison of expression levels between different genes because of the variations in methodologies used in different laboratories as well as the subjectivity of different investigators when grading the intensities of signals.

DIVERSITY CONFERRED BY HETEROMULTIMER FORMATION, ACCESSORY SUBUNITS, ALTERNATIVE SPLICING, RNA EDITING AND POSTTRANSLATIONAL MODIFICATION

Over 50 mammalian genes encoding principal subunits of K^+ channels are listed in TABLE 1. The total number of different subunits, however, is even larger since many of these genes undergo RNA processing, such as alternative splicing resulting in multiple protein products from each gene. Considering these factors, this results in a large number (>100) of different mammalian principal subunits (TABLE 1).

However, the total number of different functional types of K^+ channels is probably significantly larger. In addition to the already large number of subunits, the diversity can be magnified by virtue of the oligomeric structure of the functional channel complex (see introductory section of this paper). Many of the principal subunits can form functional homomultimeric as well as heteromultimeric channels. Depending on the number of possible combinations, this can dramatically increase the number of possible functionally distinct channels obtained from these subunits.

Finally, channel function can also be influenced by auxiliary subunits and posttranslational modifications. If the channel complex exists with the auxiliary proteins in some cells and without them in other cells, or if it is differentially modified by posttranslational modification, these factors can also increase the diversity of functional units. This section highlights the contributions of these important mechanisms to K^+ channel function and diversity.

Heteromultimeric Assembly of Principal Subunits

Heteromultimeric assembly of K^+ channel proteins can theoretically provide the cell with a "modular" system for increasing K^+ channel diversity while reducing the requirement for more genes. For example, 210 functionally distinct tetrameric channels of different subunit combinations might be formed from seven different subunits.[j] Channel diversity can be increased even more if the possibility of heteromultimerization of alternative splice variants is considered.

When considering the large overlap in the expression of different K^+ channel subunits (see TABLE 5), it is quite possible that many native channels are the result of heteromeric association of primary subunits. However, coexpression of two subunits within a given cell does not necessarily warrant the occurrence of coassembly (see below). It is thus of great importance to elucidate the mechanisms that govern subunit recognition and assembly in order to understand the potential for heteromultimer formation and the composition of native channels. Here we discuss what is known about the rules governing subunit interactions and evidence for their formation in native tissue in the different families of K^+ channels.

Heteromultimeric Assembly of Kv and KQT Principal Subunits

For Kv1–Kv4 subfamilies, coexpression of different Kv cRNAs of the same, *but not of different*, subfamilies in *Xenopus* oocytes leads to the expression of channel properties that can not be the result of the sum of two independent channels. These currents have been interpreted as resulting from novel K^+ channel proteins formed as heteromultimers from different principal subunits of the same Kv subfamily.[40–44] These heteromultimeric channels tend to have properties that are intermediary between those of the two homomultimeric channels, but in some cases certain properties dominate. For example, a channel containing three noninactivating and one N-type inactivating subunit produces an inactivating channel.[20,41–43] In another example, Kv1.6 subunits have been shown to have a specific N-type inactivation-prevention (NIP) domain, which produces noninactivating currents when heteromultimerized.[45] Subfamily selectivity among Kv subunits is the result of recognition domains located in the N-terminal region of the protein and referred to as the NAB or T1 domains.[46,47] Interestingly, these domains are also involved in the interaction of Kv1 proteins with auxiliary (Kvβ) subunits.[48,49]

Evidence for the heteromultimerization of Kv proteins from the same subfamily *in vivo* has come from coimmunoprecipitation experiments in rat and mouse brain.[50–53] (also see

[j] [p+(n-1)]!/[p!(n-1)!], where p is the aggregation number and n is the number of subunits.

Rudy *et al*., volume). For example, antibodies specific to Kv1.1 immunoprecipitate Kv1.2 and Kv1.4 proteins in nondenatured brain membrane extracts.[50,51] The coexpression of Kv1.4 and Kv1.2 in axons and terminals of many cells suggests the native A-type K^+ current may result from Kv1.4/Kv1.2 heteromultimers within these compartments.[50] Conversely, subunits of the same subfamily have also been shown to localize to separate compartments within the same cell.[54] The cellular mechanisms of subunit targeting and assembly could be important as well. Whether or not heteromultimers are formed will depend on whether channel assembly occurs before or after the subunits have been sorted and shipped to their appropriate destinations.

The two Kv2 subfamily members (Kv2.1 and Kv2.2) are able to function as homomultimeric or heteromultimeric channels. There are reports that their kinetics and voltage dependence are altered when they are coexpressed with members of other, closely related, Kv subfamilies (Kv5, Kv6, Kv8, Kv9; see FIG. 1).[55–57] An enormous potential for functional diversity is apparent when considering all of the possible combinations of these principal subunits. Interestingly, members of the Kv5, Kv6, Kv8, and Kv9 subfamilies do not express currents by themselves in heterologous expression systems. Since the primary sequence similarity of Kv5, Kv6, Kv8, and Kv9 principal subunits with the Kv2 subfamily members are particularly high in the T1 domain, one can speculate that these coassembly principal subunits may have evolved to regulate the function of Kv2-related proteins.

The KQT family currently has three members. The first to be described, KQT1 (KvLQT1), is found predominantly in the heart and liver, whereas KQT2 and KQT3 expression is restricted to the brain. Coexpression of KCNQ2 and KCNQ3 in *Xenopus* oocytes results in a 15-fold increase in current amplitude compared to expression of each subunit alone.[58] The overlapping distribution of KQT2 and KQT3 suggest they may function only as heteromultimers *in vivo*. In support of this argument, it is interesting to note that mutations of these two genes both give rise to the same genetic disorder (TABLE 1).

Heteromultimeric Assembly of eag, erg, and elk Subunits

There is currently a single published mammalian homologue of the *Drosophila* eag that produces currents in heterologous expression systems (TABLE 1). Although more eag family members have been described, the full-length cDNA coding sequences remain to be cloned and expressed (see chapter by Ganetzky, this volume). There are three members of the Erg subfamily with diverse physiological properties. However, their interactions have not been characterized. A mammalian elk homologue has been cloned and was found to produce functional currents. At least two new elk family members have been discovered.[59]

Heteromultimers between the two splice variants of erg (erg1a and erg1b; TABLE 1) have been studied *in vitro*, resulting in currents with properties more similar to those of the native current (I_{Kr}) in heart.[60] It is not yet known whether eag, erg, and elk principal subunits can coassemble as heteromultimers. With the cloning and expression of more members of each subfamily, it will be interesting to see if they follow the same rules for heteromultimerization as Kv channels. There is already evidence that subunit interactions within this family will be complicated. For example, it has been suggested that members of the eag family can interact with members of the Kv family in *Xenopus* oocytes.[61] However, whether such interactions will take place *in vivo* remains to be determined.

Heteromultimeric Assembly of Kir Subunits

There does not appear to be a consistent manner in which Kir subunits coassemble within or between subfamilies. The four members of the Kir3 subfamily serve as an example of where heteromultimerization of subunits from the same subfamily appears to be a necessary requirement for the formation of functional channels. Thus, the channels responsible for the acetylcholine-activated K^+ current in atrial muscle is a complex of Kir3.1 and Kir3.4 proteins (see chapter by Wickman *et al*., this volume). Neurons probably contain functional heteromultimers of Kir3.1 with Kir3.2 or Kir3.3 (see chapter by Kevin Wickman, this volume; see also Ref. 62). In contrast to the Kir3 subunits, the evidence for heteromultimeric assembly within other Kir subfamilies members is less strong or there are even indications to the contrary. For example, despite the colocalization of Kir2.1 and Kir2.3 in neural tissue,[63] biochemical and electrophysiological experiments examining protein-protein interactions suggest that heteromultimeric coassembly of subunits within the Kir2 subfamily may not occur.[64] Recent experiments using antisense oligonucleotides directed against Kir2.1 transcripts demonstrated a specific inhibition of a 21-pS conductance channel (which is equivalent to the unitary conductance of Kir2.1 in heterologous expression systems) in cardiac myocytes.[65] Since the occurrence of native inward rectifier K^+ channels with different unitary conductances was unchanged, one could argue that heteromultimeric assemblies of Kir2.1 with other K^+ channel principal subunits did not occur (or more unlikely that, if it did, the single-channel conductance remained unchanged). The regions responsible for determining compatibility within members of the Kir2 subfamilies have been elucidated using a combination of deletion mutants and chimeric channels.[64] The results of such experiments reveal interactions conferred by domains found within the proximal C-terminus and second transmembrane segments. However, it is possible that other regions may also play a role.[66]

There are also published examples of heteromultimerization between subunits from different Kir subfamilies. For example, Kir5.1 (which by itself expresses no current in oocytes[34]) significantly alters expression levels and the single-channel conductance of Kir4.1, a member of a different subfamily.[67] The finding that Kir5.1 altered neither current amplitude nor the macroscopic phenotype of Kir1.1, Kir2.1, Kir2.3, Kir3.1, Kir3.2, or Kir3.4 suggests that a specific interaction between Kir4.1 and Kir5.1 may occur *in vivo*.

Heteromultimeric Assembly of slo and SK Subunits

The slo family currently has two members (TABLE 1). Heteromultimerization between the two slo principal subunits has not been examined. Despite the small number of family members, slo1 (the principal subunit of BK Ca^{2+}-activitated K^+ channels) has a very large number of possible alternative spliced versions. Tested splice variants show functional variability.[68–71] Heteromultimerization between splice variants could thus allow an enormous number of possible functionally diverse channels. Single-cell RT-PCR studies of individual hair cells of the chick cochlea demonstrate that multiple splice variants of slo are found within a single cell[72,73] (see also chapter by Robert Fettiplace, this volume), suggesting that at least a proportion of this potential diversity might indeed occur *in vivo*.

The SK family now has four members (TABLE 1). SK1–3 each express small-conductance Ca^{2+}-activated K^+ channels with similar properties but differing in their pharmacology (see chapter by Adelman, this volume). The fourth (SK4) expresses an intermediary-

conductance Ca^{2+}-activated K^+ channel. Coexpression of these genes has not yet been tested, but their overlapping tissue distribution suggests that heteromultimer formation might be possible *in vivo*.[74] Although the SK1-SK3 subunits have very similar properties, the NH_2 and COOH terminal amino acid sequences vary significantly which could potentially provide additional diversity through differential modulation through associating proteins. Conversely, divergence in these regions may also prevent heteromultimer formation.

Heteromultimeric Assembly of "Leak" K^+ Channel Subunits

Heteromultimer formation within the 4TMD family of K^+ channels has not yet been explored. It can be predicted from the number of similar genes expressed in *C. elegans* that a multitude of "two-pore" subunits may exist in mammals (see chapter by Larry Salkoff, this volume). Whether or not the diversity of this family of K^+ channels is increased by heteromeric subunit interactions remains to be determined.

Auxiliary Subunits

There is increasing evidence for the existence of auxiliary subunits, some peripheral and some integral membrane proteins, that regulate the expression levels and functional properties of K^+ channel proteins (TABLE 1). Several types of K^+ channels are affected in this manner, including those consisting of Kv, KQT, eag, slo, and Kir principal subunits.

To date, the auxiliary subunits that have been characterized in most detail are the members of the Kvβ auxiliary subunit family. They are products of three genes (TABLE 1). We adopt the nomenclature shown in TABLE 1 to conform to convention and to signify their sequence relatedness. Affinity purification of brain K^+ channels using dendrotoxin led to the isolation of an auxiliary "β" subunit (β2 or Kvβ2) that binds noncovalently with a 1:1 stoichiometry to Kv1 principal subunits.[75,76] Identification of this sequence soon led to the isolation of related cDNAs. Three genes have been identified, and each has been shown to produce several isoforms by alternative splicing (TABLE 1). These subunits lack putative transmembrane domains, potential glycolsylation sites, or leader sequences, suggesting that they are cytoplasmic proteins.[76] Although they have some sequence similarities with aldo-keto reductase enzymes, Kvβ auxiliary subunits probably lack such enzymatic activity.[77] A detailed review of Kvβ subunits is present in this volume (chapter by Pongs *et al*.). Briefly, one function of the three Kvβ1 isoforms (which contain a variable inactivating ball domain) is to induce inactivation in otherwise noninactivating Kv1 channels by providing an extrinsic N-type inactivating domain.[78] In contrast, Kvβ2 accelerates inactivation only when Kv1.4 subunits form part of expressed (inactivating) Kv1 channels, probably by interacting with the intrinsic Kv1.4 inactivating ball.[79–81] For some Kv1 channels, Kvβ1 and Kvβ2 may also shift the voltage dependence of activation in heterologous expression systems.[82] A second role assigned to these auxiliary subunits is to act as chaperones during channel biosynthesis[83,84] and thus to increase expression levels, an effect first described for the interaction of Kvβ2 with Kv1.4.[79] While Kvβ1 and Kvβ2 proteins appear to interact exclusively with Kv1 principal subunits, Kvβ3 and a recently discovered K^+ channel auxiliary subunit, KChAP,[85] appear to interact also with Kv2 principal subunits and to enhance current levels without an effect on channel kinetics or gating.[85,86]

Although Kvβ3 and KChAP appear to have similar roles, their mechanisms of action might be different since chimeras between Kv2.1 and Kv2.2 indicate that the COOH-terminal end of the Kv2.2 protein is essential for its Kvβ3 sensitivity.[86] In contrast, KChAP appears to bind to the NH_2 termini of Kv1 and Kv2 principal subunits.[85]

Since assembly of Kv1 principal subunits occurs mainly in a subfamily-specific manner, it has been suggested that this subfamily specificity may also apply to their association with auxiliary subunits.[49,87] However, this may not strictly be the case, since there is evidence that the *Drosophila* auxiliary subunit homologue Hyperkinetic (*Hk*) associates with members of the *eag* and *Shaker* families and alters their expression levels and/or kinetics.[88] Recently, yet another auxiliary subunit has been identified, KCR1, which accelerates the activation of rat *eag* expressed in *Xenopus* oocytes or in COS-7 cells.[89]

MinK is a 15-kDa single-transmembrane protein that is present in cardiac and auditory cells.[5,90–93] that coassembles with KvLQT1 to form the slow cardiac repolarization current (I_{Ks}).[94–96] (see chapter by Sanguinetti, this volume) and with HERG to regulate the rapidly activating cardiac delayed rectifier (I_{Kr}).[97] Hence, minK contributes to two important outward currents that determine repolarization from the plateau phase of the action potential in ventricular myocytes.[98,99] Although it does not contain a pore domain characteristic of K^+ channels' principal subunits,[100,101] mutagenesis experiments suggest that minK may contribute to the formation of the channel pore,[102] implying that K^+-selective pores may include structures other than P domains or structures having a strict P-loop geometry.

The auxiliary subunit of high-conductance Ca^{2+}-activated K^+ channels (composed of principal subunits of the slo family) is a two-transmembrane protein of 191 amino acids and bears little sequence homology to any other known K^+ channel auxiliary subunit.[103] It has been shown that this subunit contributes to the high-affinity receptor for charybdotoxin[104] but apparently does not affect sensitivity to this drug. Mutagenesis has revealed that the large extracellular loop of the maxi K^+ channel auxiliary subunit has a restricted conformation with two important disulfide bridges. Specifically, four amino acids are critical in conferring high-affinity 251-Chtx binding to the complex. Functionally, it has been demonstrated that this subunit also confers higher Ca^{2+} sensitivity to Ca^{2+}-activated K^+ channels containing slo subunits (see TABLE 4).

Slob is a novel protein isolated by a yeast two-hybrid screen based on its interaction with the COOH-terminal domain of the *Drosophila* slowpoke (dSlo) Ca^{2+}-dependent K^+ channel.[105] Native Slob and dSlo coimmunoprecipitate together from fly head lysates, and they redistribute and colocalize in discrete intracellular structures when coexpressed in heterologous host cells. Although direct application of Slob to excised inside-out membrane patches can strongly activate dSlo (but not human slowpoke channels),[105] the *in vivo* function of Slob remains to be elucidated.

The Kir channel accessory subunit Kv2.2v (TABLE 1) acts as a negative regulator of the inward rectifier Kv2.2 through heteromeric assembly.

Finally, although Kir6 principal subunits (or C-terminal truncated Kir6 subunits) can express independently in heterologous expression systems,[106,107] the functional phenotype of native K_{ATP} channels is conferred only when Kir6 principal subunits are coexpressed with auxiliary subunits (sulfonylurea receptors, SUR1 or SUR2; see TABLE 1). SUR1 and SUR2 are members of the 12 transmembrane-spanning domain proteins, called ATP-binding cassette (ABC) proteins. SUR1 or SUR2 associate with Kir6 subunits as an octameric assembly.[108] Prevailing evidence suggests that the inhibitory effects of nucleotides on K_{ATP} channels are mediated via the principal Kir6 subunits, whereas the potentiation by

ADP is conferred by the sulfonylurea receptor subunit, SUR.[106] SUR auxiliary subunits are also responsible for conferring properties such as sensitivity to pharmacological compounds that block (e.g., glibenclamide) or increase (e.g., pinacidil) opening of the multimeric channel complex. The specific assembly between the principal and auxiliary subunits that takes place seems to be at least partly responsible for the functional diversity of native K_{ATP} channels (Table 3; reviewed by Babenko[109]).

Alternative Splicing

TABLE 1 lists alternative splice versions of principle and accessory K^+ channel subunits known to date. In many cases the use of alternative exons results in channels with diverse properties. TABLE 6 lists only the K^+ channel principal subunits studied so far where alternative splicing leads to diversity in channel function. The functional consequences of K^+ channel gene splicing have been grouped into four categories: (1) effects on electrophysiological properties, where splicing changes channel properties such as kinetics; (2) effects on expression, where splicing results in changes in gene expression and/or tissue distribution; (3) effects on subcellular localization, where alternative splicing results in changes in channel targeting to different cellular compartments; (4) effects on modulation, where splicing alters the effects of modulators (e.g., by protein kinases). Blank spaces indicate that no changes are observed or they remain to be tested. The purpose of TABLE 6 is to emphasize how K^+ channel diversity could be enhanced by mechanisms other than gene duplication and divergence. Furthermore, it should be emphasized that native channels may result from the heteromultimerization between different splice variants, thus increasing diversity even further.

RNA Editing

RNA editing by adenosine deamination has evolved as a mechanism to produce functionally diverse proteins from the same gene. The best-characterized example in the brain is the RNA editing of glutamate-activated receptor channel (GluR) mRNA[110,111] (see chapter by Sprengel in the Glutamate Receptor section, this volume). RNA editing of mammalian K^+ channels has not been described. However, in squid, five purine transitions found in cDNA clones encoding *sqKv2* K^+ channel are also generated by RNA editing.[112] The conductance-voltage relationships determined for the two most frequently edited sites of *sqKv2*, Y576C (pore region) and I597V (S6 segment), did not differ. However, the rate of channel closure upon repolarization was significantly affected by both substitutions.[112]

Posttranslational Modifications

Posttranslational modifications, particularly protein phosphorylation and dephosphorylation, are known to underlie modulation of the activity of ion channels, and hence, modulation of neuronal excitability.[113–115] Posttranslational processing or the distinct intracellular microenvironment of the channel could contribute to the diversity of K^+ channels in native cells. The modulation of Kv3.4 channels by protein kinase C (PKC) is a

good example of how channel function and phenotype can be altered in this manner.[116] Phosphorylation of the amino-terminal activation domain of Kv3.4 by PKC suppresses N-type inactivation, converting these channels from rapidly inactivating A type to noninactivating delayed rectifier type.[116,117] Similarly, Roeper and coworkers found that the balance between phosphorylated and dephosphorylated Kv1.4 channels is regulated by changes in intracellular Ca^{2+} concentration, rendering Kv1.4 inactivation gating Ca^{2+} sensitive.[118] They showed that Ca^{2+}-calmodulin–dependent protein kinase (CaMKII) phosphorylation of a single amino-terminal residue of Kv1.4 slows inactivation gating and accelerates recovery from N-type inactivated states; while on the contrary, dephosphorylation of this residue induces a 5 to 10 times faster inactivation of Kv1.4.[118]

Finally, the dynamic regulation of ion channel interactions with the cytoskeleton may contribute to the diversity of K^+ channel properties and mediate aspects of synaptic plasticity (see chapter by Sheng, this volume). For example, Kir2.3 bind to PSD-95, a cytoskeletal protein of postsynaptic densities that clusters NMDA receptors and voltage-dependent K^+ channels: Kir2.3 colocalizes with PSD-95 in neuronal populations in forebrain, and a PSD-95/Kir2.3 complex occurs in hippocampus.[119] Within the C-terminal tail of Kir2.3, a serine residue critical for interaction with PSD-95, is also a substrate for phosphorylation by protein kinase A (PKA).[119] Thus, ion channel interactions with the postsynaptic density are regulated by a physiological mechanism, since stimulation of PKA in intact cells causes rapid dissociation of the channel from PSD-95.[119,120] It also follows from this work that any posttranslational modification that accounts, directly or indirectly, for changes in the localization or clustering of K^+ channels, may contribute to the functional diversity of this family of ion channels.

SUMMARY AND PERSPECTIVE

We attempted to provide a comprehensive, yet succinct, overview of the molecular diversity of K^+ channel subunits. However, due to the rapidly evolving nature of this field of research, it is very likely that this chapter will be outdated by the time of publication. With the recent sequencing of bacterial and yeast genomes, it became clear that many genes exist for which no definite function could be assigned. Given the relatively simple genome of these organisms compared to that of humans (~100,000 genes) and the fact that only a small proportion of the human genome has currently been sequenced, it will be no surprise if many more genes coding for K^+ channel principal and auxiliary subunits are uncovered in the near future. Importantly, sequences might become available to describe a variety of other protein subunits interacting with channels and to modify their function and expression patterns. The incredible diversity of subunits and subunit interaction at the molecular level is at present hard to reconcile with the more limited (although diverse in its own right) complement of native K^+ channels in cells. The correlation between molecular subunits and native K^+ channels in normal and pathophysiological states must remain to be a priority for future research.

These advances also have the promise of providing a wealth of information that will be of benefit to those studying regulation of K^+ channel expression. Promoters, enhancers, and silencers provide yet another level of diversity by virtue of controlling expression levels in response to environmental influences, as well as tissue-specific expression patterns. The recent progress in the determination of the 3D structure of a bacterial K^+ channel

protein[17] will pave the way for similar studies on K^+ channel principal and auxiliary subunits. These structural analyses should provide better tools with which to study protein-protein interactions as well as drug-protein interaction. Ultimately, this new knowledge can be used to develop more effective protein-specific therapeutic approaches for pathophysiological states involving K^+ channel dysfunction. This, and the possibility of gene-specific treatment of diseases related to defects in channel subunit proteins, are increasingly areas of active research and will remain fertile areas for future studies.

TABLES

TABLE 1. Mammalian K^+ Channel Principal and Auxiliary Subunits

A. Principal Subunits of Voltage-Activated K^+ Channels

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
Kv1.1	KCNA1	Human	HUKI	12p13		L02750	Episodic ataxia, myokymia syndrome
		Rat	RK1 RCK1 RBK1			X12589	
		Mouse	MK1 MBK1	6		M30439	
Kv1.2	KCNA2	Human	HUKIV	12		L02752	
		Rat	RBK2 RK2 RCK5 NGK1			J04731	
		Mouse	MK2	3		M30440	
Kv1.3	KCNA3	Human	HUKIII HPCN3	1p21		M55515	
		Rat	RCK3 RGK5 KV3			M31744	
		Mouse	MK3	3		M30441	
Kv1.4	KCNA4	Human	HUKII HPCN2	11p14		M55514	
		Rat	RCK4 RHK1 RIC3			M32867	
		Mouse		2		U03723	

A. Principal Subunits of Voltage-Activated K^+ Channels (*continued*)

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
Kv1.5	KCNA5	Human	HK2	12p13		M55513	
			HPCN1				
		Rat	KV1			M27158	
			RK4				
			RCK7				
		Mouse		6		L22218	
		Mouse	Kv1.5_5′		Kv1.5a	C49507	
			Kv1.5_3′		Kv1.5b	C49507	
Kv1.6	KCNA6	Human	HBK2			X17622	
		Rat	KV2			M27159	
			RCK2				
		Mouse	MK1.6	6		M96688	
Kv1.7	KCNA7	Human		19q13.3			
		Mouse		7		AF032099	
Kv2.1	KCNB1	Human		20q13.2		L02840	
		Rat	DRK1			X16476	
		Mouse		2		M64228	
Kv2.2	KCNB2	Human				U69962	
		Rat	CDRK			M77482	
Kv3.1	KCNC1	Human	NGK2-KV4	11p15	Kv3.1a	S56770	
			KShIIIB				
		Mouse	NGK2	7		Y07521	
			Mshaw22				
		Rat	KV4		Kv3.1b	M37845	
			Raw2				
Kv3.2	KCNC2	Human		12			
		Rat	RKShIIIA		Kv3.2a	M34052	
			Rshaw12				
		Mouse	Mshaw12	10			
		Rat			Kv3.2b	M59211	
		Rat			Kv3.2c	M59213	
		Rat	Raw1		Kv3.2d	M84202	
Kv3.3	KCNC3	Human		19q13.3–13.4	Kv3.3[a]	AF055989	
		Rat	RKShIIID		Kv3.3a	M84210	
		Rat			Kv3.3b	M84211	
		Mouse	MShaw19	7	Kv3.3c	S69381	

A. Principal Subunits of Voltage-Activated K^+ Channels (*continued*)

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
Kv3.4	KCNC4	Human	HKShIIIC	1p21	Kv3.4b	M64676	
		Rat	Raw3		Kv3.4a	X62841	
		Rat		10, 7	Kv3.4c		
Kv4.1	KCND1	Human	Kv4.1	Xp11.23	Kv4.1	AJ005898	
		Mouse	MShal			M64226	
Kv4.2	KCND2	Human		7q?			
		Rat	RK5			S64320	
		Mouse		6			
Kv4.3	KCND3	Human	Kv4.3M		Kv4.3a	AF048712	
		Rat	KShIVB			U42975	
		Rat	Kv4.3S		Kv4.3b	L48619	
		Human	Kv4.3L		Kv4.3c	AF048713	
		Rat				AB003587	
Kv5.1	KCNH1	Human	KH1	2p25		AF033382	
		Rat	IK8			M81783	
Kv6.1	KCNH2	Human	KH2	20q13		AF033383	
		Rat	K13			M81784	
Kv8.1		Human		8q22.3–8q24.1			
		Rat	Kv2.3r			X98564	
		Mouse				U62810	
Kv9.1	KCNS1	Human				AF043473	
		Mouse				AF008573	
Kv9.2	KCNS2	Human		8q22.4			Cohen syndrome?
		Mouse				AF008574	
Kv9.3	KCNS3	Human				AF043472	
		Rat				AF029056	
Eag1		Rat	Reag-1		Eag1a	Z34264	
		Mouse	Meag-1			U04294	
		Bull	BTeag1			Y13430	
		Bull	BTeag2		Eag1b	Y13431	
Eag2[b]		Rat				AF073891	
Elk1[c]		Rat				AF61957	
Elk2		Human	Helk-2[d]				
		Rat				AF073892	
		Mouse	Melk-2[e]				

A. Principal Subunits of Voltage-Activated K^+ Channels (*continued*)

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
Erg1	LQT	Human	h-erg	7q35–7q36	Erg1a	U04270	LQT2 syndrome
		Rat	r-erg			Z96109	
		Mouse	Merg1a	5		AF012868	
		Mouse	Merg1a'		Erg1b	AF012871	
		Human[f]	HERGb		Erg1c		
		Mouse	Merg1b			AF012869	
Erg2		Rat				AF016192	
Erg3		Rat				AF016191	
KQT1	KCNQ1	Human	KvLQT1	11p15.5	KCNQ1a	U40990	Long QT syndrome, type I
		Mouse				U70068	
		Human	tKvLQT1		KCNQ1b	AF051426	
KQT2[g]	KCNQ2	Human		20q13.3	KCNQ2a	Y15065	
						AF033348	Benign familial neonatal convulsions (BFNC)
		Human	KQT2.1		KCNQ2b	AF074247	
KQT3	KCNQ3	Human		8q24		AF033347 (partial clone)	BFNC

[a] This sequence differs from Kv3.3a, but this could be a sequencing artifact.

[b] B. Ganetzky also described a partial rat Eag2 sequence in this volume (Reag-2). There are some differences between his sequence and the sequence submitted to Genbank (AF073891).

[c] B. Ganetzy also described a partial Elk1 sequence in this volume (Relk-1). There are clear differences between his sequence and the rat Elk1 sequence submitted to Genbank (AF61957).

[d] B. Ganetzky called this sequence Helk-2. According to the alignment on partial sequences, it seems to be the human homolog of rat Elk2 submitted to Genbank.

[e] Same case as in Helk-2.

[f] Refs. 60 and 140.

[g] The existence of 11 splice variants have been reported (no data available in databases).[141]

B. Principal Subunits of Ca^{2+}-Activated K^+ Channels

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
SK1	KCNN1	Human	hSK1			U69883	
		Rat	rSK1			U69885	
SK2	KCNN2	Rat	rSK2			U69882	
SK3	KCNN3	Human	hKCa3	22q11–22q13.1		AF031815	Schizophrenia? Bipolar disease?
			hSK3				
		Rat	rSK3			U69884	
SK4	KCNN4	Human	hKCa4	19q13.2		AF000972	
			hSK4				
			hIKCa1				
			hIK1				
		Mouse	mIK1			AF042487	
Slo1	KCNMA1	Human	hslo1	10q22.2–10q23.1		U23767	
		Rat	rslo1			U55995	
		Mouse	mslo1[a]			L16912	
Slo3		Human	hslo3			n/a	
		Mouse	mslo3			AF039213	

[a]There is alternative splicing.

C. Principal Subunits of Inward Rectifier K^+ Channels

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
Kir1.1	KCNJ1	Human	ROMK1	11q24	Kir1.1a	U12541	Barter's syndrome
		Rat	KAB-1			X72341	
		Human	ROMK2		Kir1.1b	U12542	
			ROMK1B				
		Rat				S69385	
		Mouse				AF012834	
		Human	ROMK3		Kir1.1c[a]	U12543	
			ROMK1A				
		Rat				S78155	
		Human	ROMK4		Kir1.1d	U12544	
		Human	ROMK5		Kir1.1e	U12545	
		Human	ROMK6		Kir1.1f[b]	U65406	
		Rat[c]				n/a	
		Human[d]	ROMK1C		Kir1.1g	n/a	
		Rat	ROMK6.1		Kir1.1h	AF081368	
Kir2.1	KCNJ2	Human	IRK1	17		U12507	
			HH-IRK1				
		Rat	RBL-IRK1			Q64273	
		Mouse	MMIRK1			X73052	
			MB-IRK1				
Kir2.2	KCNJ12	Human	IRK2	17p11.1		L36069	
			HIRK				
		Rat	RB-IRK2			X78461	
		Mouse	MB-IRK2			X80417	
Kir2.2v	KCNJN1	Human	HKIR2.2v	17p11.2–17p11.1		U53143	
Kir2.3	KCNJ4	Human	HIR	22q13.1		U07364	
			HRK1				
			IRK3				
		Rat	BIR11			X87635	
		Mouse	MB-IRK3			U11075	
Kir2.4	KCNJ14	Rat	IRK4			AJ003065	

C. Principal Subunits of Inward Rectifier K^+ Channels (*continued*)

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
Kir3.1	KCNJ3	Human	HGIRK1	2q24.1	Kir3.1a	U50964	
		Rat	GIRK1			L25264	
			KGA				
			KGB1				
			$Kir3.1_{10}$				
		Mouse	MBGIRK1			1582163	
		Rat	$Kir3.1_{01}$		Kir3.1b	U60025	
		Rat	$Kir3.1_{00}$		Kir3.1c	U42423	
			Kir3.1delta				
		Rat	$Kir3.1_{11}$		Kir3.1d	U72410	
			Kir3.1-deltaB				
Kir3.2	KCNJ7	Human	GIRK2	21q22.1	Kir3.2a[e]	L78480	Mapped to Down syndrome chromosome region 1
	KCNJ6		KATP2				
			BIR1				
		Rat	KATP-2			U21087	
		Mouse	GIRK2−1	16		U51122	Weaver mouse mutation
			MBGIRK2				
		Mouse	GIRK2A-1		Kir3.2b	U51123	
		Mouse	GIRK2A-2		Kir3.2c	U51124	
		Mouse	GIRK2B		Kir3.2d	U51125	
		Mouse	GIRK2C		Kir3.2e	U51126	
		Mouse	GIRK2D		Kir3.2f[f]	n/a	
Kir3.3	KCNJ9	Human	GIRK3	1q21−1q23		U52152	
		Rat	RBGIRK3			L77929	
		Mouse	MBGIRK3			U11860	
Kir3.4	KCNJ5	Human	GIRK4	11q24		U52154	
			CIR				
			hc-KATP1				
		Rat	rc-KATP1			L35771	
		Mouse				U72061	
Kir4.1 (Kir1.2)	KCNJ10	Human		1q		U52155	
		Rat	BIR10			X83585	
			KAB-2				

C. Principal Subunits of Inward Rectifier K^+ Channels (*continued*)

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
Kir4.2 (Kir1.3)	KCNJ15	Human		21q22.2		U73191	Mapped to Down syndrome chromosome region 1
Kir5.1	KCNJ16	Rat	BIR9			P52191	
Kir6.1	KCNJ8	Human[g]	uKATP–1	12p12	Kir6.1a[h]	D50312	
						AF015605	
		Rat				D42145	
		Mouse	muKATP–1	6		D88159	
		Human			Kir6.1b	AF015606	
		Human			Kir6.1c	AF015607	
Kir6.2	KCNJ11	Human	BIR hBIR IKATP	11p15.1		D50582	Familial persistent hyperinsulinemic hypoglycemia of infancy
		Rat	rBIR			D86039	
		Mouse	mBIR			D50581	
Kir7.1 (Kir1.4)	KCNJ13	Human				AF061118	
		Rat				AJ006129	

[a] The human and the rat ROMK3 transcripts are not true orthologs in terms of alternative splicing and exons usage.

[b] The human and the rat ROMK6 transcripts do not correspond in terms of alternative splicing and exons usage.

[c] Ref. 142.

[d] Ref. 143.

[e] The three mammalian transcripts (human, rat, and mouse) do not correspond to each other in terms of alternative splicing.

[f] Ref. 144.

[g] Two accession numbers are given here. D50312 represents the coding sequence, and AF015605 represents splice variant A for the 5′UTR.

[h] The three mammalian transcripts do not correspond to each other in terms of alternative splicing.

D. Principal Subunits of Two-Pore K^+ Channels

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
TWIK	KCNK1	Human	TWIK-1	1q42–1q43		U33632	
		Mouse		8		U86009	
TREK	KCNK2	Mouse				U73488	
TASK		Human				AF006823	
		Rat				AF031384	
		Mouse				AF006824	
TRAAK		Mouse				AF056492	

E. Auxiliary Subunits of Kv and eag Channels

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
Kvβ1	KCNA1B	Human	HKvβ1a	3q26.1	Kvβ1.1	U33428	
		Rat	Kvβ1			X70662	
		Mouse				X97281	
		Human	hKvβ3		Kvβ1.2	U16953	
		Human	hKvβ1.3		Kvβ1.3	L47665	
Kvβ2	KCNA2B	Human		1p36.3	Kvβ2.1	U33429	Charcot-Marie-Tooth disease, type 2A?
		Rat	RCKβ2			X76724	
			Kvβ2.1				
		Mouse		4		U31908	
		Human			Kvβ2.2	AF044253	
Kvβ3	KCNA3B	Human	KCNA3.1B	17q13	Kvβ3.1	AF016411	
		Rat	Kvβ3			X76723	
			RCKβ3				
		Mouse	mKvβ4		Kvβ3.2	U65593	
KChAP		Rat				AF032872	

F. Auxiliary Subunits of Ca^{2+}-Activated K^+ Channels

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
Slo Beta		Human				U38907	
		Rat				U40602	
		Mouse				AJ001291	

G. Auxiliary Subunits of Inward Rectifying K^+ Channels

Subunit	Gene Locus Designation	Species	Trivial Name	Chromosome Localization	Alternative Splicing	Accession Number	Associated Diseases
SUR1	SUR	Human		11p15.1		Q09428	Familial persistent hyper-insulinemic hypo-glycemia of infancy
		Rat				X97279	
		Rat			SUR1B	AF039595	
SUR2		Human		12p12.1	SUR2A	AF061324	
		Mouse	mSUR	6		D80637	
		Human			SUR2B	AF061324	
		Rat				AF019628	
		Mouse				D086038	

TABLE 2. Sequence Identity (%)[a] between Genes Coding for K^+ Channel Principal Subunits

A. 6TMD K^+ Channel Principal Subunits

	Kv1	Kv2	Kv3	Kv4	Kv5	Kv6	Kv8	Kv9	KQT	SK	eag	erg	elk	slo
Kv1	**74-88**	46-49	44-48	41-45	38-40	37-39	35-36	36-42	19-24	13-18	7-13	11-14	11-13	11-15
Kv2		**99**	42-43	40-41	52	42	46	46-50	22-23	13-14	9-14	13	11-14	14-16
Kv3			**87-92**	37-38	38-40	34-35	34-35	33-39	19-23	11-14	7-11	12-14	11-13	11-18
Kv4				**87-94**	38-39	35-37	35-37	33-35	19-25	12-13	10-13	12-14	11-15	11-16
Kv5					**100**	38	41	39-45	22-25	12-14	7-11	10-11	12-13	12-15
Kv6						**100**	41	39-40	20-22	12-14	6-12	10-11	12	10-16
Kv8							**100**	46-49	20-24	13-16	9-15	13-14	14-16	11-12
Kv9								**59-63**	20-23	12-15	8-14	13-14	12-17	11-17
KQT									**55-71**	10-15	9-14	12-14	11-15	8-13
SK										**43-91**	5-12	8-13	10-13	12-15
eag											**70**	42-51	37-48	11-12
erg												**88-89**	51-54	9-14
elk													**67**	12
slo														**59**

B. SK Family Principal Subunits

	SK2	SK3	SK4
SK1	**91**	**85**	43
SK2		**84**	43
SK3			44

C. Kir Principal Subunits

	Kir1/Kir4/Kir7	Kir2	Kir3	Kir5	Kir6
Kir1/Kir4/Kir7	36-**62**	36-50	29-42	27-35	32-46
Kir2		**61-94**	45-52	44-48	39-46
Kir3			**58-77**	36-38	42-46
Kir5				**100**	37
Kir6					**69**

D. Kir1.1, Kir4.1 and Kir4.2 Principal Subunits

	Kir4.1 (Kir1.2)	Kir4.2 (Kir1.3)	Kir7.1 (Kir1.4)
Kir1.1	47	47	36
Kir4.1		**62**	39
Kir4.2			37

[a]The percent identity values were generated by importing alignment files created by Clustal X into the program Genedoc.

TABLE 3. Native Channels and Physiological Significance of the Molecular Diversity of K^+ Channels

Channel Proteins	Native Channels
Kv1.x (probably in heteromultimeric channels also containing Kvβ subunits)	4-AP–sensitive voltage-gated K^+ channels of both delayed rectifier and "A" types, including the "D" current (a dendrotoxin–sensitive voltage-dependent current with variable kinetics and voltage dependence; also sensitive to very low 4-AP concentrations).[121,122] "D" channels are probably various combinations of Kv1.2 (or Kv1.1 or Kv1.6) with other Kv1 proteins and Kvβ subunits. Kv1.4 (possibly in homomultimeric and heteromultimeric channels) might be responsible for fast "A" type K^+ currents in terminals and axons.[50,123,124] Use of antisense oligonucleotides suggests that Kv1.5 is responsible for the ultrarapid delayed rectifier current (I_{Kur}) in human atrium.[125]
Kv2.x, possibly in combination with Kv5.1, Kv6.1, Kv8.1, and Kv9.1–9.3	4-AP–sensitive delayed rectifiers with variable kinetics, slow inactivation and voltage dependence. Oxygen-sensitive currents in pulmonary artery myocytes.[126]
Kv3.1–Kv3.4 (may exist as homo- and heteromultimeric channels)	High voltage–activating, fast deactivating voltage-dependent K^+ currents, which may contain a fast inactivating component if they include Kv3.4 proteins. Channels containing mainly Kv3.1 and Kv3.2 proteins (and perhaps Kv3.3) are most likely delayed rectifiers with slow inactivation. Currents blocked by 1 mM TEA which are key in the repolarization of short action potentials in fast spiking neurons (see chapter by Rudy *et al*., this volume).
Kv4.x (possibly in association with unidentified auxiliary subunits)	Classical low voltage– or subthreshold-activating A-type currents and the I_{to} in heart. Evidence for a relationship with I_{to} includes use of antisense oligonucleotides.[127,128] Blocked by mM concentrations of 4-AP.
KQT	KQT1 is responsible for the slowly activating delayed rectifier (I_{Ks}) in heart.[94,95] Mutations in this gene are responsible for a form of LQT syndrome (see chapter by Sanguinetti, this volume). KQT2 in association with KQT3 may form delayed rectifier type currents in neurons (see text). Mutations in these two genes cause a form of epilepsy (see TABLE 1).
eag	"M" current?[129,130]
elk	?
erg	Erg1 is responsible for the rapidly activating delayed rectifier current (I_{Kr}) in heart (in combination with minK).[97] Evidence includes use of antisense oligonucleotides.[131] LQT syndrome mapped to mutations of herg and minK (see TABLE 1 and chapter by Sanguinetti, this volume).
slo (different alternatively spliced versions, with and without a β subunit)	Maxi-K or BK Ca^{2+}-activated channels. Evidence includes biochemical purification from native tissue.[132,133]
SK 1–3	Small-conductance apamin-sensitive and -insensitive Ca^{2+}-activated K^+ channels (see chapter by Adelman, this volume).
SK4	Medium-conductance Ca^{2+}-activated K^+ channels.[134–136]
Two-pore K^+ channels	"Leak" K^+ channels, which help regulate the resting potential.[12]
Kir1.1–Kir1.3	Weak inward rectifiers.

TABLE 3. Native Channels and Physiological Significance of the Molecular Diversity of K^+ Channels (*continued*)

Channel Proteins	Native Channels
Kir2.1–2.4	Kir2.1: I_{K1} in cardiac ventricular myocytes, 21 pS channel.[65] Common strongly rectifying inward rectifier channel.
Kir3.1 + Kir3.4	G-protein–activated K^+ channels in neurons and heart (particularly in atrium).[137] Kir3.1 + Kir3.4 acetylcholine-activated K^+ current ($I_{K,Ach}$) in heart (see chapter by Kevin Wickman, this volume).
Kir6.1 plus SUR2B	K_{NDP} (33pS nucleotide–sensitive K^+ channel in vascular smooth muscle). Activated by ADP, GDP; blocked by glibenclamide (IC_{50} = 25 nM)
Kir6.2 plus SUR1	ATP-sensitive K^+ current ($I_{K,ATP}$) in pancreatic β-cells. γ = 70 pS; K_i (ATP) = 10 μM; KCOs (diazoxide > pinacidil), glibenclamide (IC_{50} < 10 nM)
Kir6.2 plus SUR2A	ATP-sensitive K^+ current ($I_{K,ATP}$) in heart and skeletal muscle. γ = 80 pS; K_i (ATP) = 175 μM; KCOs (pinacidil > diazoxide), glibenclamide (IC_{50} = 1.2 μM)
Kir6.2 plus SUR2B	ATP-sensitive K^+ current ($I_{K,ATP}$) in vascular smooth muscle. γ = 80 pS; K_i (ATP) = 53 μM; KCOs (pinacidil > diazoxide), glibenclamide (IC_{50} = 1 μM)

NOTE: γ = unitary conductance.

TABLE 4. Functional Properties of K^+ Channel Proteins Expressed in Heterologous Expression Systems

A. Functional Properties of Voltage-Activated K^+ Channels

	Electrophysiological Properties														
	Activation				Deacti-vation	Inactivation				Single Chan-nel g	Pharmacological Properties (IC_{50})				
	V_{on} (mV)	$V_{1/2}$ (mV)	k (mV)	τ^a	τ (ms)^b	$V_{1/2}$ (mV)	k (mV)	τ (ms)^c	τ_{rec}	(pS)	TEA_o (mM)	4-AP (mM)	DTX (nM)	CTX (nM)	Other Properties
Kv1.1	−60 to −50	−30	6 to 9	+++	14			Very slow[d]		≈ 10	0.5	0.16 to 1.1	12 to 21	NB	TEA (human) IC_{50} 20 mM? HgTX IC_{50} 31 pM
Kv1.2	−40	−5 to 5	13	+	23			Very slow		9.2 to 17	> 10	0.2 to 0.8	2.8 to 24	1.7 to 17	HgTX IC_{50} 170 pM
Kv1.3	−50	−30	5 to 7	++	38	−44.7		250 to 600		9.6 to 14	10 to 50	0.2 to 1.5	250?	0.5 to 2.6	MgTX IC_{50} 230 pM HgTX IC_{50} 86 pM Shows cumulative inactivation
Kv1.4	−50	−22	12	+++	15 to 55	−65 to −45	+2.3	$\tau_1 \approx 20$ $\tau_2 \approx 40$	2.2 to 3.8s (−80 mV)	4.7	NB	0.7 to 13	> 200	NB	
Kv1.5	−50	−10	7	+++	23			Very slow		8	NB	< 0.1 to 0.4	NB	NB	
Kv1.6	−50	−20	6 to 8	+++				Very slow		9	1.7 to 7	0.3 to 1.5	20 to 25	1	MgTX IC_{50} 3 nM HgTX IC_{50} 6 nM
Kv1.7	−40	−20	8	+++	5.1 to 5.3	NA	NA	14	Slow	21	NB	0.25	NA	NB	MgTX IC_{50} 116 nM NxTX IC_{50} 18 nM ShK TX IC_{50} 13 nM
Kv2.1	−20 to −30	≈ 10	5 to 19	+	15 to 20	−20	5 to 13	Very slow[e]	1.6 s (–90mV)	8 to 9	4 to 10	0.5 to 4.5	NB	NB	HaTX K_D 100 nM (see note *f*)

A. Functional Properties of Voltage-Activated K^+ Channels (*continued*)

	Electrophysiological Properties													
	Activation				Deacti-vation	Inactivation				Single Chan-nel g	Pharmacological Properties (IC_{50})				
	V_{on} (mV)	$V_{1/2}$ (mV)	k (mV)	τ[a]	τ (ms)[b]	$V_{1/2}$ (mV)	k (mV)	τ (ms)[c]	τ_{rec}	(pS)	TEA_o (mM)	4-AP (mM)	DTX (nM)	CTX (nM)	Other Properties
Kv2.2	−20 to −30	≈ 10	≈ 18	+	NA	−30	13	Very slow[e]	NA	≈ 14	≈ 8	1.5	NA	NA	Note *f*
Kv3.1	−10	+10 to 18	8 to 11	++	1.4			Very slow		16 to 27	0.15 to 0.2	0.02 to 0.6	NB	NB	Chromakalin K_D 0.237 mM
Kv3.2	−10	+10 to 13	7 to 9	++	2			Very slow		16 to 20	0.15	0.6 to 0.9	NB	NB	
Kv3.3	−10	7	6	++	2	5.2	6.1	240	NA	14	0.14	1.2			
Kv3.4	−10	+13 to 19	7 to 11	+++	NA	−20 to −32	4.8 to 8.3	10 to 20	NA	12 to 14	0.09 to 0.3	0.5 to 0.6	NB	NB	BDS-I IC_{50} 47 nM BDS-II IC_{50} 56 nM
Kv4.1	−60 to −50	≈ −10	= 13	++	NA	−69 to −50	4.7 to 8	$\tau_1$22.6 $\tau_2$86.4 $\tau_3$368[h]	200 ms (−100 mV)[g]	6 to 8	NB	9	NA	NA	
Kv4.2	≈ −50	−4 to −15	13 to 20	++	≈ 40	−41 to −66	6 to 8	τ_1 15 to 20 [≈ 80%] τ_2 61 to 120	150 to 300 ms (−80 mV)[g]	4 to 5	NB	2 to 5[i]	NB	NA	HpTX1 and HpTX2 IC_{50} 100 nM, HpTX3 IC_{50} 67 nM[j]
Kv4.3	−60 to −50	= −20	≈ 13	++	20 to 40	≈ −60	4.5 to 7	$\tau_1$30 [≈ 70%] τ_2 160	100 to 200 ms[g] (−80 to −100 mV)	NA	NB	5 to 10[i]	NA	NA	

A. Functional Properties of Voltage-Activated K^+ Channels (*continued*)

	Electrophysiological Properties														
	Activation				Deacti-vation	Inactivation				Single Chan-nel g	Pharmacological Properties (IC_{50})				
	V_{on} (mV)	$V_{1/2}$ (mV)	k (mV)	τ^a	τ (ms)[b]	$V_{1/2}$ (mV)	k (mV)	τ (ms)[c]	τ_{rec}	(pS)	TEA_o (mM)	4-AP (mM)	DTX (nM)	CTX (nM)	Other Properties
Kv5.1, Kv6.1, Kv8.1, Kv9.x	No detectable current when expressed along (see text for heteromultimer formation with Kv2.x)														
KCNQ1	−50 to −40	−11.6	12.6	>100[k]	Incomplete prepulse inactivation that does not produce current decay					NA	40% blocked by 96 mM	NB by 2 mM	NA	NB	Blocked by 10 μM Clofilium
KCNQ1 + minK	−50 to −20	7.5	16.5	>500	No inactivation					NA			NA		
KCNQ2	−60	NA	NA	>100						NA	90% blocked by 1 mM	NB by 2 mM	NA	NB	Not blocked by Clofilium
KCXNQ3	−70	NA	NA	>100	Inactivation might be similar to KCNQ1					NA	NB by 5 mM	NB by 2 mM	NA	NB	30% blocked by 10 μM clofilium
KCNQ2 +KCNQ3	−60	NA	NA							NA	20% blocked by 5 mM	NB by 2 mM	NA	NB	Low sensitivity to clofilium

A. Functional Properties of Voltage-Activated K^+ Channels (*continued*)

	Electrophysiological Properties														
	Activation				Deacti-vation	Inactivation				Single Chan-nel g	Pharmacological Properties (IC_{50})				
	V_{on} (mV)	$V_{1/2}$ (mV)	k (mV)	τ^a	τ (ms)^b	$V_{1/2}$ (mV)	k (mV)	τ (ms)^c	τ_{rec}	(pS)	TEA_o (mM)	4-AP (mM)	DTX (nM)	CTX (nM)	Other Properties
Eag1	−40	−7.5	19.6	++[f]	τ_1 4.6 $\tau_2$76 (−90 mV)	Slow				NA	28	> 100	NA	NA	M current? IKx in rod outer segment?
Erg1	−60 to −50	−21	6 to 8	Hun-dreds of ms	Erg1 and 2 behave as slowly activating delayed rectifiers (τ~100 ms), but at positive voltages (> 0 mV) there is a reduction in steady state (ss) current producing a negative slope I–V and inward rectification. Erg3 currents have a prominent transient component and activate 5–10 times faster and also have a negative slope I–V. Upon repolarization from positive voltages the 3 channels produce large currents that decay slowly. This behavior is due to the presence of a voltage-dependent "C" inactivation process, which is 2 to 10 times faster than activation at most voltages. Recovery from inactivation is very fast for all 3 channels (< 10 ms).					5 to 12 in sym-metric $[K^+]$	50	NA	NA	NA	Blocked by dofetilide E4031 K_D99 nM
											NA	NA	NA	NA	Blocked by 2 μM MK-499
Erg2	−40	−3.5	8.3							NA	NA	NA	NA	NA	E4031 K_D 116 nM
Erg3	−80 to −70	−44	7.2							NA		NA	NA	NA	E4031 K_D 193 nM
Elk1	−40[n]	9.3	13.1		69					NA	NB by 10 mM	NB by 10 mM			NB by 10 μM E4031

A. Functional Properties of Voltage-Activated K^+ Channels (*continued*)

NOTE: Data from mammalian cells used when available, oocytes if not. If considered in several papers and there is a consensus, we have placed an average. Sometimes we have selected papers in which there is a very detailed and careful analysis. If not consensus, we give the range. All values reported at ~20 °C.

ABBREVIATIONS: IC_{50}, Concentration at which 50% of inhibition is reached; V_{on}, activation voltage; $V_{1/2}$, voltage at which 50% of activation or inactivation is reached; k, slope; τ, time constant; TEA_o, extracellular tetraethyl ammonium; 4-AP, 4 aminopiridine; DTX, dendrotoxin; CTX, charibdotoxin; HgTX, hongotoxin; MgTX, margatoxin; HpTX, heteropodatoxin; NxTX, noxiustoxin; HaTX, hanatoxin, K_D, dissociation constant; NB, not blocked at high pharmacological concentrations; NA, no data available.

[a] τ of activation for fast activating currents: +++ < 10 ms; ++ 10–20 ms; + > 20 ms at + 20 to + 40 mV.

[b] At –60 mV unless otherwise stated.

[c] At 40 mV unless otherwise stated.

[d] Very slow = seconds.

[e] Incomplete inactivation.

[f] Several properties are modified by coexpression with Kv5.1, Kv6.1, Kv8.1, and Kv9.x (see section on heteromultimer formation).

[g] Recovery from inactivation calculated from fits to a single exponential but may not be monoexponential. Recovery from inactivation significantly accelerated by coexpression with 2 to 4 Kb brain mRNA.

[h] τ of inactivation for Kv4 channels from pulses at 20 mV. [%] = fractional amplitude of τ.

[i] Incomplete block. Complete block when coexpressed with 2 to 4 Kb brain mRNA.

[j] Blocked in a voltage dependent manner.

[k] Slow deactivation (>100 ms) with an initial hook. Deactivation is slowed down by coexpression with minK.

[l] Depends on V_H. Slowed down by hyperpolarization.

[m] Voltage dependence is highly sensitive to pH.

B. Functional Properties of Ca^{2+}-Activated K^+ Channels

	Voltage Dependence	Ca^{2+} Sensitivity	Single Channel γ (pS)	Pharmacology (IC_{50} or K_D)	Other Properties
Slo1	Conductance is voltage dependent. $V_{1/2}$ shifts with Ca^{2+} concentration from ≈50 mV at 4 μM [Ca^{2+}] to −30 mV at 100 μM [Ca^{2+}]. Voltage dependence is also shifted by coexpression with β subunit.	Ca^{2+} sensitivity is lower than channels from SK family and changes significantly depending on the alternative spliced version and on the presence of the β subunit.	> 200 in symmetric [K^+]	TEA 80 to 330 μM	CTX IC_{50} 2 to 40 nM. Iberiotoxin (IbTX) IC_{50} 6 to 11 nM. β subunit decreases sensitivity to IbTX (IC_{50} 102 to 160 nM) and confers sensitivity to the agonist DHS-1, and does not affect CTX sensitivity.
Slo3	Conductance is sensitive to voltage and pH but apparently not to Ca^{2+}		106 in symmetric [K^+]	TEA 49 mM	Expresses only in testis
SK1	Voltage independent	$K_{0.5}$ 0.71 μM Hill coefficient 3.9	9.2 in symmetric [K^+]	Apamin insensitive d-Tubocurarine 76.2 μM	
SK2	Voltage independent	$K_{0.5}$ 0.63 μM Hill coefficient 4.8	9.9 in symmetric [K^+]	Apamin 63 pM d-Tubocurarine 2.4 μM	
SK3	Voltage independent	Similar to SK1 and SK2	≈ 10	Apamin 1–2 nM	
SK4	Voltage independent	K_D 270 nM Hill coefficient 2.7	33 in symmetric [K^+]	Apamin insensitive	Not blocked by IbTX and MgTX; inwardly rectifying
			9 in asymmetric [K^+]	TEA 30 mM; CTX 10 nM Cortrimazole 387 nM	

C. Functional Properties of Inward-Rectifier K^+ Channels

					Blockers				
	γ (pS)[b]	Mean Open Time (ms)	Mean Closed Time (ms)	Rectification[c]	Spermidine[d]	Spermine[d]	Ba^{2+}_o (μM)	Cs^+_o (μM)	Special Properties
Kir1.1	31–39	24 ms (–80 mV)	1.1 & 35 ms (–80 mV)	Weak	2.16 mM	ND	70 (–100 mV)	1.2 mM (–120 mV)	Activated by ATP_i (blocked by Mg^{2+}; IC_{50} = 1.7–4.2 mM)[e]
Kir2.1	21–23	117–185 ms (–100 mV)	0.8 & 26ms (–100 mV)	Strong	8 nM & 2.9 μM	0.9 nM & 0.6 μM	0.15 (–140 mV)	14 (–140 mV); 54 mM (0 mV)	Blocked by Mg^{2+}; IC_{50} = 17 & 2170 μM[e]
Kir2.2	34–41	71 ms (–100 mV)	0.7 ms & 11.9 ms (–100 mV[f])	Strong	ND	ND	6 (–80 mV)	ND	
Kir2.3	13–16	ND	ND	Strong	ND	ND	93–183 (–130 mV)	30–47 (–130 mV)	Sensitive to pH_o and ATP_i
Kir2.4	15	ND	ND	Strong	ND	ND	390 (–80 mV)	8.06 mM (–80 mV)	
Kir3.1	27–42 (39[g])	0.26, 1.2 & 7.2 ms (–60 mV)	ND	Strong	ND	ND	10–94	94	Expresses as a heteromultimer with Kir3.2 or Kir3.4
Kir3.2	30 (35[h])	0.1 & 0.5 ms (0.5 & 3.5 ms[h]) (–80 mV[i])	ND	Strong	ND	10 μM	94 (–120 mV)	94 (–120 mV)	Expresses as a heteromultimer with Kir3.1 or Kir3.4
Kir3.3	—	—	—	—	—	—	—	—	No expression alone Coassembly subunit of Kir3.1 & Kir3.2

C. Functional Properties of Inward-Rectifier K^+ Channels (*continued*)

					Blockers				
	γ (pS)[b]	Mean Open Time (ms)	Mean Closed Time (ms)	Rectification[c]	Spermidine[d]	Spermine[d]	Ba^{2+}_o (μM)	Cs^+_o (μM)	Special Properties
Kir3.4	31–33 (35[h])	1.3 ms (–80 mV[h])		Strong	ND	ND	92 (–60 mV)	61 (–60 mV)	Coassembly subunit of Kir3.1 Inhibits expression of Kir3.2 May form stretch-activated K^+ channels
Kir4.1	22 & 36[j]	100–200 ms (–100 mV)	1 & 30 ms (–100 mV)	Weak	40 nM	ND	99 (–120 mV)	112 (0 mV)	Activated by ATP_i; inhibited by pH_i (pK_a = 6.2)
Kir4.2	—	—	—	—	—	—	—	—	No expression as homomultimeric subunits; inhibits expression of Kir1.1 or Kir1.2 currents
Kir5.1	—	—	—	—	—	—	—	—	No expression as homomultimeric subunits[k]
Kir7.1	0.05	ND	ND	Strong	ND	ND	1000	10,000	

[a] Excluding K_{ATP} channels, for which see TABLE 4D.
[b] Single-channel conductance (γ) was measured at high (140–150 mM) symmetrical K^+ concentrations.
[c] Rectification is conferred by block of the open channel by intracellular Mg^{2+} and polyamines.
[d] Measured at +40 mV.
[e] All Kir channels are blocked to some extent by Mg^{2+} (one of the prime reasons for rectification). IC_{50} values are not available in all cases.
[f] Channel activity of Kir2.2 occurred in bursts, separated by closings of >200 ms. The gap duration increases with hyperpolarization.
[g] When coexpressed with Kir3.4.
[h] When coexpressed with Kir3.1.
[i] Openings occur in bursts; the mean open time or burst kinetics were not analyzed.
[j] The 36 pS channel was only observed in *Xenopus* oocytes and not in mammalian cells, suggesting coassembly with endogenous *Xenopus* subunits.
[k] Has been reported to form functional heteromultimeric assemblies with Kir4.1

D. Functional Properties of ATP-Sensitive K^+ Channels

Principal Subunit with/ without Auxiliary Subunit	Single-Channel Conductance γ (pS)	Mean Open Time (ms)	Mean Closed Time (ms)	Mean Burst Duration (ms)	Interburst Duration (ms)	Nucleotide Block (μM)	Blockers (nM)	Openers (μM)
Kir6.1 alone	70	3.31 (–60 mV)	0.9 (–60 mV)	ND	ND	ND	Glib (no block)	No effect
Kir6.1+SUR1	ND	ND	ND	ND	ND	ND	Tol (17.7 μM)	ND
Kir6.1+SUR2B	32.9	ND‘	ND	ND	ND	ATP = GTP (3)[a]	Glib (< 3 μM)	Pinacidil (< 100 μM)
Kir6.2 alone	57.6[b] 70	0.8–1.9 (–60 mV[b])	0.31&12.6 (–60 mV[b])	2.4–8.3 (–60 mV[b])	ND	Mg-ATP (106) Mg-ATP (115–145)[b]	No block	No effect
Kir6.2+SUR1	58–76 (73)[b]	2.1 (–80 mV)	0.56 (–80 mV)	17.9 (–60 mV)	24 & 243 (–60 mV)	ATP (6–34); Mg-ATP (28); ATP (13–18)[b]	Glib (1.8–8.6) > Tol (4 –32 μM)	Diazoxide (20–100 μM) > pinacidil
Kir6.2+SUR2A	79–80	1.3 (–80 mV)	0.16 (–80 mV)	ND	ND	ATP (100–148) > ADP>AMP Mg-ATP (172)	Glib (160) Glib (350)[c] Glib (630)[d] Tol (120 μM)	Pinacidil (10) > nicorandil >> diazoxide
Kir6.2+SUR2B	80.3	ND	ND	ND	ND	ATP (67.9) > Mg-ATP (300)	Glib (< 1 μM)	Pinacidil > diazoxide

[a] Activated by nucleotides.
[b] C-terminal truncated form of Kir6.2.
[c] Rb^+ efflux measurements.
[d] Binding assays.

E. Functional Properties of Two-Pore K^+ Channels

				Pharmacology	
	γ (pS)[a]	Rectification	Special Properties	Ba_0^{2+}	Cs_0^{2+}
TWIK	35	Inward (weak)		35–100 μM	Not blocked
TREK	14	Outward[b]		100 μM	Not blocked
TASK	16	Outward[b]	Highly sensitive to extracellular pH pKa = 6.3 Hill = 1.6	29% blocked by 100 μM	30% blocked by 100 μM
TRAAK	45	Outward[b]	Regulated by arachidonic acid and polyunsaturated fatty acids	1 mM at 30 mV	Not blocked

[a] Single-channel conductance (γ) was measured at high (140–150 mM) symmetrical K^+ concentrations.
[b] Obeys Goldman-Hodgkin-Katz current equation for changes in $[K]_o$.

TABLE 5. Tissue Expression of K^+ Channel Principal Subunits

	Tissue Distribution[a]							Brain Region							
	sp	He	Ki	SK	Lu	Br	Other	sp	CX	Th	CB	OB	HC	Other	Protein Distribution
Kv1.1	r	–	–	–	–	+		r	+	+	+	+	+		Axons and terminals.
Kv1.2	r	+[i]	–	ND	ND	+		r	+	+	+	+	+	Hb	Axons and nerve terminals Paranodal in nodes of Ranvier
Kv1.3	r	–	±	–	+	+	Re, spleen, lymph	r	ND	ND	+	+	+		Somatodendritic
Kv1.4	r	+	–	–	ND	+		r	+	+	+	+	+	CP	Axons and terminals
Kv1.5	r	+	+	+	+	+	Pituitary, aorta	r	ND	ND	ND	ND	+		Somas and proximal dendrites
Kv1.6	r/h	–	–	–	–	+		r	ND	ND	±	±	+		Somatodendritic
Kv1.7	r	+	±	+	+	±		ND							
Kv2.1	r	+	–	±	–	±		r	+	±	+	+	+	Hb	Somatic and proximal dendrites
Kv2.2	r	ND	ND	ND	ND	+		r	+	+	+	+	+		Somatic and neuropil
Kv3.1	r	±	–	±	–	+	T-lymph	r	+	+	+	+	+	RT	Somatic and axonal, terminals
Kv3.2	r	±	–	–	–	+		r	+	+	±	±	+		Somas and axon collaterals
Kv3.3	r	±	–	–	ND	+	Thy	r	+	±	+	+	+		
Kv3.4	r	±	–	+	–	+		r	±	–	±	–	±		
Kv4.1	r	±	ND	ND	ND	±		r	–	–	–	+	+		
Kv4.2	r	+	ND	ND	ND	+	Vas deferens[e]	r	+	+	+	+	+	Hb, CP	Somatodendritic
Kv4.3	r	+	+[e]	+[e]	+[e]	+	Vas deferens[e]	r	+	+	+	+	+	Hb, SNPC, CP	
Kv5.1	r	±	±	±	–	+		r	±	±	–	+	±		
Kv6.1	r	–	±	±	+	±	Li	r	+	+	+	+	+	A, CP	

TABLE 5. Tissue Expression of K^+ Channel Principal Subunits (*continued*)

	Tissue Distribution[a]							Brain Region							
	sp	He	Ki	SK	Lu	Br	Other	sp	CX	Th	CB	OB	HC	Other	Protein Distribution
KQT1	h	+	+	–	+	–	Pla, Pa	ND							
KQT2	h	–	–	–	–	+		h[a]	+	+	+	ND	+	A, C. nucl.	
KQT3	h	–	–	–	–	+		h	+	+	±	ND	+	A, C. nucl.	
Kv8.1[b]	r	–	–	–	–	+		r	+	–	+	+	+	CP	
Kv9.1	m/r	–	–	–	–	+		m	+	–	+	+	+		
Kv9.2	m	–	–	–	–	+		m	+	–	+	+	+	Hb, BAN	
Kv9.3	r	±	±	–	+	+		ND							
Kir1.1	r	–	+	–	±	+	Spleen	r	–[a]	±?[a]	–[a]	ND	–[a]	Hypothalamus	
Kir2.1	m	+	–	+	ND	+		r	+	+	+	+	+	Purkinje cells, CP	
Kir2.2	h/r/m	+/+/+	ND/+/+	ND/+/+	ND/+/+	ND/+/+		r	+	+	+	±	±	CP, Strong in Th and CB	
Kir2.3	h/r/m	+/–/–	–?/–/–	±/–/–?	–/–/ND	+		r	+	±	±?	+	+	CP, Th ret. nucleous, amygdala[a]	
Kir2.4	h/r	–/+	ND/+	ND/–	–/±	+		ND						Midbrain, brainstem	
Kir3.1	r/m	+	ND/–	±?	+/ND	+	Atrium > ventricle	r	+	+	+	+	+	Not in Purkinje cells	
Kir3.2	r/m	–	–	–	–	+	High in rat pancreas	r	+	+	–	+	+	C3 pyramidal cells	
Kir3.3	m	–	–	–	–	+		r	+	+	+	+	+	Brainstem, midbrain	
Kir3.4	r/m	+	+[e]/ND	–[e]/ND	–[e]/ND	+/–		r	+	+	±	+	±		
Kir4.1 (Kir1.2)	h/r	–/–	±/±	–/–	–/ND	+/+		r	ND	±	+	ND	±	A, C. callosum, S. nigra	

TABLE 5. Tissue Expression of K^+ Channel Principal Subunits (*continued*)

	Tissue Distribution[a]							Brain Region							
	sp	He	Ki	SK	Lu	Br	Other	sp	CX	Th	CB	OB	HC	Other	Prot. Dist.
Kir4.2 (Kir1.3)	h	–	+	–	±	–	Pa	ND							
Kir5.1	r[e]	+	±	+	±	+		r[e]	+[f]	±	+	ND	+[g]		
Kir6	r	+	+[h]	+	ND	?	Li	ND							
Kir6.2	r	+	ND	+	–	+	Pituitary, pa	r	+	+	+	+	+	Midbrain, CP, brainstem	
Kir7.1	h	–[e]	+[e]	–[e]	–[e]	+[e]	Prostate, testis, small intestine	ND						Purkinje and pyramidal cell layer	
Eag1	r	–	–	–	–	+		r	+	–	+	+	+		
Erg1	h[i]	+	ND	ND	ND	+	SCG, CG, SMG, Re, adr, thy	ND							
Erg2	r[h]	–	ND	ND	ND	–	CG, SMG, Re	ND							
Erg3	r[h]	–	ND	ND	ND	+	SCG, CG, SMG	ND							
SK1	r	+	–	–	–	+	Adr	r	+	–	+	+	+		
SK2	r	+	–	–	–	+	Adr	r	+	+	+	+	+	Pontine nucleus	
SK3	r	+	ND	ND	ND	+	Adr	r	–	+	–	+	–	Supraoptic nucleus	
SK4	h	–	–	–	+	–	Adr, pla	NA							
SKCa3	h	ND	ND	ND	ND	ND		ND							
SKCa4	h	+	-	+	+	-	Pla, thy, co, T-lymph., Li	NA							

TABLE 5. Tissue Expression of K^+ Channel Principal Subunits (*continued*)

	Tissue Distribution[a]							Brain Region							
	sp	He	Ki	SK	Lu	Br	Other	sp	CX	Th	CB	OB	HC	Other	Prot. Dist.
IK1	h	-	-	-	+	ND	Thy, pla, stomach, co, bla, prostate	h	-	ND	-	ND	ND		
Slo	h	ND	-	+	+	+	Pancreatic islets, Li	d						Optic lobes	
Slo3	m/h	-	-	-	-	-	Testis	NA							
TWIK	m	+	+	±	+	+	Li	m	+	-	+	-	+		
TREK	m	+	+	±	+	+	Mainly in brain	m	±	-	+	+	+		
TASK	h/m/r	+/+/+	+/±/±	±?/−/±	+/+/+	+/±/±	Pla, pa, atria, not ventricle	m/r	+/+	+/ND	+/ND	ND/ND	+/+	CP	
TRAAK	m	-	-	-	-	+		m	+	±	+	+	+	CP	

ABBREVIATIONS: sp, specie; He, heart; Ki, kidney; Pa, pancreas; Lu, lung; Sk, skeletal muscle; S.M., vascular smooth muscle; Li, Liver; T-lymph, T-lymphocytes; Br, brain; thy, thymus; Adr, adrenal gland; co, colon; bla, bladder; pla, placenta; SCG, superior cervical ganglia; CG, celiac ganglia; SMG, superior mesenteric ganglia; re, retina; CX, cerebral cortex; HC, hippocampus; Th, dorsal thalamus; CB, cerebellum; OT, olfactory bulb; H, hypothalamus; CP, caudate putamen; Th ret. Nucleus, thalamic reticulate nucleolus; BAN, basolateral amygdaloid nucleus, C. nucl., caudate nucleus; SNPC, substantia nigra pars compacta; Rt, reticular thalamus; A, amygdala; Hb, medial hebenula; ND: not determined; NA: not applicable; d, *drosophila*; m, mouse; r, rat; h, human.

[a] Determined by Northern (RNA) analysis.
[b] Kv8.1/Kv2.3r differ in thalamus by species.
[c] Detected only in human, not in rat or mouse.
[d] Detected only in human and rat and not in mouse.
[e] Determined by RT-PCR of total RNA.
[f] Only BIR 10 isoform.
[g] Only BIR 10 and BIR 11 isoforms.
[h] Neonate.
[i] Determined by RNase protection analysis.

TABLE 6. Functional Diversity Conferred by Alternative Splicing

Splice Version	Comments	Effects on Functional Properties	Effects on Expression	Effects on Subcellular Localization or Modulation
Kv1.5Δ5′	Unusual splicing results in truncated 5′ end			
Kv1.5Δ3′	Truncated 3′ end	Nonfunctional, possible dominant negative	Predominant splice version	
Kv3.1a	(Alternative C-termini in all isoforms)		Predominant isoform during early development	Axons
Kv3.1b			Predominant in adults	Prox. dendrites, soma, axons
Kv3.2a–d	(Alternative C-termini in all isoforms)			Kv3.2a in basolateral membrane, Kv3.2b in apical membrane when expressed in MDCK cells. Kv3.2b but not Kv3.2a modulated by PKC
Kv4.3S	(Alternative C-termini in all isoforms)		Weak in heart, strong in brain	
Kv4.3M			Most abundant in brain, skeletal muscle, pancreas	
Kv4.3L			Weak in brain, major product in smooth muscle, heart, lung & kidney	
LQT1 isoform 2	N-terminal truncation	Dominant negative	Heart ventricle	
KQT2.1–2.11			Some isoforms demonstrate different temporal expression patterns	
Kir1.1a–f	Splicing of Kir1.1b,d–f results in alternative 5′ UTR's; Kir1.1a&c have alternative N-termini		Alternative exon usage results in changes in tissue expression	

TABLE 6. Functional Diversity Conferred by Alternative Splicing (*continued*)

Splice Version	Comments	Effects on Functional Properties	Effects on Expression	Effects on Subcellular Localization or Modulation
Kir3.1a–d	(Alternative C-termini in all isoforms)	Changes in G protein activation in Kir3.1c/3.1a heteromultimers	Alternative exon usage results in changes in tissue expression	
Kir3.2a–e	In Kir3.2a–e splicing results in alternative C-termini; Kir3.2e also has truncated N-terminus.		Kir3.2b&c expression in testes is restricted to a subset of tubules	
Kir6.1a	(Alternative 5′ UTR's in all isoforms)		Heart and pancreas	
Kir6.1b			Heart and skeletal muscle	
Kir6.1c			Heart	
slo	(slo channels have the ability to generate numerous splice isoforms. Human slo contains 5 splicing cassettes within the C-terminus)	(Tested isoforms demonstrate variations in kinetics and calcium sensitivity)	(Tested isoforms demonstrate unique expression patterns. Expression of isoforms in adrenal chromaffin tissue controlled by ACTH)	
Eag1a		Faster activation kinetics	Predominant isoform	
Eag1b	27aa insertion between S3 and S4			
Erg1a		Slower deactivation kinetics	Heart, brain, testes	
Erg1a′	N-terminal truncation	Deactivation kinetics more rapid	Not expressed abundantly	
Erg1b	Shorter/divergent N terminus	Deactivation kinetics more rapid than Erg1a, heteromultimerization with Erg1a increases deactivation kinetics	Heart	

REFERENCES

1. PAPAZIAN, D.M., T.L. SCHWARZ, B.L. TEMPEL, Y.N. JAN & L.Y. JAN. 1987. Cloning of genomic and complementary DNA from *Shaker*, a putative potassium channel gene from Drosophila. Science **237:** 749–753.
2. TEMPEL, B.L., D.M. PAPAZIAN, T.L. SCHWARZ, Y.N. JAN & L.Y. JAN. 1987. Sequence of a probable potassium channel component encoded at Shaker locus of Drosophila. Science **237:** 770–775.
3. KAMB, A., L.E. IVERSON & M.A. TANOUYE. 1987. Molecular characterization of Shaker, a Drosophila gene that encodes a potassium channel. Cell **50:** 405–413.
4. STUHMER, W., M. STOCKER, B. SAKMANN, P. SEEBURG, A. BAUMANN, A. GRUPE & O. PONGS. 1988. Potassium channels expressed from rat brain cDNA have delayed rectifier properties. FEBS Lett. **242:** 199–206.
5. TAKUMI, T., H. OHKUBO & S. NAKANISHI. 1988. Cloning of a membrane protein that induces a slow voltage-gated potassium current. Science **242:** 1042–1045.
6. JAN, L.Y. & Y.N. JAN. 1997. Voltage-gated and inwardly rectifying potassium channels. J. Physiol. (Lond.) **505:** 267–282.
7. AGUILAR-BRYAN, L., J.P. CLEMENT, G. GONZALEZ, K. KUNJILWAR, A. BABENKO & J. BRYAN. 1998. Toward understanding the assembly and structure of K_{ATP} channels. Physiol. Rev. **78:** 227–245.
8. ISOMOTO, S., KONDO, C. & KURACHI, Y. 1997. Inwardly rectifying potassium channels: Their molecular heterogeneity and function. Jpn. J. Physiol. **47:** 11–39.
9. NICHOLS, C.G. & A.N. LOPATIN. 1997. Inward rectifier potassium channels. Ann. Rev. Physiol. **59:** 171–191.
10. BARRY, D.M. & J.M. NERBONNE. 1996. Myocardial potassium channels: Electrophysiological and molecular diversity. Ann. Rev. Physiol. **58:** 363–394.
11. QUAYLE, J.M., M.T. NELSON & N.B. STANDEN. 1997. ATP-sensitive and inwardly rectifying potassium channels in smooth muscle. Physiol. Rev. **77:** 1165–1232.
12. GOLDSTEIN, S.A.N., K.W. WANG, N. ILAN & M.H. PAUSCH. 1998. Sequence and function of the two P domain potassium channels: Implication of an emerging superfamily. J. Mol. Med. **76:** 13–20.
13. VEGA-SAENZ DE MIERA, E., M. WEISER, C. KENTROS, D. LAU, H. MORENO, P. SERODIO & B. RUDY. 1994. Shaw-related K^+ channels in mammals. *In* Handbook of Membrane Channels. 41–78. Academic Press. New York.
14. LEHMANN-HORN, F. & R. RUDEL. 1996. Molecular pathophysiology of voltage-gated ion channels. Rev. Physiol. Biochem. Pharmacol. **128:** 195–268.
15. DOLLY, J.O. & D.N. PARCEJ. 1996. Molecular properties of voltage-gated K^+ channels. J. Bioenerg. Biomembr. **28:** 231–253.
16. CHANDY, K.G. & G.A. GUTMAN. 1995. Voltage-gated potassium channel genes. *In* Handbook of Receptors and Channels: Ligand and Voltage-Gated Ion Channels. ed. R.A. North, Ed.: 1–71. CRC Press. Boca Raton, FL.
17. DOYLE, D.A., J.M. CABRAL, R.A. PFUETZNER, A. KUO, J.M. GULBIS, S.L. COHEN, B.T. CHAIT & R. MACKINNON. 1998. The structure of the potassium channel: Molecular basis of K^+ conduction and selectivity. Science **280:** 69–77.
18. CATTERALL, W.A. 1993. Structure and modulation of Na^+ and Ca^{2+} channels. Ann. N.Y. Acad. Sci. **707:** 1–19.
19. MACKINNON, R. 1991. Determination of the subunit stoichiometry of a voltage- activated potassium channel. Nature **350:** 232–235.
20. MACKINNON, R., R.W. ALDRICH & A.W. LEE. 1993. Functional stoichiometry of Shaker potassium channel inactivation. Science **262:** 757–759.
21. RUDY, B. 1988. Diversity and ubiquity of K channels. Neuroscience **25:** 729–749.
22. HILLE, B. 1992. Ionic Channels of Excitable Membranes. Sinauer Associates, Inc. Sunderland, MA.
23. HO, K., C.G. NICHOLS, W.J. LEDERER, J. LYTTON, P.M. VASSILEV, M.V. KANAZIRSKA & S.C. HEBERT. 1993. Cloning and expression of an inwardly rectifying ATP-regulated potassium channel. Nature **362:** 31–38.
24. KUBO, Y., T.J. BALDWIN, Y.N. JAN & L.Y. JAN. 1993. Primary structure and functional expression of a mouse inward rectifier potassium channel. Nature **362:** 127–133.

25. Dascal, N., W. Schreibmayer, N.F. Lim *et al*. 1993. Atrial G protein–activated K+ channel: Expression cloning and molecular properties. Proc. Natl. Acad. Sci. USA. **90:** 10235–10239.
26. Lesage, F., E. Guillemare, M. Fink, F. Duprat, M. Lazdunski, G. Romey & J. Barhanin. 1996. TWIK-1, a ubiquitous human weakly inward rectifying K^+ channel with a novel structure. EMBO J. **15:** 1004–1011.
27. Lesage, F., R. Reyes, M. Fink, F. Duprat, E. Guillemare & M. Lazdunski. 1996. Dimerization of TWIK-1 K^+ channel subunits via a disulfide bridge. EMBO J. **15:** 6400–6407.
28. Fink, M., F. Lesage, F. Duprat, C. Heurteaux, R. Reyes, M. Fosset & M. Lazdunski. 1998. A neuronal two P domain K^+ channel stimulated by arachidonic acid and polyunsaturated fatty acids. Embo J. **17:** 3297–3308.
29. Taglialatela, M., M.S. Champagne, J.A. Drewe & A.M. Brown. 1994. Comparison of H5, S6, and H5-S6 exchanges on pore properties of voltage-dependent K^+ channels. J. Biol. Chem. **269:** 13867–13873.
30. Heginbotham, L., Z. Lu, T. Abramson & R. MacKinnon. 1994. Mutations in the K^+ channel signature sequence. Biophys. J. **66:** 1061–1067.
31. Bailie, T.L. & C. Elkan 1994. Fitting a mixture model by expectation maximization to discover motifs in biopolymers. AAAI Press. Menlo Park, CA.
32. Chandy, K.G. 1991. Simplified gene nomenclature. Nature **352:** 26.
33. Doupnik, C.A., N. Davidson & H.A. Lester. 1995. The inward rectifier potassium channel family. Curr. Opin. Neurobiol. **5:** 268–277.
34. Bond, C.T., M. Pessia, X.M. Xia, A. Lagrutta, M.P. Kavanaugh & J.P. Adelman. 1994. Cloning and expression of a family of inward rectifier potassium channels. Recept. Channels **2:** 183–191.
35. Shuck, M.E., T.M. Piser, J.H. Bock, J.L. Slightom, K.S. Lee & M.J. Bienkowski. 1997. Cloning and characterization of two K+ inward rectifier (Kir) 1.1 potassium channel homologs from human kidney (Kir1.2 and Kir1.3). J. Biol. Chem. **272:** 586–593.
36. Gosset, P., G.A. Ghezala, B. Korn, M.L. Yaspo, A. Poutska, H. Lehrach, P.M. Sinet & N. Créau. 1997. A new inward rectifier potassium channel gene (KCNJ15) localized on chromosome 21 in the Down syndrome chromosome region 1 (DCR1). Genomics **44:** 237–241.
37. Shuck, M.E., T.M. Piser, J.H. Bock, J.L. Slightom, K.S. Lee & M.J. Bienkowski. 1997. Cloning and characterization of two K^+ inward rectifier (K_{ir}) 1.1 potassium channel homologs from human kidney (K_{ir}1.2 and K_{ir}1.3). J. Biol. Chem. **272:** 586–593.
38. Krapivinsky, G., I. Medina, L. Eng, L. Krapivinsky, Y.H. Yang & D.E. Clapham. 1998. A novel inward rectifier K^+ channel with unique pore properties. Neuron **20:** 995–1005.
39. Hedin, K.E., N.F. Lim & D.E. Clapham. 1996. Cloning of a Xenopus laevis inwardly rectifying K^+ channel subunit that permits GIRK1 expression of I_{KACh} currents in oocytes. Neuron **16:** 423–429.
40. Christie, M.J., R.A. North, P.B. Osborne, J. Douglass & J. Adelman. 1990. Heteropolymeric potassium channels expressed in Xenopus oocytes from cloned subunits. Neuron **4:** 405–411.
41. Isacoff, E.Y., Y.N. Jan & L.Y. Jan. 1990. Evidence for the formation of heteromultimeric potassium channels in Xenopus oocytes. Nature **345:** 530–534.
42. McCormack, K., J.W. Lin, L.E. Iverson & B. Rudy. 1990. Shaker K^+ channel subunits from heteromultimeric channels with novel functional properties. Biochem. Biophys. Res. Commun. **171:** 1361–1371.
43. Ruppersberg, J.P., K.H. Schroter, B. Sakmann, M. Stocker, S. Sewing & O. Pongs. 1990. Heteromultimeric channels formed by rat brain potassium-channel proteins. Nature **345:** 535–537.
44. Weiser, M., E. Vega-Saenz De Miera, C. Kentros, H. Moreno, L. Franzen, D. Hillman, H. Baker & B. Rudy. 1994. Differential expression of Shaw-related K^+ channels in the rat central nervous system. J. Neurosci. **14:** 949–972.
45. Roeper, J., S. Sewing, Y. Zhang, T. Sommer, S.G. Wanner & O. Pongs. 1998. NIP domain prevents N-type inactivation in voltage-gated potassium channels. Nature **391:** 390–393.
46. Li, M., Y.N. Jan & L.Y. Jan. 1992. Specification of subunit assembly by the hydrophilic amino-terminal domain of the Shaker potassium channel. Science **257:** 1225–1230.
47. Shen, N.V. & P.J. Pfaffinger. 1995. Molecular recognition and assembly sequences involved in the subfamily-specific assembly of voltage-gated K^+ channel subunit proteins. Neuron **14:** 625–633.

48. YU, W., J. XU & M. LI. 1996. NAB domain is essential for the subunit assembly of both alpha-alpha and alpha-beta complexes of shaker-like potassium channels. Neuron **16:** 441–453.
49. SEWING, S., J. ROEPER & O. PONGS. 1996. Kv β1 subunit binding specific for shaker-related potassium channel α subunits. Neuron **16:** 455–463.
50. SHENG, M., Y.J. LIAO, Y.N. JAN & L.Y. JAN. 1993. Presynaptic A-current based on heteromultimeric K^+ channels detected in vivo. Nature **365:** 72–75.
51. WANG, H., D.D. KUNKEL, T.M. MARTIN, P.A. SCHWARTZKROIN & B.L. TEMPEL. 1993. Heteromultimeric K^+ channels in terminal and juxtaparanodal regions of neurons. Nature **365:** 75–79.
52. CHOW, A., C. FARB, A. ERISIR & B. RUDY. 1998. K^+ channel expression distinguishes between two subpopulations of parvalbumin-containing cortical interneurons. Submitted for publication.
53. HERNÁNDEZ-PINEDA, R., A. CHOW, Y. AMARILLO, H. MORENO, M. SAGANICH & B. RUDY. 1999. Kv3.1-Kv3.2 heteromultimeric channels underlie a high voltage-activating component of the delayed rectifier K^+ current in projecting neurons from the Globus Pallidus. J. Neurophysiol. In press.
54. MI, H., T.J. DEERINCK, M.H. ELLISMAN & T.L. SCHWARZ. 1995. Differential distribution of closely related potassium channels in rat Schwann cells. J. Neurosci. **15:** 3761–3774.
55. KRAMER, J.W., M.A. POST, A.M. BROWN & G.E. KIRSCH. 1998. Modulation of potassium channel gating by coexpression of Kv2.1 with regulatory Kv5.1 or Kv6.1 alpha-subunits. Am. J. Physiol. **274:** C1501–C1510
56. SALINAS, M., F. DUPRAT, C. HEURTEAUX, J.P. HUGNOT & M. LAZDUNSKI. 1997. New modulatory alpha subunits for mammalian Shab K^+ channels. J. Biol. Chem. 272: 24371–24379.
57. PATEL, A.J., M. LAZDUNSKI & E. HONORÉ. 1997. Kv2.1/Kv9.3, a novel ATP-dependent delayed-rectifier K^+ channel in oxygen-sensitive pulmonary artery myocytes. EMBO J. **16:** 6615–6625.
58. YANG, W.P., P.C. LEVESQUE, W.A. LITTLE, M.L. CONDER, P. RAMAKRISHNAN, M.G. NEUBAUER & M.A. BLANAR. 1998. Functional expression of two KvLQT1-related potassium channels responsible for an inherited idiopathic epilepsy. J. Biol. Chem. **273:** 19419–19423.
59. SHI, W., H.S. WANG, Z. PAN, R.S. WYMORE, I.S. COHEN, D. MCKINNON & J.E. DIXON. 1998. Cloning of a mammalian elk potassium channel gene and EAG mRNA distribution in rat sympathetic ganglia. J. Physiol. (Lond.) **511:** 675–682.
60. LONDON, B., M.C. TRUDEAU, K.P. NEWTON, A.K. BEYER, N.G. COPELAND, D.J. GILBERT, N.A. JENKINS, C.A. SATLER & G.A. ROBERTSON. 1997. Two isoforms of the mouse *ether-a-go-go*–related gene coassemble to form channels with properties similar to the rapidly activating component of the cardiac delayed rectifier K^+ current. Circ. Res. **81:** 870–878.
61. CHEN, M.L., T. HOSHI & C.F. WU. 1996. Heteromultimeric interactions among K^+ channel subunits from *Shaker* and *eag* families in Xenopus oocytes. Neuron **17:** 535–542.
62. LIAO, Y.J., Y.N. JAN & L.Y. JAN. 1996. Heteromultimerization of G-protein–gated inwardly rectifying K^+ channel proteins GIRK1 and GIRK2 and their altered expression in weaver brain. J. Neurosci. **16:** 7137–7150.
63. FINK, M., F. DUPRAT, C. HEURTEAUX, F. LESAGE, G. ROMEY, J. BARHANIN & M. LAZDUNSKI. 1996. Dominant negative chimeras provide evidence for homo and heteromultimeric assembly of inward rectifier K^+ channel proteins via their N-terminal end. FEBS Lett. **378:** 64–68.
64. TINKER, A., Y.N. JAN & L.Y. JAN. 1996. Regions responsible for the assembly of inwardly retifying potassium channels. Cell **87:** 857–868.
65. NAKAMURA, T.Y., M. ARTMAN, B. RUDY & W.A. COETZEE. 1998. Inihibition of rat ventricular I_{K1} with antisense oligonucleotides targeted to Kir2.1 mRNA. Am. J. Physiol. **274:** H892–H900
66. FINK, M., F. DUPRAT, C. HEURTEAUX, F. LESAGE, G. ROMEY, J. BARHANIN & M. LAZDUNSKI. 1996. Dominant negative chimeras provide evidence for homo and heteromultimeric assembly of inward rectifier K^+ channel proteins via their N-terminal end. FEBS Lett. **378:** 64–68.
67. PESSIA, M., S.J. TUCKER, K. LEE, C.T. BOND & J.P. ADELMAN. 1996. Subunit positional effects revealed by novel heteromeric inwardly rectifying K^+ channels. EMBO J. **15:** 2980–2987.
68. ADELMAN, J.P., K.Z. SHEN, M.P. KAVANAUGH, R.A. WARREN, Y.N. WU, A. LAGRUTTA, C.T. BOND & R.A. NORTH. 1992. Calcium-activated potassium channels expressed from cloned complementary DNAs. Neuron **9:** 209–216.

69. TSENG-CRANK, J., C.D. FOSTER, J.D. KRAUSE, R. MERTZ, N. GODINOT, T.J. DICHIARA & P.H. REINHART. 1994. Cloning, expression, and distribution of functionally distinct Ca^{2+}-activated K^+ channel isoforms from human brain. Neuron **13:** 1315–1330.
70. XIE, J. & D.P. MCCOBB. 1998. Control of alternative splicing of potassium channels by stress hormones. Science **280:** 443–446.
71. BUTLER, A., S. TSUNODA, D.P. MCCOBB, A. WEI & L. SALKOFF. 1993. mSlo, a complex mouse gene encoding "maxi" calcium-activated potassium channels. Science **261:** 221–224.
72. NAVARATNAM, D.S., T.J. BELL, T.D. TU, E.L. COHEN & J.C. OBERHOLTZER. 1997. Differential distribution of Ca^{2+}-activated K^+ channel splice variants among hair cells along the tonotopic axis of the chick cochlea. Neuron **19:** 1077–1085.
73. ROSENBLATT, K.P., Z.P. SUN, S. HELLER & A.J. HUDSPETH. 1997. Distribution of Ca^{2+}-activated K^+ channel isoforms along the tonotopic gradient of the chicken's cochlea. Neuron **19:** 1061–1075.
74. KOHLER, M., B. HIRSCHBERG, C.T. BOND, J.M. KINZIE, N.V. MARRION, J. MAYLIE & J.P. ADELMAN. 1996. Small-conductance, calcium-activated potassium channels from mammalian brain. Science **273:** 1709–1714.
75. REHM, H. & M. LAZDUNSKI. 1988. Purification and subunit structure of a putative K^+ channel protein identified by its binding properties to dendrotoxin I. Proc. Natl. Acad. Sci. USA **85:** 4919–4923.
76. SCOTT, V.E.S., J. RETTIG, D.N. PARCEJ, J.N. KEEN, J.B.C. FINDLAY, O. PONGS & J.O. DOLLY. 1994. Primary structure of a beta subunit of alpha-dendrotoxin-sensitive K^+ channels from bovine brain. Proc. Natl. Acad. Sci. USA **91:** 1637–1641.
77. MCCORMACK, T. & K. MCCORMACK. 1994. Shaker K^+ channel beta subunits belong to an NAD(P)H-dependent oxidoreductase superfamily [letter]. Cell **79:** 1133–1135.
78. RETTIG, J., S.H. HEINEMANN, F. WUNDER, C. LORRA, R. WITTKA, O. DOLLY & O. PONGS. 1994. Inactivation properties of voltage gated K^+ channels altered by the presence of β-subunit. Nature **369:** 289–294.
79. MCCORMACK, K., T. MCCORMACK, M. TANOUYE, B. RUDY & W. STÜHMER. 1995. Alternative splicing of the human Shaker K^+ channel β1 gene and functional expression of the β2 gene product. FEBS Lett. **370:** 32–36.
80. HEINEMANN, S.H., J. RETTIG, F. WUNDER & O. PONGS. 1995. Molecular and functional characterization of a rat brain Kv beta 3 potassium channel subunit. FEBS Lett. **377:** 383–389.
81. WANG, Z., J. KIEHN, Q. YANG, A.M. BROWN & B.A. WIBLE. 1996. Comparison of binding and block produced by alternatively spliced Kvbeta1 subunits. J. Biol. Chem. **271:** 28311–28317.
82. ENGLAND, S.K., V.N. UEBELE, J. KODALI, P.B. BENNETT & M.M. TAMKUN. 1995. A novel K^+ channel β-subunit (hKvβ1.3) is produced via alternative mRNA splicings. J. Biol. Chem. **270:** 28531–28534.
83. SHI, G.Y., K. NAKAHIRA, S. HAMMOND, K.J. RHODES, L.E. SCHECHTER & J.S. TRIMMER. 1996. β Subunits promote K^+ channel surface expression through effects early in biosynthesis. Neuron **16:** 843–852.
84. NAGAYA, N. & D.M. PAPAZIAN. 1997. Potassium channel α and β subunits assemble in the endoplasmic reticulum. J. Biol. Chem. **272:** 3022–3027.
85. WIBLE, B.A., Q. YANG, Y.A. KURYSHEV, E.A. ACCILI & A.M. BROWN. 1998. Cloning and expression of a novel K^+ channel regulatory protein, KChAP. J. Biol. Chem. **273:** 11745–11751.
86. FINK, M., F. DUPRAT, F. LESAGE, C. HEURTEAUX, G. ROMEY, J. BARHANIN & M. LAZDUNSKI. 1996. A new K^+ channel β subunit to specifically enhance Kv2.2 (CDRK) expression. J. Biol. Chem. **271:** 26341–26348.
87. RHODES, K.J., B.W. STRASSLE, M.M. MONAGHAN, Z. BEKELE-ARCURI, M.F. MATOS & J.S. TRIMMER. 1997. Association and colocalization of the Kvβ1 and Kvβ2 β-subunits with Kv1 α-subunits in mammalian brain K^+ channel complexes. J. Neurosci. **17:** 8246–8258.
88. WILSON, G.F., Z. WANG, S.W. CHOUINARD, L.C. GRIFFITH & B. GANETZKY. 1998. Interaction of the K channel beta subunit, Hyperkinetic, with eag family members. J. Biol. Chem. **273:** 6389–6394.
89. HOSHI, N., H. TAKAHASHI, M. SHAHIDULLAH, S. YOKOYAMA & H. HIGASHIDA. 1998. KCR1, a membrane protein that facilitates functional expression of non-inactivating K+ currents associates with rat EAG voltage-dependent K+ channels [In Process Citation]. J. Biol. Chem. **273:** 23080–23085.

90. FOLANDER, K., J.S. SMITH, J. ANTANAVAGE, C. BENNETT, R.B. STEIN & R. SWANSON. 1990. Cloning and expression of the delayed-rectifier Isk channel from neonatal rat heart and diethylstilbestrol-rrimed rat uterus. Proc. Natl. Acad. Sci. USA **87:** 2975–2979.
91. SAKAGAMI, M., K. FUKAZAWA, T. MATSUNAGA, H. FUJITA, N. MORI, T. TAKUMI, H. OHKUBO & S. NAKANISHI. 1991. Cellular localization of rat Isk protein in the stria vascularis by immunohistochemical observation. Hear. Res. **56:** 168–172.
92. FREEMAN, L.C. & R.S. KASS. 1993. Expression of a minimal K+ channel protein in mammalian cells and immunolocalization in guinea pig heart. Circ. Res. **73:** 968–973.
93. VARNUM, M.D., A.E. BUSCH, C.T. BOND, J. MAYLIE & J.P. ADELMAN. 1993. The min K channel underlies the cardiac potassium current IKs and mediates species-specific responses to protein kinase C. Proc. Natl. Acad. Sci. USA **90:** 11528–11532.
94. BARHANIN, J., F. LESAGE, E. GUILLEMARE, M. FINK, M. LAZDUNSKI & G. ROMEY. 1996. K_vLQT1 and IsK (minK) proteins associate to form the I_{Ks} cardiac potassium current. Nature **384:** 78–80.
95. SANGUINETTI, M.C., M.E. CURRAN, A. ZOU, J. SHEN, P.S. SPECTOR, D.L. ATKINSON & M.T. KEATING. 1996. Coassembly of K_vLQT1 and minK (IsK) proteins to form cardiac I_{Ks} potassium channel. Nature **384:** 80–83.
96. SALATA, J.J., N.K. JURKIEWICZ, J. WANG, B.E. EVANS, H.T. ORME & M.C. SANGUINETTI. 1998. A novel benzodiazepine that activates cardiac slow delayed rectifier K+ currents. Mol. Pharmacol. **54:** 220–230.
97. MCDONALD, T.V., Z.H. YU, Z. MING, E. PALMA, M.B. MEYERS, K.W. WANG, S.A.N. GOLDSTEIN & G.I. FISHMAN. 1997. A minK-HERG complex regulates the cardiac potassium current I_{Kr}. Nature **388:** 289–292.
98. SANGUINETTI, M.C. & N.K. JURKIEWICZ. 1990. Two components of cardiac delayed rectifier K^+ current: Differential sensitivity to block by class III antiarrhythmic agents. J. Gen. Physiol. **96:** 194–214.
99. SANGUINETTI, M.C. & N.K. JURKIEWICZ. 1991. Delayed rectifier outward K+ current is composed of two currents in guinea pig atrial cells. Am. J. Physiol. **260:** H393–399.
100. BUSCH, A.E., M.P. KAVANAUGH, M.D. VARNUM, J.P. ADELMAN & R.A. NORTH. 1992. Regulation by second messengers of the slowly activating, voltage-dependent potassium current expressed in Xenopus oocytes. J. Physiol. **450:** 491–502.
101. BLUMENTHAL, E.M. & L.K. KACZMAREK. 1994. The minK potassium channel exists in functional and nonfunctional forms when expressed in the plasma membrane of Xenopus oocytes. J. Neurosci. **14:** 3097–3105.
102. TAI, K.K. & S.A.N. GOLDSTEIN. 1998. The conduction pore of a cardiac potassium channel. Nature **391:** 605–608.
103. KNAUS, H.G., K. FOLANDER, M. GARCIA-CALVO, M.L. GARCIA, G.J. KACZOROWSKI, M. SMITH & R. SWANSON. 1994. Primary sequence and immunological characterization of beta-subunit of high conductance Ca(2+)-activated K+ channel from smooth muscle. J. Biol. Chem. **269:** 17274–17278.
104. HANNER, M., R. VIANNA-JORGE, A. KAMASSAH, W.A. SCHMALHOFER, H.G. KNAUS, G.J. KACZOROWSKI & M.L. GARCIA. 1998. The beta subunit of the high conductance calcium-activated potassium channel. Identification of residues involved in charybdotoxin binding. J. Biol. Chem. **273:** 16289–16296.
105. SCHOPPERLE, W.M., M.H. HOLMQVIST, Y. ZHOU, J. WANG, Z. WANG, L.C. GRIFFITH, I. KESELMAN, F. KUSINITZ, D. DAGAN & I.B. LEVITAN. 1998. Slob, a novel protein that interacts with the slowpoke calcium-dependent potassium channel. Neuron **20:** 565–573.
106. TUCKER, S.J., F.M. GRIBBLE, C. ZHAO, S. TRAPP & F.M. ASHCROFT. 1997. Truncation of Kir6.2 produces ATP-sensitive K+ channels in the absence of the sulphonylurea receptor. Nature **387:** 179–183.
107. JOHN, S.A., J.R. MONCK, J.N. WEISS & B. RIBALET. 1998. The sulphonylurea receptor SUR1 regulates ATP-sensitive mouse Kir6.2 K^+ channels linked to the green fluorescent protein in human embryonic kidney cells. J. Physiol. (Lond.) **510:** 333–346.
108. SHYNG, S. & C.G. NICHOLS. 1997. Octameric stoichiometry of the K_{ATP} channel complex. J. Gen. Physiol. **110:** 655–664.
109. BABENKO, A.P., L. AGUILAR-BRYAN & J. BRYAN. 1998. A view of sur/KIR6.X, KATP channels. Ann. Rev. Physiol. **60:** 667–687.

110. SEEBURG, P.H., M. HIGUCHI & R. SPRENGEL. 1998. RNA editing of brain glutamate receptor channels: Mechanism and physiology. Brain Res. Brain Res. Rev. **26:** 217–229.
111. MAAS, S., T. MELCHER & P.H. SEEBURG. 1997. Mammalian RNA-dependent deaminases and edited mRNAs. Curr. Opin. Cell Biol. **9:** 343–349.
112. PATTON, D.E., T. SILVA & F. BEZANILLA. 1997. RNA editing generates a diverse array of transcripts encoding squid Kv2 K+ channels with altered functional properties. Neuron **19:** 711–722.
113. JONAS, E.A. & L.K. KACZMAREK. 1996. Regulation of potassium channels by protein kinases. Curr. Opin. Neurobiol. **6:** 318–323.
114. LEVITAN, I.B. 1994. Modulation of ion channels by protein phosphorylation and dephosphorylation. Ann. Rev. Physiol. **56:** 193–212.
115. KACZMERECK, K.L. & I.B. LEVITAN. 1987. Neuromodulation: The Biochemical Control of Neuronal Excitability. Oxford University Press. Oxford.
116. COVARRUBIAS, M., A. WEI, L. SALKOFF & T.B. VYAS. 1994. Elimination of rapid potassium channel inactivation by phosphorylation of the inactivation gate. Neuron **13:** 1403–1412.
117. BECK, E.J., R.G. SORENSEN, S.J. SLATER & M. COVARRUBIAS. 1998. Interactions between multiple phosphorylation sites in the inactivation particle of a K+ channel. Insights into the molecular mechanism of protein kinase C action. J. Gen. Physiol. **112:** 71–84.
118. ROEPER, J., C. LORRA & O. PONGS. 1997. Frequency-dependent inactivation of mammalian A-type K+ channel KV1.4 regulated by Ca2+/calmodulin-dependent protein kinase. J. Neurosci. **17:** 3379–3391.
119. COHEN, N.A., J.E. BRENMAN, S.H. SNYDER & D.S. BREDT. 1996. Binding of the inward rectifier K^+ channel Kir 2.3 to PSD-95 is regulated by protein kinase A phosphorylation. Neuron **17:** 759–767.
120. COHEN, N.A., Q. SHA, E.N. MAKHINA, A.N. LOPATIN, M.E. LINDER, S.H. SNYDER & C.G. NICHOLS. 1996. Inhibition of an inward rectifier potassium channel (Kim2.3) by G-protein βgamma subunits. J. Biol. Chem. **271:** 32301–32305.
121. STORM, J.F. 1988. Temporal integration by a slowly inactivating K+ current in hippocampal neurons. Nature **336:** 379–381.
122. WU, R.L. & M.E. BARISH. 1992. Two pharmacologically and kinetically distinct transient potassium currents in cultured embryonic mouse hippocampal neurons. J. Neurosci. **12:** 2235–2246.
123. SHENG, M., M.L. TSAUR, Y.N. JAN & L.Y. JAN. 1992. Subcellular segregation of two A-type K^+ channel proteins in rat central neurons. Neuron **9:** 271–284.
124. DEBANNE, D., N.C., GUERINEAU, B.H. GAHWILER & S.M. THOMPSON. 1997. Action-potential propagation gated by an axonal I(A)-like K^+ conductance in hippocampus. Nature **389:** 286–289.
125. FENG, J.L., B. WIBLE, G.R. LI, Z.G. WANG & S. NATTEL. 1997. Antisense oligodeoxynucleotides directed against Kv1.5 mRNA specifically inhibit ultrarapid delayed rectifier K^+ current in cultured adult human atrial myocytes. Circ. Res. **80:** 572–579.
126. PATEL, A.J., M. LAZDUNSKI & E. HONORE. 1997. Kv2.1/Kv9.3, a novel ATP-dependent delayed-rectifier K^+ channel in oxygen-sensitive pulmonary artery myocytes. EMBO J. **16:** 6615–6625.
127. FISET, C., R.B. CLARK, Y. SHIMONI & W. GILES. 1997. Shal-type channels contribute to the Ca^{2+}-independent transient outward K^+ current in rat ventricle. J. Physiol. (Lond.) **500:** 51–63.
128. NAKAMURA, T.Y., W.A. COETZEE, E. VEGA-SAENZ DE MIERA, M. ARTMAN & B. RUDY. 1997. Modulation of Kv4 channels, key components of rat ventricular transient outward K^+ current by PKC. Am. J. Physiol. **273:** H1775–H1786.
129. MARRION, N.V. 1997. Does r-EAG contribute to the M-current? Trends Neurosci. **20:** 243–244.
130. MATHIE, A. & C.S. WATKINS. 1997. Is EAG the answer to the M-current? Trends Neurosci. **20:** 14.
131. FENG, J.L., B. WIBLE, G.R. LI, Z. WANG & S. NATTEL. 1996. Antisense oligonucleotides directed against Kv1.5 mRNA specifically inhibit the ultrarapid delayed rectifier in cultured adult human atrial myocytes. Circulation **94:** I-528(Abstr.).
132. GARCIA-CALVO, M., H.G. KNAUS, O.B. MCMANUS, K.M. GIANGIACOMO, G.J. KACZOROWSKI & M.L. GARCIA. 1994. Purification and reconstitution of the high-conductance, calcium-activated potassium channel from tracheal smooth muscle. J. Biol. Chem. **269:** 676–682.

133. KNAUS, H.G., A. EBERHART, R.O. KOCH, P. MUNUJOS, W.A. SCHMALHOFER, J.W. WARMKE, G.J. KACZOROWSKI & M.L. GARCIA. 1995. Characterization of tissue-expressed alpha subunits of the high conductance Ca^{2+}-activated K^+ channel. J. Biol. Chem. **270:** 22434–22439.
134. ISHII, T.M., C. SILVIA, B. HIRSCHBERG, C.T. BOND, J.P. ADELMAN & J. MAYLIE. 1997. A human intermediate conductance calcium-activated potassium channel. Proc. Natl. Acad. Sci. USA **94:** 11651–11656.
135. LOGSDON, N.J., J. KANG, J.A. TOGO, E.P. CHRISTIAN & J. AIYAR. 1997. A novel gene, hKCa4, encodes the calcium-activated potassium channel in human T lymphocytes. J. Biol. Chem. **272:** 32723–32726.
136. JOINER, W.J., L.Y. WANG, M.D. TANG & L.K. KACZMAREK. 1997. hSk4, a member of a novel subfamily of calcium-activated potassium channels. Proc. Natl. Acad. Sci. USA **94:** 11013–11018.
137. COREY, S.G. KRAPIVINSKY, L. KRAPIVINSKY & D.E. CLAPHAM. 1998. Number and stoichiometry of subunits in the native atrial G-protein–gated K^+ channel, I_{KACh}. J. Biol. Chem. **273:** 5271–5278.
138. SWOFFORD, D.L. 1993. PAUP. (3.1.1). (Computer Program). Smithsonian Institution. Washington DC, Sinauer Associates. Sunderland, MA.
139. GATESY, J., R. DESALLE & W. WHEELER. 1993. Alignment-ambiguous nucleotide sites and the exclusion of systematic data. Mol. Phylogenet. Evol. **2:** 152–157.
140. LEES-MILLER, J.P., C. KONDO, L. WANG & H.J. DUFF. 1997. Electrophysiological characterization of an alternatively processed ERG K^+ channel in mouse and human hearts. Circ. Res. **81:** 719–726.
141. NAKAMURA, M., H. WATANABE, Y. KUBO, M. YOKOYAMA, T. MATSUMOTO, H. SASAI & Y. NISHI. 1998. KQT2, a new putative potassium channel family produced by alternative splicing. Isolation, genomic structure, and alternative splicing of the putative potassium channels. Recep. Channels **5:** 255–271.
142. KONDO, C., S. ISOMOTO, S. MATSUMOTO, M. YAMADA, Y. HORIO, S. YAMASHITA, K. TAKEMURA-KAMEDA, Y. MATSUZAWA & Y. KURACHI. 1996. Cloning and functional expression of a novel isoform of ROMK inwardly rectifying ATP-dependent K^+ channel, ROMK6 (Kir1.1f). FEBS Lett. **399:** 122–126.
143. YANO, H., L.H. PHILIPSON, J.L. KUGLER, Y. TOKUYAMA, E.M. DAVIS, M.M. LE BEAU, D.J. NELSON, G.I. BELL & J. TAKEDA. 1994. Alternative splicing of human inwardly rectifying K+ channel ROMK1 mRNA. Molecular Pharmacology **45:** 854–860.
144. WEI, J., M.E. HODES, R. PIVA, Y. FENG, Y. WANG, B. GHETTI & S.R. DLOUHY. 1998. Characterization of murine girk2 transcript isoforms: Structure and differential expression. Genomics **51:** 379–390.

[**NOTE ADDED IN PROOF:** After this paper was submitted, Wang *et al.* (1998, Science **282:** 1890–1893) have presented strong evidence that KCNQ2 and KCNQ3 subunits form channels mediating the "M-current."]