

# Potassium Channels: Molecular Defects, Diseases, and Therapeutic Opportunities

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**Abstract**—Potassium channels play important roles in vital cellular signaling processes in both excitable and nonexcitable cells. Over 50 human genes encoding various K<sup>+</sup> channels have been cloned during the past decade, and precise biophysical properties, subunit stoichiometry, channel assembly, and modulation by second messenger and ligands have been elucidated to a large extent. Recent advances in genetic linkage analysis have greatly facilitated the identification of many disease-producing loci, and naturally occurring mutations in various K<sup>+</sup> channels have been identified in diseases such as long-QT syndromes, episodic ataxia/myokymia, familial convul-

sions, hearing and vestibular diseases, Bartter's syndrome, and familial persistent hyperinsulinemic hypoglycemia of infancy. In addition, changes in K<sup>+</sup> channel function have been associated with cardiac hypertrophy and failure, apoptosis and oncogenesis, and various neurodegenerative and neuromuscular disorders. This review aims to 1) provide an understanding of K<sup>+</sup> channel function at the molecular level in the context of disease processes and 2) discuss the progress, hurdles, challenges, and opportunities in the exploitation of K<sup>+</sup> channels as therapeutic targets by pharmacological and emerging genetic approaches.

## I. Background

Potassium channels are a diverse and ubiquitous family of membrane proteins present in both excitable and nonexcitable cells. Members of this channel family play critical roles in cellular signaling processes regulating neurotransmitter release, heart rate, insulin secretion, neuronal excitability, epithelial electrolyte transport, smooth muscle contraction, and cell volume regulation. Over 50 human genes encoding various K<sup>+</sup> channels have been cloned during the past decade (Fig. 1), and precise biophysical properties, subunit stoichiometry, channel assembly and modulation by second messenger and ligands have been addressed to a large extent. More recently, the crystal structure of a K<sup>+</sup> channel from *Streptomyces lividans* has become available (Doyle et al., 1998).

Concurrent with this remarkable progress in our understanding of molecular diversity, structure, and func-

<sup>2</sup> Abbreviations: Kv, voltage-gated K<sup>+</sup> channel; A $\beta$ ,  $\beta$ -amyloid;  $\beta$ -APP,  $\beta$ -amyloid protein precursor; BFNC, benign familial neonatal convulsion; BK<sub>Ca</sub>, large conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channel; EA, episodic ataxia; EAG, *ether-a-go-go* K<sup>+</sup> channel; 1-EBIO, 1-ethyl-2-benzimidazolinone; hERG, human *ether-a-go-go*-related K<sup>+</sup> channel; IK<sub>Ca</sub>, intermediate conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channel; IKr, cardiac rapid delayed rectifier; IKs, cardiac slow delayed rectifier; IK<sub>ur</sub>, ultrarapid delayed rectifier; I<sub>TO</sub>, transient outward delayed rectifier; K<sub>ATP</sub>, ATP-sensitive K<sup>+</sup>; KCSA, K<sup>+</sup> channel from *Streptomyces lividans*; Kir, inward rectifier K<sup>+</sup> channel; KCO, K<sup>+</sup> channel opener; LQT, long-QT syndrome; M-channel, muscarine-sensitive K<sup>+</sup> channel; MiRP, minK related peptide; PHHI, persistent hyperinsulinemic hypoglycemia of infancy; P-loop, pore loop; PS, presenilin; sAPP, secreted form of  $\beta$ -amyloid precursor protein; SK<sub>Ca</sub>, small conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channel; SUR, sulfonylurea receptor; TEA, tetraethylammonium; TM, transmembrane segment; TREK, two-pore weak inward rectifier-related K<sup>+</sup> channel.

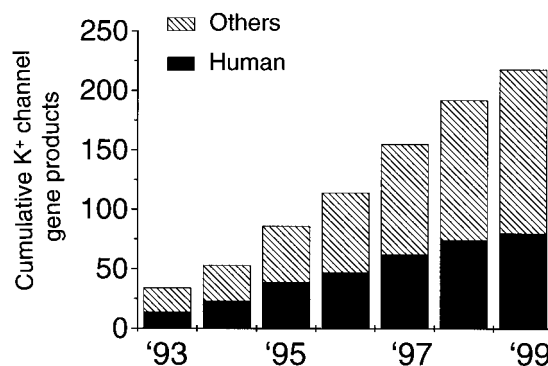


FIG. 1. Growth of genes encoding diverse K<sup>+</sup> channels. The *Shaker* K<sup>+</sup> channel gene was first cloned from *Drosophila* (Papazian et al., 1987). The gene products indicated along the y-axis include both K<sup>+</sup> channel  $\alpha$ - and auxiliary subunits. The data were obtained from the *Entrez* database of the National Center for Biotechnology Information (NCBI).

tion, a growing number of discoveries have linked K<sup>+</sup> channel gene mutations with various diseases. Such diseases of the heart, kidney, pancreas, and central nervous system involve either mutation(s) in K<sup>+</sup> channel gene(s) and/or altered regulation of K<sup>+</sup> channel function. The enhanced understanding of these diseases, facilitated by a combination of genomic and biophysical approaches, has helped our understanding of how various mutations affect channel function, contributes to disease etiology, and rationalizes novel treatment strategies. In this review, we provide a comprehensive overview of our recent understanding of molecular defects of K<sup>+</sup> channels in various diseases and its implications for the development of novel prophylactic or therapeutic approaches targeting distinct types of K<sup>+</sup> channels.

A brief overview of the structural and functional diversity of K<sup>+</sup> channels is initially provided to enable

familiarity with the nomenclature and biophysical and pharmacological characteristics of diverse K<sup>+</sup> channels. Several extensive reviews are already available on this subject that may be consulted for additional details (Doupnik et al., 1995; Coetzee et al., 1999). Diseases involving other voltage-gated ion channels have been reviewed elsewhere (Ackerman and Clapham, 1997; Lehmann-Horn and Rüdell, 1997; Cooper and Jan, 1999).

### A. Channel Diversity and Classification

K<sup>+</sup> channels are membrane-spanning proteins that selectively conduct K<sup>+</sup> ions across the cell membrane along its electrochemical gradient at a rate of 10<sup>6</sup> to 10<sup>8</sup> ions/s. To accomplish this, K<sup>+</sup> channels are endowed with a set of salient features: 1) a water-filled permeation pathway (pore) that allows K<sup>+</sup> ions to flow across the cell membrane; 2) a selectivity filter that specifies K<sup>+</sup> as permeant ion species; and 3) a gating mechanism that serves to switch between open and closed channel conformations (Hille, 1992). Since the first gene encoding a K<sup>+</sup> channel was cloned from *Drosophila Shaker* mutant (Papazian et al., 1987), more than 200 genes encoding a variety of K<sup>+</sup> channels have been identified (Fig. 1), all containing a homologous pore segment (S5-S6 linker) selective for K<sup>+</sup> ions (Hartmann et al., 1991; Yellen et al., 1991). Accordingly, a general classification of K<sup>+</sup> channels into families is based upon the primary amino acid sequence of the pore-containing subunit. Three groups with six, four, or two putative transmembrane segments are recognized. These include 1) voltage-gated K<sup>+</sup> channels (*Shaker*-like) containing six transmembrane regions (S1-S6) with a single pore; 2) inward rectifier K<sup>+</sup> channels containing only two transmembrane regions and a single pore; and 3) two-pore K<sup>+</sup> channels containing four transmembranes with two pore regions (Fig. 2). Table 1 lists a generalized classification of various cloned K<sup>+</sup> channel subunits.

**1. Six Transmembrane One-Pore Channels.** Voltage-gated K<sup>+</sup> channels (Kv), whose members include *Shaker*-related channels, human *ether-a-go-go*-related K<sup>+</sup> channels (hERG), Ca<sup>2+</sup>-activated K<sup>+</sup> channels, and KCNQ channels, are activated by depolarization.

**a. Pore and Selectivity Filter.** The tripeptide sequence motif G(Y/F)G located in the S5-S6 linker is common to the pore or P-loop of these and other K<sup>+</sup> channels and hence is considered as the K<sup>+</sup>-selectivity signature motif (Heginbotham et al., 1994). The residues immediately adjacent to either side of this motif are also generally conserved within the K<sup>+</sup> channel superfamily. Four of the pore loop domains contribute to the formation of a functional K<sup>+</sup>-conducting pore (MacKinnon, 1991). Accordingly, the heteromultimeric complex of voltage-gated K<sup>+</sup> channels is thought to be composed of four pore loop-containing  $\alpha$ -subunits arranged in a tetrameric fashion (MacKinnon, 1995; Jan and Jan, 1997). The external entry to the channel pore consisting of portions of the P-loop and adjacent residues in both S5

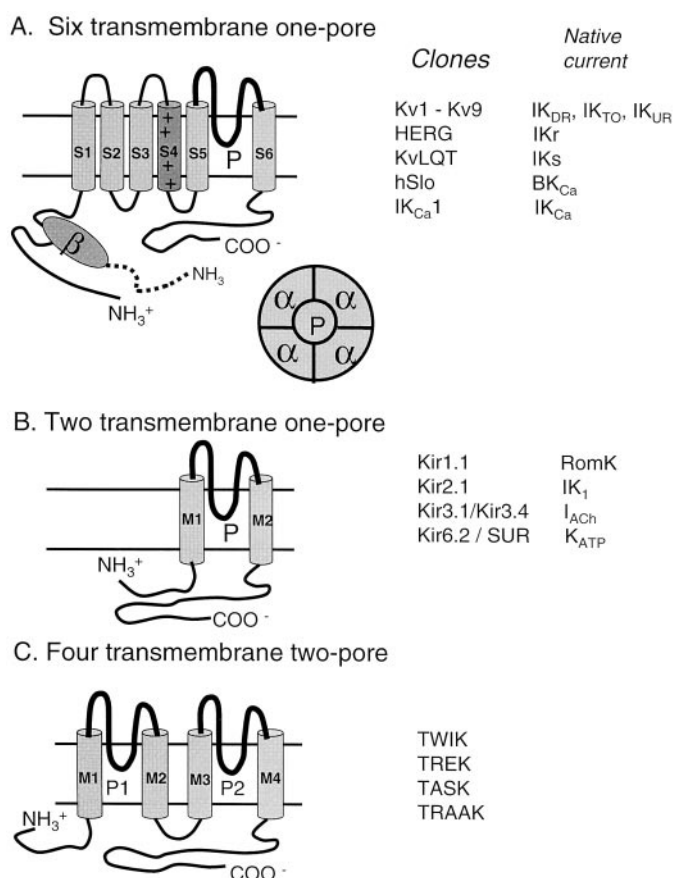


FIG. 2. Schematic representation of the structural classification of K<sup>+</sup> channel subunits. A, 6-TM subunits. The voltage-gated K<sup>+</sup> channels are composed of four subunits each containing six transmembrane segments (S1-S6) and a conducting pore (P) between S5 and S6 with a voltage sensor (positive charge of amino acid residues) located at S4. Some of the voltage-gated K<sup>+</sup> channels include an auxiliary  $\beta$ -subunit (Kv $\beta$ ), which is a cytoplasmic protein with binding site located at the N terminus of the  $\alpha$ -subunit. The inset shows the general assembly of K<sup>+</sup> channels. The homotetrameric K<sup>+</sup> channel consists of four identical subunits while different  $\alpha$ -subunits form heterotetrameric K<sup>+</sup> channels. B, 2-TM subunits. The inward rectifier K<sup>+</sup> channel belongs to a superfamily of channels with four subunits each containing two transmembrane segments (M1 and M2) with a P-loop in between. C, 4-TM subunits. This represents a class of the K<sup>+</sup> channels that has four transmembranes with two P-loops. I<sub>ACh</sub>, muscarine-activated K<sup>+</sup> current; IK<sub>DR</sub>, delayed rectifying K<sup>+</sup> current; IK<sub>TO</sub>, transient outward delayed rectifier; IK<sub>UR</sub>, ultrarapid delayed rectifier; IKr, cardiac rapid delayed rectifier; IKs, cardiac slow delayed rectifier; IK<sub>1</sub>, inward rectifier; TWIK, two-pore weak inward rectifier; TASK, TWIK-related acid-sensitive K<sup>+</sup> channel; TAAK, TWIK-related arachidonic acid-stimulated K<sup>+</sup> channel.

and S6 segments constitutes binding sites for toxins and K<sup>+</sup> channel blockers (MacKinnon and Miller, 1988; MacKinnon et al., 1990; Yellen et al., 1991; Goldstein et al., 1993; Pascual et al., 1995). On the other hand, the internal vestibule of pore composed of residues from S5 and S6 segments facing the intracellular side contributes to binding sites for compounds such as 4-aminopyridine, tetraethylammonium, and quinidine (Choi et al., 1993; Lopez et al., 1994; Shieh and Kirsch, 1994; Yeola et al., 1996). The S4-S5 linker lies close to the permeation pathway and forms part of the receptor for the inactivation ball (Isacoff et al., 1991).

**b. Voltage Sensor and Channel Activation.** In voltage-dependent ion channels, membrane depolarization

TABLE 1  
*Potassium Channel Genes and Ancillary Subunits: Localization, Modulators, and Diseases*

Type	Gene	Nomenclature	Chromosome	Tissue Expression	Modulators	Disorder/Mechanisms	References	
Voltage-gated K <sup>+</sup> channels ( <i>Shaker</i> )	<i>KCNA1</i>	Kv1.1	12p13	Neurons, heart, retina, pancreatic islet	Blocker: $\alpha$ -DTX, HgTX1, MgTX	Episodic ataxia/myokymia syndrome	Ramashwami et al., 1990 Litt et al., 1994 Browne et al., 1994, 1995 Adelman et al., 1995 Albrecht et al., 1995 Comu et al., 1996 Boland et al., 1999 D'Adamo et al., 1999 Ramashwami et al., 1990 Klocke et al., 1993 Grissmer et al., 1990 Aftali et al., 1992 Folander et al., 1994 Hanson et al., 1999 Tamkun et al., 1991 Philipson et al., 1993 Hanson et al., 1999 Curran et al., 1992 Phromchotikul et al., 1993 Albrecht et al., 1995 Grupe et al., 1990 Klocke et al., 1993 Albrecht et al., 1995 Kalman et al., 1998	
	<i>KCNA2</i>	Kv1.2	1	Brain, heart, pancreatic islet	Blocker: CTX, $\alpha$ -DTX, HgTX1, MgTX, NvTX			
	<i>KCNA3</i>	Kv1.3	1p21-p13.3	Lymphocyte, brain, lung, thymus, spleen	Blocker: AgTX2, $\alpha$ -DTX, HgTX1, KTX, MgTX, CTX, NvTX, UK78282, WIN 17317-3, correolide Blocker: UK78282	Missense mutations (11 variants)		
	<i>KCNA4</i>	Kv1.4	11q13.4-q14.1	Brain, heart, pancreatic islet	Blocker: $\alpha$ -DTX			
	<i>KCNA5</i>	Kv1.5	12p13	Brain, heart, kidney, lung, skeletal muscle	Blocker: 4-AP, clofilium, loratadine, perhexiline			
	<i>KCNA6</i>	Kv1.6	12p13	Brain	Blocker: $\alpha$ -DTX			
	<i>KCNA7</i>	Kv1.7	19q13.3	Heart, pancreatic islet, skeletal muscle	Blocker: 4-AP, capsaicin, tedisamil, NvTX, MgTX			
	<i>KCNA10</i>	Kv1.10	1p13.1	Aorta, brain, kidney	a. Blocker: 4-AP, CTX, ketoconazole, pimoziide b. Opener: cGMP			
	Voltage- and cGMP-gated K <sup>+</sup> channel	<i>KCNAB1</i>	Kv $\beta$ 1	3q26.1	Brain (Kv $\beta$ 1.1) Heart (Kv $\beta$ 1.2)			Yao et al., 1995 Orias et al., 1997a Lang et al., 2000 Rettig et al., 1994 England et al., 1995 McCormack et al., 1995 Majumder et al., 1995 Leicher et al., 1996 Schultz et al., 1996 Scott et al., 1994 McCormack et al., 1995 Morales et al., 1995 Schultz et al., 1996
		<i>KCNAB2</i>	Kv $\beta$ 2	1p36.3	Brain, heart			Leicher et al., 1998 Frech et al., 1989 Hwang et al., 1992 Melis et al., 1995 Yokoyama et al., 1989 Grissmer et al., 1992 Yokoyama et al., 1989 Ito et al., 1992 Haas et al., 1993 Ghanshani et al., 1992 Ito et al., 1992 Haas et al., 1993 Ghanshani et al., 1992 Klocke et al., 1993 Serodio et al., 1994 Isbrandt et al., 2000 Diochot et al., 1999 Zhu et al., 1999b Postma et al., 2000 Kong et al., 1998 Diochot et al., 1999 Postma et al., 2000 Drewe et al., 1992 Drewe et al., 1992
<i>Shab</i>	<i>KCNAB3</i>	Kv $\beta$ 3	17p13.1	Brain	Blocker: hanatoxin, TEA			
	<i>KCNB1</i>	Kv2.1-Kv2.2	20q13.2	Brain, heart, kidney, skeletal muscle, retina				
<i>Shaw</i>	<i>KCNK1</i>	Kv3.1	11p15	Brain, muscle, lymphocyte	Blocker: 4-AP			
	<i>KCNK2</i>	Kv3.2	19q13.3-q13.4	Brain	Blocker: 4-AP			
<i>Shal</i>	<i>KCNK3</i>	Kv3.3	19q13.3-q13.4	Brain, liver	Blocker: 4-AP			
	<i>KCNK4</i>	Kv3.4	1p21	Brain, skeletal muscle	Blocker: 4-AP			
	<i>KCND1</i>	Kv4.1	Xp11.23-p11.3	Heart, brain, liver, kidney, lung, placenta, pancreas	Blocker: 4-AP			
	<i>KCND2</i>	Kv4.2	7q31-32	Brain	Blocker: 4-AP, PaTX			
	<i>KCND3</i>	Kv4.3	1p13.2	Heart, brain	Blocker: 4-AP, PaTX			
		Kv5.1		Brain				
		Kv6.1		Brain				

TABLE 1  
Continued

Type	Gene	Nomenclature	Chromosome	Tissue Expression	Modulators	Disorder/Mechanisms	References
	<i>KCNF2</i>	Kv6.2	18q22-18q23	Heart			Zhu et al., 1999a
	<i>KCNK1</i>	Kv8.1	8q22.3-8q24.1	Brain			Hugnot et al., 1996
	<i>KCNK2</i>	Kv9.1		Brain			Salinas et al., 1997
	<i>KCNK3</i>	Kv9.2	8q22	Brain			Salinas et al., 1997
	<i>KCNK4</i>	Kv9.3	2p24	Lung, brain, artery			Patel et al., 1997
	<i>KCNK5</i>	Kv9.3	2p25	Heart, skeletal muscle			Su et al., 1997
	<i>KCNK6</i>	Kv9.3	20q13	Brain, placenta, skeletal muscle			Su et al., 1997
<i>Ether-a-go-go</i>	<i>KCNH1</i>	EAG	1q32-q41	Brain			Warmke and Ganetzky, 1994
	<i>KCNH2</i>	hERG	7q35-q36	Brain, heart	Blocker: clofilium, dofetilide, E4031, LY97241, terfenadine, sertindole	LQT2 a. Missense mutations b. Deletion (2 variants) c. Substitution in intron 3	Ochiodoro et al., 1998 Jiang et al., 1994 Warmke and Ganetzky, 1994 Curran et al., 1995 Benson et al., 1996 Satler et al., 1996 Itoh et al., 1998 Lee-Chen et al., 1999 Jongbloed et al., 1999 Larsen et al., 2000 Banfi et al., 1996 Miyake et al., 1999 Miyake et al., 1999 Murai et al., 1989 Chevallier et al., 1993 Schulze-Bahr et al., 1997 Splawski et al., 1997b Duggal et al., 1998 Tyson et al., 1997 Abbott et al., 1999
MinK	<i>KCNH3</i>	BEC1	12q13	Brain			
	<i>KCNH4</i>	BEC2		Brain			
	<i>KCNH5</i>	MinK	21q22.1-q22.2	Kidney, uterus, heart, cochlea, retina		LQT5 Missense mutations (5 variants)	
	<i>KCNH6</i>	MinK-related peptide 1 (MiRP1)	21q22.1				
	<i>KCNH7</i>	MiRP2		Small intestine, colon, kidney		LQT6 Missense mutations (3 variants)	Schroeder et al., 2000b
KvLQT1	<i>KCNQ1</i>	KvLQT1	11p15.5	Heart, cochlea, kidney, lung, placenta, colon	a. Blocker: chromanol-293B b. Opener: L-364,373, stilbenes, fenamates	LQT1; Jervell-Lange Neilsen syndrome a. Missense mutations (17 variants) b. Deletions (6 variants) c. Insertions (2 variants) (1 variant) d. Splice variant (1)	Russell et al., 1996 Wang et al., 1996 Donger et al., 1997 Neyroud et al., 1997 Splawski et al., 1997a Yang et al., 1997 Ackerman et al., 1998 Kanters et al., 1998 Li et al., 1998 Neyroud et al., 1998 Priori et al., 1998 Splawski et al., 1998 Ackerman et al., 1999 Chen et al., 1999c Jongbloed et al., 1999 Larsen et al., 1999 Murray et al., 1999 Neyroud et al., 1999 Biervert et al., 1998 Singh et al., 1998 Tinel et al., 1998 Yang et al., 1998
	<i>KCNQ2</i>	KvLQT2	20q13.3	Brain, neuron	a. Blocker: TEA, linopirdine, XE991, L-735,821 b. Opener: retigabine	Benign neonatal epilepsy a. Missense mutation (2 variants) b. Insertion (1 variant) c. Deletion (1 variant)	Biervert and Steinlein, 1999 Cooper et al., 2000 Charlier et al., 1998 Hirose et al., 2000
	<i>KCNQ3</i>	KvLQT3	8q24	Brain, neuron	a. Blocker: TEA, linopirdine, XE991 b. Opener: retigabine	Missense mutation (2 variants)	

TABLE 1  
Continued

Type	Gene	Nomenclature	Chromosome	Tissue Expression	Modulators	Disorder/Mechanisms	References
Inward rectifier	<i>KCNQ4</i>	KvLQT4	1p34	Outer hair cells, inner ear, central auditory pathway		Hearing loss	Coucke et al., 1999 Kubisch et al., 1999 Talebizadeh et al., 1999 Van Hauwe et al., 2000
	<i>KCNQ5</i>	KvLQT5	6q14	Brain, skeletal muscle	Blocker: linopirdine	a. Missense mutation (6 variants) b. Deletion (1 variant)	Lerche et al., 2000 Schroeder et al., 2000a Ho et al., 1993 Shuck et al., 1994 Yano et al., 1994 Krishnan et al., 1995
	<i>KCNJ1</i>	Kir1.1-Kir1.3	11q24	Kidney, pancreatic islets	Blocker: Ba <sup>2+</sup>	Bartter's syndrome, type 2; Bartter's syndrome, antenatal onset	Simon et al., 1996b Feldmann et al., 1998
	<i>KCNJ2</i>	Kir2.1		Heart, brain, smooth muscle, skeletal muscle, lung, placenta, kidney	Blocker: Ba <sup>2+</sup> , spermine, spermidine, Mg <sup>2+</sup>	a. Missense mutation (9 variants) b. Deletion (2 variants)	Kubo et al., 1993a Raab-Graham et al., 1994
	<i>KCNJ3</i>	Kir3.1	2q24.1	Heart, cerebellum	Blocker: Ba <sup>2+</sup>		Kubo et al., 1993b Stoffel et al., 1994
	<i>KCNJ4</i>	Kir2.3	22q13.1	Heart, brain, skeletal muscle	Blocker: Ba <sup>2+</sup>		Schoots et al., 1996 Schoots et al., 1997 Makhina et al., 1994 Perier et al., 1994 Budarf et al., 1995
	<i>KCNJ5</i>	Kir3.4	11q24	Heart, pancreas	Blocker: Ba <sup>2+</sup> , Cs <sup>+</sup>		Tucker et al., 1995
	<i>KCNJ6</i>	Kir3.2	21q22.1-q22.2	Cerebellum, pancreatic islet	Blocker: Ba <sup>2+</sup> , Cs <sup>+</sup>	Mouse <i>wearer</i>	Lesage et al., 1994 Sakura et al., 1995 Patil et al., 1995
	<i>KCNJ8</i>	Kir6.1/ uK <sub>ATP</sub> -1	12p11.23	Various	Blocker: Ba <sup>2+</sup> , Cs <sup>+</sup>	Missense mutation (1 variant)	Tsaur et al., 1995 Inagaki et al., 1995b Inagaki et al., 1995c Erginel-Unaltuna et al., 1998
	<i>KCNJ9</i>	Kir3.3	1q21-23	Brain	Blocker: Ba <sup>2+</sup> , Cs <sup>+</sup>		Lesage et al., 1994 Kobayashi et al., 1995 Vaughn et al., 2000
	<i>KCNJ10</i>	Kir4.1	1q	Glia	Blocker: Ba <sup>2+</sup> , Cs <sup>+</sup>		Takami et al., 1995 Tada et al., 1997
	<i>KCNJ11</i>	Kir6.2 (subunit of K <sub>ATP</sub> channel)	11p15.1	Various		Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)	Inagaki et al., 1995a Thomas et al., 1995a Thomas et al., 1996a Nestorowicz et al., 1997
	<i>KCNJ12</i>	Kir2.2	17p11.2-p11.1	Atrium, ventricle	Blocker: Ba <sup>2+</sup> , Cs <sup>+</sup>	a. Nonsense mutation (1 variant) b. Missense mutation (1 variant)	Wible et al., 1995 Hugnot et al., 1997 Namba et al., 1997
<i>KCNJ13</i>	Kir7.1	2q37	GI, kidney, cerebellum, hippocampus, thyroid	Blocker: Ba <sup>2+</sup> , Cs <sup>+</sup>		Derst et al., 1998 Krapivinsky et al., 1998 Partisei et al., 1998 Nakamura et al., 1999	

TABLE 1  
Continued

Type	Gene	Nomenclature	Chromosome	Tissue Expression	Modulators	Disorder/Mechanisms	References
	<i>KCNJ14</i>	Kir2.4	19q13	Brain, retina	Blocker: Ba <sup>2+</sup> , Cs <sup>+</sup>		Topert et al., 1998 Hughes et al., 2000 Topert et al., 2000 Gosset et al., 1997 Bond et al., 1994 Suzuki et al., 1999 Aguilar-Bryan et al., 1995 Thomas et al., 1995b Thomas et al., 1995a Nestorowicz et al., 1996 Thomas et al., 1996b Glaser et al., 1999 Dunne et al., 1997 Verkarre et al., 1998 Otonkoski et al., 1999 Tanizawa et al., 2000 Chutkow et al., 1996 Inagaki et al., 1996 Isomoto et al., 1996
Sulfonyleurea receptor	<i>KCNJ15</i> <i>Kir4.2</i> <i>Kir5.1</i>		21q22.2	Kidney, lung, brain Brain, periphery	Blocker: glyburide, tolbutamide, glipizide, ciclazindol	PHHI a. Missense mutations (11 variants) b. Deletion (4 variants)	
	<i>SUR1</i>	Sulfonyleurea receptor 1 (subunit of K <sub>ATP</sub> channel)	11p15.1	Pancreas, neurons, skeletal muscle	a. Blocker: glyburide, tolbutamide, glipizide, ciclazindol b. Opener: diazoxide		
	<i>SUR2</i>	Sulfonyleurea receptor 2 (2A, 2B) (subunit of K <sub>ATP</sub> channel)	12p12.1	2A: Heart, skeletal muscle 2B: Brain, liver, skeletal and smooth muscle	a. Blocker: glyburide, ciclazindole b. Opener: P1075, pinacidil, cromakalim		
Large conductance Ca <sup>2+</sup> -activated	<i>KCNMA1</i>	<i>Sl<sub>o</sub></i> (BK <sub>Ca</sub> channel $\alpha$ - subunit)	10q23.1	Brain, smooth muscle, cochlea, pancreatic islets	a. Blocker: IBTX, CTX, TEA b. Opener: NS1619, NS8, BMS- 204352, dehydrosoyasaponin I		Dworetzky et al., 1994 Pallanck and Ganetzky, 1994 Tseng-Crank et al., 1994 McCobb et al., 1995 Ferrer et al., 1996 Yogalis et al., 1996 Bowles et al., 2000 Knaus et al., 1994 Tseng-Crank et al., 1996 Jiang et al., 1999 Wallner et al., 1999a Uebele et al., 2000 Riazi et al., 1999 Behrens et al., 2000 Brenner et al., 2000 Uebele et al., 2000 Behrens et al., 2000 Brenner et al., 2000 Meera et al., 2000 Weiger et al., 2000 Kohler et al., 1996 Litt et al., 1999 Shah and Haylett, 2000 Kohler et al., 1996 Jager et al., 2000 Syme et al., 2000
	<i>KCNMB1</i>	BK <sub>Ca</sub> $\beta$ 1-subunit	5q34	Smooth and skeletal muscle			
	<i>KCNMB2</i>	BK <sub>Ca</sub> $\beta$ 2-subunit		Kidney, heart, uterus, small intestine			
	<i>KCNMB3</i>	BK <sub>Ca</sub> $\beta$ 3-subunit	3q26.3-q27	Testis			
	<i>KCNMB4</i>	BK <sub>Ca</sub> $\beta$ 4-subunit	12q14.1-q15	Brain, heart, kidney, lung			
Small conductance Ca <sup>2+</sup> -activated	<i>KCNN1</i>	SK1	19p13.1	Brain, heart	a. Blocker: tubocurarine, dequalinium, UCL 1848		
	<i>KCNN2</i>	SK2		Brain, adrenal gland, Jurkat T cells	a. Blocker: apamin, ScTX, d-tubocurarine, 4-AP b. Opener: chlorzoxazone, zoxazolamine, 1-EBIO		Kohler et al., 1996 Chandy et al., 1998 Wittekindt et al., 1998 Antonarakis et al., 1999 Austin et al., 1999
	<i>KCNN3</i>	SK3	1q21.3	Brain, heart, liver	Blocker: apamin		

TABLE 1  
Continued

Type	Gene	Nomenclature	Chromosome	Tissue Expression	Modulators	Disorder/Mechanisms	References
Intermediate conductance Ca <sup>2+</sup> -activated	<i>KCNN4</i>	IKCa1	19q13.2	T lymphocytes, colon, smooth muscles, prostate, red blood cells, neurons, placenta, thymus	a. Blocker: CTX, clotrimazole, nitrendipine, miconazole, cetiedil, econazole, TRAM-34		Ishii et al., 1997 Joiner et al., 1997 Logsdon et al., 1997 Ghanshani et al., 1998 Jensen et al., 1998 Neylon et al., 1999 Wulff et al., 2000 Lesage et al., 1996a Lesage et al., 1996b Orias et al., 1997b Fink et al., 1996 Lesage and Lazdumski, 1998
					b. Opener: 1-EBIO, chlorzoxazone, zoxazolamine		
Two-pore K <sup>+</sup> channel	<i>KCNK1</i>	TWIK1	1q42-q43	Brain, kidney, heart	Blocker: Ba <sup>2+</sup> , quinidine, quinine		Patel et al., 1999 Meadows et al., 2000 Duprat et al., 2000 Maingret et al., 2000 Duprat et al., 1997 Lesage and Lazdumski, 1998 Manjunath et al., 1999 Patel et al., 1999 Reyes et al., 1998
					<i>KCNK2</i>		
	<i>KCNK3</i>	TASK	2p23	Heart, brain, pancreas, placenta	a. Sensitive to external pH b. Activated by halothane, isoflurane		Chavez et al., 1999 Gray et al., 1999 Pountney et al., 1999 Salinas et al., 1999 Salinas et al., 1999 Duprat et al., 2000 Lesage et al., 2000 Maingret et al., 2000
	<i>KCNK5</i>	TASK2	6p21	Kidney	a. Sensitive to external pH b. Blocker: quinine, quinidine Sensitive to internal pH		Manjunath et al., 1999 Patel et al., 1999 Reyes et al., 1998
	<i>KCNK6</i>	TWIK2, TOSS	19q13.1	Eyes, lung, stomach, embryo			Chavez et al., 1999 Gray et al., 1999 Pountney et al., 1999 Salinas et al., 1999 Salinas et al., 1999 Duprat et al., 2000 Lesage et al., 2000 Maingret et al., 2000
	<i>KCNK7</i>	TRAAK	11q13 11q13	Brain, spinal cord, retina	a. Blocker: gadolinium b. Opener: unsaturated fatty acid (arachidonic acid), riluzole, lysophosphatidylcholine c. Stretch-activated		Chavez et al., 1999 Gray et al., 1999 Pountney et al., 1999 Salinas et al., 1999 Salinas et al., 1999 Duprat et al., 2000 Lesage et al., 2000 Maingret et al., 2000
		CTBAK-1		Heart, brain, kidney	Blocker: Ba <sup>2+</sup>		Kim et al., 1998

4-AP, 4-aminopyridine; AgTX2, angiotoxin 2; CTX, charybdotoxin;  $\alpha$ -DPTX,  $\alpha$ -dendrotoxin; HgTX1, honggotoxin 1; IbTX, iberiotoxin; KTX, kaliotoxin; MgTX, margatoxin; NsTX, noxiustoxin; PaTX, phrixotoxin; ScTX, scyllatoxin.



is required to cause conformational changes leading to channel opening, which allows permeant ions to flow. The movement of this voltage sensor sensing changes in membrane potential has been monitored electrically as the gating current (Armstrong and Bezanilla, 1974). Mutational analysis and gating current measurements have suggested that the transmembrane S4 segment represents the major component of the voltage sensor (Papazian et al., 1991; Perozo et al., 1994). The S4 segment that contains positively charged residues (lysine or arginine) at approximately every third position resulting in a regularly spaced array of 5 to 7 positive charges is conserved within the voltage-gated K<sup>+</sup> channel family. The rearrangement of S4 in response to membrane depolarization has also been confirmed by the means of fluorescence techniques (Mannuzzu et al., 1996; Cha and Bezanilla, 1997). While the S4 segment comprises the major part of the voltage sensor required for the K<sup>+</sup> channel activation, the electrostatic interaction of negative charges in S2 and S3 with the S4 segment also contributes to the gating mechanism (Papazian et al., 1995; Seoh et al., 1996). The nature of the gate that ultimately controls access of permeant ions to the pore is not conclusively established. Studies involving mutational analysis, gating current measurements, and the substituted cysteine accessibility method point to several residues in the S5 and S6 segments that might form the activation gate regulating access of ions to the pore (Liu et al., 1997; Shieh et al., 1997; Kanevsky and Aldrich, 1999).

*c. Inactivation.* Many voltage-dependent K<sup>+</sup> channels activate and inactivate rapidly when membrane potential becomes more positive. Inactivation is a non-conducting state during maintained depolarization. Three types of inactivation, i.e., N-, P-, and C-type, have been characterized and associated with distinct molecular domains of the channel. For example, the N-terminal residues (amino acids 6–46) of the *Shaker* K<sup>+</sup> channel involved in N-type inactivation moves into the internal vestibule (in S4-S5 linker) to occlude the pore when the channel opens (Hoshi et al., 1990; Isacoff et al., 1991). After removal of this N terminus region, inactivation can be restored in the mutant K<sup>+</sup> channel by the corresponding synthetic peptide (Zagotta et al., 1990). In contrast to the fast process of N-type inactivation, the C- and P-type inactivation involves a slower rearrangement of outer mouth and specific residues in the pore, respectively (Hoshi et al., 1991; De Biasi et al., 1993; Yellen et al., 1994; Liu et al., 1996).

*d. Subunit Interaction and Assembly Domains.* As noted previously, K<sup>+</sup> channels contain four  $\alpha$ -subunits, which surround a water-filled, K<sup>+</sup>-selective pore (Fig. 2). Among diverse voltage-gated K<sup>+</sup> channels, only closely related subfamilies of  $\alpha$ -subunits are capable of co-assembling to form heteromultimers. For example, in the Kv1 subfamily, a highly conserved cytoplasmic sequence immediately preceding the first transmembrane seg-

ment (amino acid residues 83 to 196) was identified as important to subfamily-specific channel assembly (Li et al., 1992). In *Shaker* channels, a conserved region (T1, or tetramerization domain 1) in the first transmembrane segment is involved in formation of tetramers (Shen et al., 1993). However, in more distantly related voltage-gated K<sup>+</sup> channels, *ether-a-go-go* (EAG), hERG, and KCNQ1 K<sup>+</sup> channel subfamilies, channel assembly primarily involves C-terminal domains (Ludwig et al., 1997; Kupersmidt et al., 1998). As discussed in the following sections, patients with Jervell and Lange-Nielsen long-QT (LQT) syndrome are characterized by the absence of KCNQ1 heteromultimers caused by mutations in the C terminus that impair subunit assembly (Schmitt et al., 2000).

*2. Two Transmembrane One-Pore Channels.* The inward rectifier K<sup>+</sup> channels (Kirs) belong to a distant superfamily of channels with four subunits each containing a two-transmembrane segment (M1 and M2) and a pore loop in between (Ho et al., 1993; Kubo et al., 1993). These channels conduct K<sup>+</sup> currents more in the inward direction than outward, and they are important in setting the resting membrane potential. This inward rectification is attributed to gating mechanisms by internal Mg<sup>2+</sup> and polyamines (spermine, spermidine, etc.) that occlude access of K<sup>+</sup> to the internal vestibule of a conducting pore (Matsuda, 1991; Ficker et al., 1994; Lu and MacKinnon, 1994; Wible et al., 1994). Like the voltage-gated K<sup>+</sup> channels, these channels are organized as tetramers (Yang et al., 1995), although a more complex octameric arrangement has been described, as in the case of the ATP-sensitive K<sup>+</sup> channels involving four inward rectifiers contributing to ion conducting pore and four peripheral sulfonylurea receptors as regulatory subunits (Clement et al., 1997; Inagaki et al., 1997; Shyng and Nichols, 1997).

*3. Four Transmembrane Two-Pore Channels.* The more recently discovered tandem-pore domain family are weak inward rectifiers with four putative transmembrane domains and two pore domains (Ketchum et al., 1995; Lesage et al., 1996a). They represent perhaps the most abundant class of K<sup>+</sup> channels (at least in *C. elegans*), with >50 distinct members (Wang et al., 1999). The G(Y/F)G residues of K<sup>+</sup>-selective motif is preserved in the first pore loop of the two-pore K<sup>+</sup> channel, but it is replaced by GFG or GLG in the second pore loop. Although all the two-pore channels have a conserved core region between transmembrane segments M1 and M4, the amino- and carboxyl-terminal domains are quite diverse. With two-pore domain subunits, two such subunits would presumably form a channel to retain the tetrameric arrangement.

## B. Auxiliary Subunits

Auxiliary subunits that associate with many of the pore-forming subunits have also been described (reviewed in Isom et al., 1994). For example, the Kv1 channels associate

with cytoplasmic  $\beta$ -subunits to alter channel kinetics (reviewed in Xu and Li, 1998). More recently, chaperone proteins, such as KChAP, regulating the function and expression of some of the Kv channels, such as Kv2.1, Kv1.3, and Kv4.3, have been reported (Kuryshv et al., 2000b). Certain other Kv channels, such as Kv5, Kv6, Kv8, and Kv9, do not form functional channels themselves but associate with Kv2.1 channels to alter the biophysical properties (Salinas et al., 1997; Kramer et al., 1998). Other examples include distinct  $\beta$ -subunits that associate with the calcium-activated  $K^+$  channels (Tseng-Crank et al., 1996; Wallner et al., 1999a; Behrens et al., 2000; Brenner et al., 2000; Meera et al., 2000), sulfonyleurea receptors for the inward rectifiers Kir6.1 or Kir6.2 (Aguilar-Bryan et al., 1995; Inagaki et al., 1995a), and minK and minK-related peptides (MiRPs) for the cardiac delayed rectifier channels (Barhanin et al., 1996; Sanguinetti et al., 1996; Abbott et al., 1999). These subunits play roles as diverse as modulation of gating properties such as inactivation, cell surface expression, and/or trafficking of the ion channel complex, to serving as binding sites for both endogenous and exogenous ligands. Given the diversity of  $K^+$  channel subunits and the potential to vary the constituents to form diverse  $\alpha$ - $\alpha$  or  $\alpha$ - $\beta$  heteromeric channel complexes to alter expression, cellular targeting, and biophysical and pharmacological properties in native cell types, understanding the precise composition of channel complexes in vivo remains a challenge.

### C. Crystal Structure of $K^+$ Channels

Initial studies of the structure and function of  $K^+$  channels by a combination of mutagenesis and biophysical approaches have revealed domains that are responsible for  $K^+$  selectivity, gating, channel assembly, subunit interaction, and drug binding sites. However, the three dimensional structural implications remained largely speculative. Recent discovery of the crystal structure of the KCsA channel established a blueprint of  $K^+$  channel structure with 3.2 Å resolution (Doyle et al., 1998). The KCsA channel is encoded by a bacterial gene cloned from *S. lividans* on the basis of sequence homology to  $K^+$ -selective motif GYG in the P-loop (Schrepf et al., 1995). The KCsA channel contains only two transmembrane domains with an intervening pore loop, although at the amino acid sequence level, this channel is more similar to the voltage-gated  $K^+$  channels. Functionally, it lacks any hint of voltage gating because of the lack of S4 region. X-ray analysis revealed that four identical subunits form a tetramer creating an inverted cone, cradling the selectivity filter of the pore in its outer end. The overall length of the conducting pore is 45 Å, and its diameter is variable along its distance. The internal vestibule of the pore begins as a tunnel of 18 Å in length that widens into a cavity ( $\sim 10$  Å across) near the middle of the membrane, with the narrow selectivity filter only 12 Å long. The remainder of the pore is wider and lined with hydrophobic amino acids. The selectivity filter is

lined by the carbonyl oxygen atoms of the GYG signature sequence, which is held open by structural constraints to coordinate  $K^+$  ions ( $\sim 3$  Å) but not smaller  $Na^+$  ions because the diameter is too wide to substitute for the hydration energy of the  $Na^+$  ions (Doyle et al., 1998). The crystal structure of KCsA channel provides the first three-dimensional structure of the conduction pore that fits consistently with current understanding of the core functionality of  $K^+$  channels. However, structural information of the remaining transmembrane segments (S1-S4), particularly the voltage sensor and the gate coupling to channel opening and closing, remains to be elucidated. Nevertheless, the understanding of structural information can be applied to design selective compounds targeting  $K^+$  channels. For example, a structure-based design strategy allowed several charybdotoxin analogs to be prepared with about 20-fold higher affinity to block  $Ca^{2+}$ -activated  $K^+$  channels versus voltage-gated Kv1.3 channels (Rauer et al., 2000). It is to be anticipated that a detailed understanding of the structural aspects would revolutionize and refine approaches targeting  $K^+$  channels for therapeutic purposes.

## II. Pathophysiologic Regulation of $K^+$ Channels: Genetically Linked Diseases

Advances in genetic linkage analysis during the past decade have greatly facilitated the identification of many disease-producing loci. Both positional cloning and candidate gene approaches have been used. Using positional cloning techniques, it has become possible to identify the location of genetic locus responsible for a given hereditary syndrome without prior knowledge of the biochemical or physiological abnormalities underlying the disease. Alternatively, following identification of genes encoding proteins that may be logically altered in a particular disease, the candidate gene approach may be used to examine genetic linkage to the hereditary disease of interest and screened for mutations.

As  $K^+$  channels play fundamental roles in the regulation of membrane excitability, it is to be expected that both genetic and acquired diseases involving altered functioning of neurons, smooth muscle, and cardiac cells could arise subsequent to abnormalities in  $K^+$  channel proteins. Genetically linked diseases of the cardiac, neuronal, renal, and metabolic systems involving members of voltage-gated  $K^+$  channels, inward rectifiers, and channel-associated proteins are discussed in the following sections (Table 1).

### A. Cardiac Diseases

$K^+$  channels are critical to cardiac excitability because they play a fundamental role in repolarization of the action potential. Unlike the action potentials of nerves that last only a few milliseconds, the action potentials of ventricular myocytes can last several hundred milliseconds. This prolonged depolarization phase is essential

for normal excitation-contraction coupling process and renders the myocytes relatively refractory to premature excitation. Various classes of K<sup>+</sup> channels with different time and voltage dependencies and pharmacological properties function in concert to regulate the heart rate by setting the resting membrane potential, amplitude, and duration of action potential and its refractoriness (Barry and Nerbonne, 1996; Roden and Kupershmidt, 1999; Snyders, 1999). The Kir2.1 current sets the resting membrane potential and contributes to the terminal phase of repolarization. The transient outward K<sup>+</sup> current (Kv4.3 or Kv1.4), which is Ca<sup>2+</sup>-independent and expressed in a species- and cell type-specific fashion, is important for the early phase of repolarization. The long ventricular action potentials that result from the slow onset of repolarization are controlled mainly by two types of delayed rectifier K<sup>+</sup> currents, i.e., IKs (derived from KCNQ1/minK) and IKr (derived from hERG/MiRP1). Both genetic linkage analysis and the candidate gene approach revealed that mutations in these delayed rectifier K<sup>+</sup> channel subunits form the molecular basis of LQT syndromes (Curran et al., 1995; Sanguinetti et al., 1995; Schott et al., 1995; Wang et al., 1996; Neyroud et al., 1997; Splawski et al., 1997b; Abbott et al., 1999).

The LQT syndromes are inherited genetic disorders characterized by prolonged or delayed ventricular repolarization, manifested on the electrocardiogram (ECG) as a prolongation of the QT interval. Table 2 lists K<sup>+</sup> and other ion channel genes involved in various forms of inherited LQT syndromes, LQT1 through LQT6. The inherited LQT causes syncopal attacks and high risk of sudden death as result of torsade de pointes polymorphic ventricular tachycardia, typically triggered by adrenergic arousal (Ackerman and Clapham, 1997; Sanguinetti and Spector, 1997; Vincent et al., 1999). Based on genetic origins, two allelic diseases are recognized: 1) the Romano-Ward syndrome inherited as a dominant trait and 2) the autosomal recessive Jervell and Lange-Nielsen syndrome. In the case of the latter, the patient suffers from a severe congenital bilateral deafness in addition to the cardiac disorder (Vincent et al., 1999). Note that in addition to genetically linked LQT syndromes, many drugs are also known to cause QT prolongation leading to torsade de pointes (see *Section III*).

TABLE 2  
K<sup>+</sup> channel genes involved in long-QT syndromes

Type	Gene	Current/Channel Type
LQT1	KCNQ1 (KvLQT1)	Component of slowly inactivating delayed rectifier IKs
LQT2	hERG	Delayed rectifier IKr rapidly inactivating cardiac Na <sup>+</sup> channel
LQT3	SCN5A	
LQT4	Chromosome 4q25-27	Subunit involved in regulation of cardiac repolarization?
LQT5	KCNE1 (MinK)	Component of IKs
LQT6	MiRP1	Component of IKr

1. *Long-QT1 and Long-QT5 Syndromes: KCNQ1 (KvLQT1) and minK.* KvLQT1, encoded by the KCNQ1 gene, in association with the minK subunit, a short peptide of 130 residues, constitutes the IKs responsible for phase 3 repolarization in the heart (Barhanin et al., 1996; Sanguinetti et al., 1996b). Several mutations in the *KCNQ1* gene, including missense mutations, intragenic deletion, and insertions, are involved in chromosome 11-linked LQT1 syndrome, the most common form of inherited LQT in families with Jervell and Lange-Nielsen and Romano-Ward syndromes (Russell et al., 1996; Wang et al., 1996; Donger et al., 1997; Tanaka et al., 1997; van den Berg et al., 1997; Saarinen et al., 1998; Li et al., 1998; Neyroud et al., 1999). Functional analysis of mutant channels in COS cells cotransfected with the minK subunit revealed that these mutations either alter gating properties or fail to produce functional homomeric channels and reduced K<sup>+</sup> current when coexpressed with the wild-type subunit (Chouabe et al., 1997; Shalaby et al., 1997; Wollnik et al., 1997; Franquenza et al., 1999).

Two separate mutations (D76N and S74L) in the minK subunit were identified in patients phenotypically characterized with LQT5 syndrome by single strand conformation polymorphism analyses (Splawski et al., 1997b; Duggal et al., 1998). Again, functionally, these mutations yield diminished IKs current when coinjected with *KCNQ1* either by suppressing channel function in a dominant-negative fashion, increasing rate of channel deactivation, or by shifting the voltage dependence of channel activation in a positive direction. It is likely that the mutations in *KCNQ1* associated with LQT1 will decrease the availability of IKs by altering gating properties or by a dominant-negative loss of channel function leading to a prolonged ventricular repolarization. Accordingly, activators that restore the function of IKs may prove useful in the treatment of LQT1 and LQT5 syndromes. Recently, Abitbol et al. (1999) have shown that stilbenes and fenamates, by binding the extracellular domain flanking the minK transmembrane segment, restored inactive IKs mutant channels, including the naturally occurring LQT5 mutant, D76N.

Neyroud et al. (1997) have also identified a homozygous deletion-insertion event in the C-terminal domain of *KCNQ1* in three affected children from two families with congenital bilateral deafness associated with QT prolongation. By *in situ* hybridization studies in mice, it was shown that the *KCNQ1* gene was expressed by the marginal cells of the stria vascularis. It has been suggested that, in conjunction with the minK subunit, *KCNQ1* forms a functional channel in marginal cells that is responsible for secretion of endolymph, in the inner ear, which bathes the stereocilia of sensory hair cells. Thus, *KCNQ1* plays a key role not only in the ventricular repolarization but also in normal hearing, probably via control of endolymph homeostasis (see *Section II.C*).

*2. Long-QT2 Syndrome and Human ether-a-go-go-Related K<sup>+</sup> Channel.* The hERG gene encoding a rapidly activating IKr is a major subunit responsible for repolarization during cardiac action potential (Sanguinetti et al., 1995). Interaction with hERG channels has been shown to be a primary mechanism involved in the therapeutic actions of the class III antiarrhythmic agents and the potential cardiotoxicity of second generation H<sub>1</sub> receptor antagonists, such as terfenadine and astemizole, as well as certain antidepressants and neuroleptics (Vincent et al., 1999).

By linkage analysis and single strand conformation polymorphism, Curran et al. (1995) first demonstrated that missense mutations, intragenic deletions, and splice donor mutations in the hERG gene resulted in chromosome 7-linked LQT2 syndrome. This finding was further confirmed by studying several mutations in different regions of the hERG subunit in families associated with LQT syndromes (Benson et al., 1996; Dausse et al., 1996; Satler et al., 1996, 1998; Tanaka et al., 1997). Similar to KCNQ1, mutations of hERG decrease repolarizing current and thus lengthen the duration of cardiac action potential. The mutant hERG cRNA, when expressed alone or in combination with wild-type channel, yields nonfunctional channels or evokes dominant negative suppression of hERG function (Sanguinetti et al., 1996a; Li et al., 1997; Babij et al., 1998; Nakajima et al., 1998). By green fluorescent protein tagging and Western blot analyses, it was found that the hERG-G601S mutant was deficient in the trafficking of functional protein to the plasma membrane (Furutani et al., 1999), which could explain the reduction in functional channels available for repolarization of the cardiac action potential. Other LQT-associated mutations identified in the amino-terminal region of hERG form functional channels, but with altered gating properties such as accelerated channel deactivation, and positively shifted voltage dependence of channel open probability. Collectively, these alterations lead to reduced outward current during the repolarization phase of the cardiac action potential and prolonged QT interval (Chen et al., 1999a). The diversity of mutations in the hERG gene impairing channel function in varying proportions likely contributes to variable degrees of clinical severity in LQT2 patients.

Although channels formed of hERG subunits appear similar to IKr, and although mutations in hERG gene are associated with LQT2 syndrome, the recombinant channels differ in gating, single channel conductance, and sensitivity to antiarrhythmic drugs compared with native currents. Another small membrane subunit, MiRP1, cloned by searching the expressed sequence tag (EST) database, was found to assemble with hERG to alter its function (Abbott et al., 1999). Injection of MiRP1 cRNA alone into oocytes revealed no currents by itself, whereas MiRP1 had significant effects on the properties of channels formed with hERG subunits but

not with other K<sup>+</sup> channels, including KCNQ1, *Shaker*, and Kv members. Coexpression of MiRP1 with hERG revealed functional current with gating and sensitivity to E-4031 similar to native cardiac IKr. Three missense mutations associated with the LQT6 syndrome and ventricular fibrillation have been identified in the MiRP1 gene. The mutant channels open slowly and close rapidly, thereby evoking diminished K<sup>+</sup> currents. One variant, associated with clarithromycin-induced arrhythmia, increases sensitivity to channel blockade by the antibiotic. The latter finding reveals an important mechanism for acquired arrhythmia wherein a genetically based reduction in K<sup>+</sup> currents remains silent until combined with additional factors.

β-Adrenoceptor antagonists have been used in the treatment of LQT1 and LQT2 syndromes since episodes of syncope and sudden death occur more frequently with exercise and at times of adrenergic surges (Vincent et al., 1999). The mechanism of dysfunction of hERG and MiRP1 associated with LQT suggests that activators for these channels may be therapeutically useful. Expression of hERG alone reveals little outward K<sup>+</sup> current upon depolarization, whereas large inward K<sup>+</sup> currents are seen when the membrane voltage is hyperpolarized due to removal of C-type inactivation (Smith et al., 1996; Spector et al., 1996). Elevation of external K<sup>+</sup> levels reduces this C-type inactivation, thereby increasing outward K<sup>+</sup> currents and reducing the prolongation of cardiac action potential with LQT2. Indeed, Compton et al. (1996) have shown that elevation of serum [K<sup>+</sup>] using K<sup>+</sup> supplements and spironolactone in patients with LQT2 demonstrated a significant reduction of the QT interval. Although it is difficult to maintain an elevated level of serum K<sup>+</sup>, these findings suggest that the patients could avoid administration of drugs that cause hypokalemia.

## B. Neuronal Diseases

K<sup>+</sup> channels are critical to neurotransmission in the nervous system. Alterations in the function of these channels lead to remarkable perturbations in membrane excitability and neuronal function. Significant progress has been made in linking many neuronal disorders, including episodic ataxia and benign familial neonatal convulsions, to K<sup>+</sup> channel mutations.

*1. Episodic Ataxia/Myokymia and Kv1.1.* Episodic ataxia (EA) is an autosomal dominant disorder in which the affected individuals have brief episodes of ataxia triggered by physical or emotional stress. On the basis of the duration and severity of the attacks, two types of episodic ataxia are recognized. In EA type 1 with onset in early childhood, the ataxia occurs several times during the day, lasts for seconds to minutes, and is associated with dysarthria and motor neuron activity, which causes muscle rippling (myokymia) between and during attacks. In contrast, in EA type 2, the attacks last for hours to several days and are precipitated by emotional

stress and exercise, but they do not startle. This type of ataxia is associated with nystagmus and cerebellar atrophy, unlike the EA-1 type in which the affected children do not develop persistent ataxia or cerebellar atrophy.

Linkage analysis has mapped episodic ataxia to two different ion channel genes. EA-2 is associated with missense mutations in *CACNA1A*, encoding a brain-specific P/Q-type Ca<sup>2+</sup> channel located on chromosome 19p13, the same region associated with familial hemiplegic migraine, suggesting the possibility that both EA-2 and familial hemiplegic migraine are allelic disorders (Ophoff et al., 1996; Jen et al., 1999). By linkage studies, Litt et al. (1994) localized the EA-1 gene to chromosome 12p, where the *KCNA1* gene encoding the voltage-gated K<sup>+</sup> channel in brain and peripheral nervous systems has been mapped. Mutational analysis of *KCNA1* in several families with EA-1 has identified at least ten missense mutations (Browne et al., 1994; Scheffer et al., 1998). These mutations alter Kv1.1 function by reducing channel expression (dominant-negative effect), altering gating properties by shifting the midpoint of current activation some 10 to 40 mV in the depolarization direction, or enhancing deactivation or C-type inactivation rates (Adelman et al., 1995; Zerr et al., 1998; Boland et al., 1999; Bretschneider et al., 1999). Accordingly, it could be inferred that altered Kv1.1 function could impair the capacity of the affected neurons to repolarize effectively following an action potential. Further support for the notion that the diminished function of *KCNA1* leads to ataxia is obtained from gene knockout studies in which the homozygous mutant mice exhibit attacks of tremors and marked ataxia after cold-temperature stress (Smart et al., 1998).

Acetazolamide, a carbonic anhydrase inhibitor, has been effective in reducing attack episodes in some patients suffering from EA-1. However, this compound did not affect Kv1.1 wild-type or mutant channels (Bretschneider et al., 1999). Pharmacological agents that either shift the voltage dependence of Kv1.1 channel activation to more negative potentials or enhance the magnitude of current could, in principle, prevent both ataxia and myokymia (Sanguinetti and Spector, 1997).

**2. Benign Familial Neonatal Convulsions and *KCNQ2/KCNQ3*.** Recent application of genetic analysis to hereditary epilepsy has provided the impetus for the identification of mutations in genes encoding various ion channels, including K<sup>+</sup> channels (Biervert et al., 1998; Charlier et al., 1998; Singh et al., 1998). BFNC is an idiopathic form of epilepsy beginning within the first six months after birth. Seizures are generalized and mixed, starting with tonic posture, ocular symptoms, and apnea, and often progress to clonic movements and motor automatisms. Seizures last 1 to 2 s and occur three to six times per day. Two forms of benign familial neonatal convulsions, BFNC1 and BFNC2, are typically observed in families as an autosomal dominant inheri-

ance and have been previously mapped into chromosomes 20q and 8q, respectively (Leppert and Singh, 1999). By positional cloning techniques, the voltage-gated K<sup>+</sup> channel *KCNQ2*, spanning the deletion region of chromosome 20q13.3 that cosegregates with seizures in a BFNC family, was identified (Biervert et al., 1998; Singh et al., 1998). Missense mutation, frameshifts, and splice-site mutations in *KCNQ2* were also found in other BFNC families. By a homology search of expressed sequence tag database and genotyping approaches, a missense mutation in the pore region of another voltage-gated K<sup>+</sup> channel, *KCNQ3*, was also identified from families with BFNC2 previously linked to chromosome 8q24 (Biervert et al., 1998; Charlier et al., 1998; Schroeder et al., 1998).

It is now understood that both *KCNQ2* and *KCNQ3* subunits coassemble to constitute properties of the M-channel (M for *muscarine*) described in neurons (Brown and Adams, 1980). First described in the peripheral sympathetic neurons and subsequently in the CNS, this channel is one of the most important regulators of neuronal excitability because it plays a critical role in determining the excitability threshold, firing properties, and responsiveness of neurons to synaptic inputs. In the absence of acetylcholine, the M-channel activity hyperpolarizes the cell membrane potential, leading to a dampening of neuronal responsiveness to synaptic inputs. However, in the presence of released acetylcholine, the M-channels are inhibited. This change in M-channel activity provides a mechanism for neurons to respond to synaptic input and to favor firing a burst of spikes, rather than a single spike, upon excitation (Hille, 1992). By voltage-clamp recording of neurons from rat superior cervical ganglion, Marrion et al. (1989) determined that ACh-evoked suppression of the M-channel is mediated by the activation of muscarinic M1 receptors. Seizures in mice induced by a muscarinic agonist, pilocarpine, were sensitive to inhibition by a muscarinic M1 antagonist, pirezepine (Maslanski et al., 1994). Furthermore, in transgenic mice lacking muscarinic M1 receptors, the robust suppression of the M-current activity evoked by muscarinic agonists in sympathetic ganglion neurons was eliminated. Both homozygous and heterozygous mutant mice were also resistant to seizures evoked by systemic administration of pilocarpine (Hamilton et al., 1997). Taken together, these studies suggest that M-channels play a key role in controlling seizure activity.

Both *KCNQ2* and *KCNQ3* belong to the *KCNQ* family of K<sup>+</sup> channels that includes *KCNQ1* (KvLQT1), whose aberrant function leads to the congenital bilateral deafness associated with QT prolongation. The *KCNQ2* protein exhibits 62% identity with *KCNQ3* within the coding region and is also highly conserved with *KCNQ1* in transmembrane S1-S6 region with 60% identity and 70% similarity (Biervert et al., 1998; Charlier et al., 1998; Tinel et al., 1998). Unlike *KCNQ1*, which is expressed strongly in human heart and pancreas, *KCNQ2*

and *KCNQ3* transcripts are detectable only in brain (Biervert et al., 1998; Wang et al., 1998; Yang et al., 1998) and in rat sympathetic ganglia (Wang et al., 1998). Expression of human *KCNQ2* was found to be high in the hippocampus, caudate nucleus, and amygdala, moderate in the thalamus, and weak in the subthalamic nucleus, substantia nigra, and corpus callosum. A similar expression pattern for *KCNQ3* was found in the human brain (Biervert et al., 1998; Tinel et al., 1998; Yang et al., 1998).

In human brain, four splice variants of *KCNQ2* were identified, among which only two forms generated  $K^+$ -selective currents when heterologously expressed in oocytes or COS cells (Tinel et al., 1998). These currents resemble those of *KCNQ1* in their permeability sequence of cations, voltage dependence, and kinetics (Biervert et al., 1998; Tinel et al., 1998). When expressed in *Xenopus* oocytes, *KCNQ3* elicited currents that were only slightly above background but resembled the larger depolarization-activated  $K^+$  currents observed with *KCNQ2* (Schroeder et al., 1998; Wang et al., 1998). Unlike *KCNQ1* (KvLQT1), where coinjection with minK (*KCNE1*) dramatically alters the amplitude and gating kinetics of the *KCNQ1* channel and produces current resembling cardiac IKs, neither *KCNQ2* or *KCNQ3* currents were altered when coinjected with the minK subunit (Yang et al., 1998). However, when *KCNQ2* and *KCNQ3* mRNAs were coinjected in the *Xenopus* oocytes, the resultant current was more than 10-fold larger than that observed in cells injected with either *KCNQ2* or *KCNQ3* alone (Schroeder et al., 1998; Wang et al., 1998; Yang et al., 1998). The expressed  $K^+$  current by coinjection with *KCNQ2* and *KCNQ3* has gating kinetics and sensitivities to blockade by classical M-channel inhibitors such as linopirdine and XE991, indicating that the M-channel is a heteromultimer composed of *KCNQ2* and *KCNQ3* subunits (Wang et al., 1998).

No detectable currents were expressed when cRNA of the truncated *KCNQ2* identified from families with BFNC1 alone were injected. When mutant and wild-type cRNA were coinjected at a 1:1 ratio to mimic the situation in a heterozygous patient, the currents were reduced, compared with those recorded from oocytes injected with similar amounts of wild-type cRNA. Thus, although there was no obvious dominant negative effect, haploinsufficiency may be enough to explain the dominant mode of inheritance of this disorder, which generally occurs transiently during infancy (Biervert et al., 1998). Two single mutations in *KCNQ2* (Y284C and A306T), as well as insertion mutant associated with BFNC1, were analyzed for current amplitude when coexpressed with *KCNQ3*. The function of these mutant heteromeric channels was significantly reduced, and no dominant negative effect was observed. Likewise, when the *KCNQ3* mutant G310V was coexpressed with wild-type *KCNQ2*, a loss function effect rather than a dominant-negative effect was seen (Schroeder et al., 1998).

Together, Schroeder et al. (1998) suggested that a 25% loss of heteromeric *KCNQ2/KCNQ3* function is sufficient to cause the hyperexcitability in BFNC. Recently, another missense mutation that replaced tryptophan with arginine (W309R) in the P-loop of *KCNQ3* was also reported from patients with BFNC (Hirose et al., 2000).

The cytoplasmic N terminus of *KCNQ2* contains a consensus site for cAMP-dependent phosphorylation, and increases in intracellular cAMP concentration have been shown to enhance *KCNQ2/KCNQ3* current by 50% (Schroeder et al., 1998). Compounds that open or enhance the activity of the M-currents, such as retigabine, or elevate associated intracellular cAMP levels may serve as useful antiepileptic agents. It should be pointed out that in addition to M-channel mutations linking to BFNC disorders, mutations in other ion channels have been associated with varying forms of epilepsy (Steinlein, 1999). These include mutations of the neuronal nicotinic acetylcholine receptor  $\alpha 4$ -subunit (*CHRNA4*), identified to be responsible for the autosomal dominant nocturnal frontal lobe epilepsy (Steinlein et al., 1995, 1997), and those involving voltage-gated sodium channel  $\alpha 1$ -subunit (*SCN1B*) identified in families associated with generalized epilepsy with febrile seizures (Wallace et al., 1998). Collectively, the discoveries of these ion channels as epilepsy disease genes emphasize the potential roles of ion channels in epilepsy and suggest that compounds that directly or indirectly modulate these channels may prove helpful in suppressing seizures.

**3. Neurodegeneration and Kir3.2.** The progressive loss of dopaminergic neurons in the *weaver* mouse is similar to the pathological symptom of Parkinson's disease where cell death of dopaminergic neurons in the substantia nigra is observed, leading to striatal dopaminergic deficit and a clinical syndrome dominated by disorders of movement (Yamada et al., 1990; Gaspar et al., 1994). The *weaver* phenotype in mice is an autosomal recessive neurological and reproductive disorder characterized behaviorally by severe ataxia, hyperactivity, and tremors that are manifested within 2 weeks after birth. These behavioral changes are attributable to the degeneration of cerebellar granule cells and dopaminergic neurons in the substantia nigra (Rakic and Sidman, 1973a,b). In addition, *wv/wv* genotype causes death or impaired function of dopaminergic neurons in the substantia nigra, male infertility, and sporadic tonic-clonic seizures (Hess, 1996; Harrison and Roffler-Tarlov, 1998). While heterozygous mice are not ataxic, they have seizures and a significant reduction in the number of granule cells.

The *weaver* mutation was mapped to mouse chromosome 16 in a region of conserved linkage with human chromosome 21 (Reeves et al., 1989). By a combination of physical and transcript mapping of the homologous segment on human chromosome 21, Patil et al. (1995) identified two potential candidate genes in this region: 1) *mmb*, encoding a serine/threonine-specific protein

kinase, and 2) Kir3.2, encoding a G protein-gated inwardly rectifying K<sup>+</sup> channel. Sequence analysis yielded no mutations in *mmB*, whereas a single missense mutation replacing a glycine with serine at residue 156 (G156S) was observed in Kir3.2 associated with *weaver* mouse in a location within the pore-forming region, critical for ion selectivity and conserved within the K<sup>+</sup> channel family (MacKinnon, 1995). The mutation renders the channel nonselective, leading to conduction of Na<sup>+</sup> ions instead of the highly selective K<sup>+</sup> ions (Navarro et al., 1996; Slesinger et al., 1996). Ribonuclease protection and reverse transcriptase-polymerase chain reaction studies have shown that the overall expression pattern of Kir3.2 gene parallels the developmental loss of the cells in cerebellum, substantia nigra, and testes (Patil et al., 1995; Slesinger et al., 1996).

It has been shown that Kir3.2 coassembles with Kir3.1 to form the G protein-gated, K<sup>+</sup>-selective inward rectifier channels in neurons (Duprat et al., 1995; Liao et al., 1996; Velimirovic et al., 1996). Immunohistochemical localization studies indicate that Kir3.2 and Kir3.1 proteins are expressed in the cerebellar neurons of mice at postnatal day 4, at a time when neurons normally undergo differentiation (Slesinger et al., 1996). Functional analysis of expression of *wv*Kir3.2 and Kir3.2 in *Xenopus* oocytes or Chinese hamster ovary cells revealed that the mutant channel showed reduced sensitivity to muscarinic M2 receptor activation, failed to respond to G<sub>α</sub> subunit, and evoked diminished K<sup>+</sup> currents. Furthermore, the loss in selectivity for K<sup>+</sup> and increased basal current resulting from increased Na<sup>+</sup> permeability leads to alterations in membrane excitability, cell differentiation, and ultimately cell death (Kofuji et al., 1996; Navarro et al., 1996; Silverman et al., 1996; Slesinger et al., 1996; Rossi et al., 1998). Results from transgenic studies confirmed that the *weaver* phenotypes arise from a gain-of-function mutation of Kir3.2. Although the transgenic mice lacking Kir3.2 (-/-) are morphologically indistinguishable from the wild type, they have much reduced Kir3.1 expression in the brain, develop spontaneous seizures, and are more susceptible to pharmacologically induced seizures induced by pentylenetetrazol (Signorini et al., 1997).

The nonselective cation current in cells expressing *wv*Kir3.2 can be blocked by MK-801 and calcium channel blockers (Kofuji et al., 1996). These compounds have been shown to enhance cell viability and neurite outgrowth of cultured *weaver* granule cells, but not of wild-type granule cells. In addition, neurite outgrowth and migration of the *weaver* granule neurons has also been shown to be enhanced by Fab2 fragments of antibodies raised against a neurite outgrowth domain of the laminin B2 chain (Liesi and Wright, 1996).

As mentioned previously, the degeneration of noncalbindin-positive dopaminergic neurons in substantia nigra of *weaver* mice shares similarity to Parkinson's disease, in which the dopaminergic neurons that are

progressively lost in the substantia nigra are also noncalbindin-positive. These observations suggest the possibility of a shared genetic defect in *weaver* mouse and Parkinson's disease (Yamada et al., 1990; Gaspar et al., 1994). However, Bandmann et al. (1996) did not detect mutations by sequencing analysis of the pore-forming region of Kir3.2 gene from patients with familial and sporadic cases of Parkinson's disease, suggesting a differing etiology of nigral cell loss in Parkinson's disease and *weaver* mice. Nevertheless, the finding that *weaver* phenotype results from a single amino acid mutation in Kir3.2 leading to alterations in membrane excitability provides a reasonable avenue for understanding the molecular nature of this neuronal disorder.

4. *Schizophrenia and SK3 (hKCa3)*. Although initially differentiated on the basis of biophysical and differential toxin sensitivity, distinct genes are now known to encode various calcium-activated K<sup>+</sup> channels (Vergara et al., 1998; Castle, 1999; Wallner et al., 1999b). Abnormal function of calcium-activated K<sup>+</sup> channels has been noted in platelets of patients with Alzheimer's disease, although its relevance to the pathology is not clear (de Silva et al., 1998). The CAG triplet repeat in *KCNN3* gene encoding a small conductance calcium-activated K<sup>+</sup> channel, hKCa3, mapped to chromosome 1q21 has been reported to be associated with schizophrenia (Chandy et al., 1998), although subsequent investigations to confirm these findings have been met with mixed results (Austin et al., 1999; Dror et al., 1999).

#### C. Hearing and Vestibular Diseases: Nonsyndromic Dominant Deafness and *KCNQ4*

Much progress has been made in the area of identifying genes defective in hearing and balance disorders, with over 40 such genes described (Holt and Corey, 1999). One of the genes reported to be the locus for hereditary hearing impairment is another K<sup>+</sup> channel belonging to the *KCNQ* channel superfamily, i.e., *KCNQ4*. The *KCNQ4* gene, isolated from a human retina library using *KCNQ3* partial cDNA as a probe, exhibits 38, 44, and 37% identity to *KCNQ1*, *KCNQ2*, and *KCNQ3*, respectively (Kubisch et al., 1999). Reverse transcriptase-polymerase chain reaction analysis revealed high expression of *KCNQ4* in the vestibular system and brain. In cochlea sections from mice at postnatal day P12, sensory outer hair cells were strongly labeled with a *KCNQ4* antisense probe but not in the inner hair cells and stria vascularis where *KCNQ1* expression was detected. Expression of *KCNQ4* in *Xenopus* oocytes generated a voltage-dependent K<sup>+</sup> current, similar to *KCNQ1*, *KCNQ2*, and *KCNQ3*, except with slower activation. Unlike *KCNQ1*, *KCNQ4* did not interact with minK. However, coexpression of *KCNQ3* with *KCNQ4* yielded currents resembling an M-channel, but with only weak inhibition (75% inhibition at 200 μM) by linopirdine, unlike those observed with the *KCNQ2*/*KCNQ3* combination. The similarity of currents from

*KCNQ3/KCNQ4* to M-channel indicated that *KCNQ3/KCNQ4* might potentially form another M-channel variant in the nervous system (Kubisch et al., 1999).

Using fluorescence in situ hybridization to human chromosomes, *KCNQ4* was mapped to chromosome 1p34, a region also hosting *DFNA2*, a locus for autosomal dominant progressive hearing loss (Kubisch et al., 1999). One 13-bp deletion mutation and four missense mutations (G285S, G285C, W276S, and G321S) were identified from families with autosomal dominant progressive hearing loss linked to the *DFNA2* locus (Coucke et al., 1999; Kubisch et al., 1999). The G285S and G285C mutations alter the first glycine residue in the GYG signature sequence of K<sup>+</sup> channel pore. Mutations in these amino acids disrupt the selectivity filter and, in most cases, abolish channel function. An identical change in amino acids at the equivalent position has also been reported in the *KCNQ1* gene of a patient with the dominant LQT1 (Russell et al., 1996). Functional analysis reveals that the mutant channel did not produce current when the cRNA was injected into oocytes, whereas the mutation exerted a dominant-negative effect when coexpressed with wild-type *KCNQ1*. Whereas mutations in *KCNQ1* affect endolymph secretion, the mechanism leading to *KCNQ4*-related hearing loss appears to be in outer hair cells (Kubisch et al., 1999), inner ear, and the central auditory pathway (Kharkovets et al., 2000).

It must be pointed out that in addition to mutations in *KCNQ4*, mutations in *GJB3*, which encodes the connexin 31 component of gap junctions and was mapped to human chromosome 1p33-p35, were identified from the *DFNA2* family with nonsyndromic autosomal dominant hearing loss (Xia et al., 1998). Although at least two or three genes responsible for hearing impairment are located close together on chromosome 1p34, *KCNQ4* mutations may be a relatively frequent cause of autosomal dominant hearing loss.

#### D. Renal Diseases: Bartter's Syndrome and Kir1.1

Several transporters and ion channels in the renal epithelium play important roles in urine production, fluid balance, and electrolyte metabolism. Genetic analysis reveals that dysfunction of an inward rectifier K<sup>+</sup> channel Kir1.1 is linked to Bartter's syndrome, an autosomal recessive inherited renal tubular disorder characterized by hypokalemia, metabolic alkalosis, hyperreninism and hyperaldosteronism. Patients have normal or low blood pressure and renal salt loss despite increased plasma renin activity and high serum aldosterone levels (Karolyi et al., 1998; Simon and Lifton, 1998; Scheinman et al., 1999). At least three phenotypically different renal tubulopathies have been identified: antenatal Bartter's syndrome (hyperprostaglandin E syndrome), classic Bartter's syndrome, and Gitelman's syndrome. Of these, polyhydramnios, premature delivery, hypokalemic alkalosis, hypercalciuria, and dehydration

at birth characterize the antenatal Bartter's syndrome (hypokalemic alkalosis with hypercalciuria). Children with the antenatal Bartter's syndrome present the typical pattern of impaired salt reabsorption in the thick ascending limb of Henle's loop resulting in the marked ante- and postnatal salt wasting.

Genetic heterogeneity of antenatal Bartter's syndrome has been demonstrated initially by identification of mutations in the *SLC12A1* gene, encoding for the bumetanide-sensitive sodium potassium 2 chloride cotransporter (NKCC2) leading to defective reabsorption of sodium chloride in the thick ascending limb of Henle's loop (Simon et al., 1996a; Vargas-Poussou et al., 1998). Subsequently, several mutations in *KCNJ1*, encoding the apical renal outer medullary inward rectifying K<sup>+</sup> channel (Kir1.1), were identified in patients with antenatal Bartter's syndrome by single strand conformation polymorphism analysis (Simon et al., 1996b; Derst et al., 1997; Feldmann et al., 1998; Vollmer et al., 1998). Functional studies revealed that mutant channels expressed none or significantly reduced currents compared with the wild-type channel. This impaired K<sup>+</sup> flux and loss of tubular K<sup>+</sup> channel function probably prevents apical membrane potassium recycling with secondary inhibition of Na-K-2Cl cotransport in the thick ascending limb of Henle's loop (Derst et al., 1997). The mechanisms underlying impaired Kir1.1 function involve abnormalities in phosphorylation, proteolytic processing, and/or protein trafficking (Schwalbe et al., 1998).

The signs and symptoms of Bartter's syndrome are usually a consequence of hypokalemia. Maintaining normal serum K<sup>+</sup> levels and limiting the degree of metabolic alkalosis are some of the treatment approaches, and potassium supplements and potassium-sparing diuretics are frequently used (Gordon and Stokes, 1994).

#### E. Metabolic Diseases: Familial Persistent Hyperinsulinemic Hypoglycemia of Infancy and Sulfonylurea Receptor 1

Various types of ion channels are involved in the regulation of electrical activity in the pancreatic  $\beta$ -cell. Of these, the ATP-sensitive K<sup>+</sup> (K<sub>ATP</sub>) channel plays a critical role in directly linking cellular metabolism to the electrical activity. Opening the ATP-sensitive K<sup>+</sup> channels leads to membrane hyperpolarization and consequently suppression of insulin secretion. Recent genetic analysis has revealed mutations in the ATP-sensitive K<sup>+</sup> channel subunits that may contribute to inappropriate and excessive secretion of insulin.

PHHI is an autosomal recessive disorder characterized by increased irregularity in insulin secretion leading to hypoglycemia, coma, and severe brain damage in children. Both sporadic and familial variants of PHHI are recognized; familial forms are common in communities with high rates of consanguinity where the incidence may be as high as 1 in 2500 live births and is the most common cause of hypoglycemia in newborns



(Aynsley-Green and Hawdon, 1997). Recent genetic linkage analysis has identified mutations in the K<sub>ATP</sub> channel complex that regulates insulin secretion from pancreatic  $\beta$ -cells. The K<sub>ATP</sub> channels predominantly determine the resting potential of  $\beta$ -cell and couple cellular metabolism to electrical activity (Ashcroft and Rorsman, 1989; Dukes and Philipson, 1996). When plasma glucose is elevated, increases in intracellular ATP/ADP ratio lead to closure of K<sub>ATP</sub> channels and membrane depolarization that, in turn, lead to the activation of voltage-dependent Ca<sup>2+</sup> channel, rise in intracellular Ca<sup>2+</sup>, and insulin secretion.

The  $\beta$ -cell K<sub>ATP</sub> channel, like other K<sub>ATP</sub> channels described in neurons, cardiac, smooth, and skeletal muscle, are inhibited by intracellular ATP, and recent molecular cloning has shown that the channel is an octamer composed of four subunits of the sulfonylurea receptor SUR1 coupled to four subunits of the inward rectifier Kir6.2 (Inagaki et al., 1995a, 1997; Clement et al., 1997; Shyng and Nichols, 1997). Over 28 naturally occurring mutations in SUR1 (Thomas et al., 1995b; Dunne et al., 1997; Verkarre et al., 1998) and two different mutations in Kir6.2 subunits have been identified in families with PHHI (Thomas et al., 1996a; Nestorowicz et al., 1997; Meissner et al., 1999). No K<sub>ATP</sub> channel activity was observed in  $\beta$ -cells isolated from a homozygous patient or after coexpression of recombinant Kir6.2 and mutant SUR1 (V187D) (Otonkoski et al., 1999). Detailed functional analysis in COS cells by cotransfection of Kir6.2 with various single mutations of SUR1 identified in the PHHI family suggested this lack of K<sub>ATP</sub> channel activity or reduction of K<sub>ATP</sub> channel sensitivity to MgADP (Shyng et al., 1998). In fact, patients with mutations in SUR1 either failed to respond to diazoxide or showed diminished sensitivity to treatment (Thornton et al., 1998).

The role of K<sub>ATP</sub> channels in  $\beta$ -cell function has been evaluated in transgenic mice carrying a dominant-negative form of Kir6.2 (G132S) generated by substituting the glycine lining the pore with serine (Miki et al., 1997). These mice develop hypoglycemia with hyperinsulinemia in neonates and hyperglycemia with hypoinsulinemia and decreased  $\beta$ -cell population in adults. K<sub>ATP</sub> channel function was found to be impaired in the  $\beta$ -cell of transgenic mice with hyperglycemia. These results imply that the K<sub>ATP</sub> channel complex might play a significant role in  $\beta$ -cell survival and regulation in insulin secretion, suggesting that modulation of Kir6.2 may offer additional opportunities in treatment of diabetes and related conditions of abnormal glucose regulation. More recently, it has been shown that the SUR1 knockout mice, unlike the Kir6.2 counterpart, are not insulin-hypersensitive, although their  $\beta$ -cells lacks K<sub>ATP</sub> channels and show spontaneous Ca<sup>2+</sup> transients similar to those seen in PHHI patients. SUR1 knockout mice were normoglycemic until stressed, unlike in PHHI patients whose glucose levels are persistently low suggestive of a

role for K<sub>ATP</sub>-independent pathways that regulate insulin secretion, at least in mice (Seghers et al., 2000).

### III. Disease- and Drug-Induced Regulation of K<sup>+</sup> Channels

#### A. Cardiac Failure and Hypertrophy

K<sup>+</sup> channels are targets for the actions of transmitters, hormones, or drugs that modulate cardiac functions. Changes in the densities and/or properties of these K<sup>+</sup> channels that occur during the normal development or as a result of damage or disease can have profound physiological consequences (Matsubara et al., 1993; Xu et al., 1996; Yao et al., 1999). Cardiac failure, a pathophysiologic condition with numerous etiologies including myocardial infarction, hypertension, and myocarditis (Wilson, 1997) is characterized by action potential prolongation and, accordingly, altered expression of a variety of depolarizing and hyperpolarizing membrane currents. In an attempt to compensate for the reduction in cardiac function in cardiac failure, the sympathetic nervous system, the renin-angiotensin-aldosterone systems, and other neurohumoral mechanisms are activated. Adaptive changes at the level of the cardiac myocyte include cellular hypertrophy and altered gene expression. Electrical remodeling in cardiac myocytes leading to action potential prolongation is a common finding in human heart failure and in animal models of cardiac hypertrophy. Changes in a wide range of plasma membrane receptors and intracellular signals such as increased intracellular calcium, cAMP, inositol phosphates, and diacylglycerol concentrations are associated with cardiac hypertrophy and failure (Morgan and Baker, 1991; Gopalakrishnan and Triggle, 1990; Wickenden et al., 1998).

A reduction in the current density of the transient outward current (I<sub>TO</sub>) is the most consistent ionic current change in cardiac hypertrophy and failure (Nabauer and Kaab, 1998; Wickenden et al., 1998; Pinto and Boyden, 1999; Tomaselli and Marban, 1999). This outward repolarizing K<sup>+</sup> current activates and inactivates rapidly with an inactivation constant of ~60 ms (Dixon et al., 1996; Kong et al., 1998). The down-regulation of this current has profound effects on phase 1 and the level of plateau of the action potential, and it also alters currents that are subsequently active along the cardiac action potential. The Kv4.3-containing channel is thought to underlie the bulk of I<sub>TO</sub> found in the mammalian heart, although Kv1.4 or Kv4.2 channels might represent another fraction of I<sub>TO</sub> with distinct kinetics in different regions of the heart (Dixon et al., 1996; Kong et al., 1998). By ribonuclease protection assays and whole-cell electrophysiological recording, Kaab et al. (1998) found that the level of Kv4.3 mRNA decreased by 30% in human failing hearts compared with nonfailing controls. This observation correlated with the reduction

in peak  $I_{TO}$  density measured in ventricular myocytes isolated from adjacent regions of the heart.

It has been known that action potential durations vary across the myocardial wall and in different regions of the mammalian heart (Litovsky and Antzelevitch, 1989; Fedida and Giles, 1991; Lukas and Antzelevitch, 1993; Di Diego et al., 1996). The density of  $I_{TO}$  also varies regionally and transmurally in the heart (Wettwer et al., 1994; Nabauer et al., 1996). Electrophysiological recording from myocytes isolated from patients with aortic stenosis and compensated left ventricular hypertrophy indicates that macroscopic  $I_{TO}$  was absent in superficial subendocardial cells, whereas  $I_{TO}$  current density was not significantly altered in the deeper layers (Bailey et al., 1997). A region-dependent alteration in the density of  $I_{TO}$  current was also observed in the catecholamine-induced hypertrophy in animals (Bryant et al., 1999). It is possible that this region-dependent suppression of  $I_{TO}$  current might, in part, underlie the regional heterogeneity in action potential prolongation in cardiac hypertrophy and may predispose to ventricular arrhythmias, a cause of sudden death in patients with cardiac failure.

As discussed later, an approach to the treatment of heart failure would be to normalize  $K^+$  channel gene expression by gene transfer or pharmacologic modulation. Recent studies have shown that thyroid hormone treatment can increase Kv4.2 or Kv4.3 expression at the transcriptional level and enhance the recovery rate from the inactivation of  $I_{TO}$  in rat ventricular myocytes (Shimoni et al., 1997; Wickenden et al., 1997). Accordingly, agents with thyroid hormone-like properties might be useful in the treatment of heart failure.

### B. Atrial Fibrillation

Atrial fibrillation, the most common arrhythmia in man, is characterized by a marked shortening of the action potential duration, effective refractory period of atria, and a decreased rate of atrial repolarization resulting in increased dispersion of refractoriness as well as changes in atrial conduction velocity (Zipes, 1997; Nattel, 1999). The development of atrial fibrillation can be triggered by rapidly discharging atrial foci (mainly from pulmonary veins) or degeneration of atrial flutter or atrial tachycardia into fibrillation (Chen et al., 1999b; Scheinman, 2000). Risk factors for atrial fibrillation include cardiac diseases such as congestive heart failure, valvular heart disease, and myocardial infarction (Ryder and Benjamin, 1999).

It has been shown that sustained atrial tachycardia causes changes in electrophysiological function to promote the occurrence and maintenance of atrial fibrillation, a process referred to as atrial electrophysiological remodeling (Morillo et al., 1995; Wijffels et al., 1995). Recent studies have revealed that changes in ion channel functions play important roles in atrial electrophysiological remodeling caused by atrial fibrillation. In the

canine atrial fibrillation model induced by chronic atrial tachycardia (rapid pacing), isolated atrial myocytes showed significant reductions in L-type  $Ca^{2+}$  current and  $I_{TO}$  densities, without changes in Kir2.1, hERG, KCNQ1-minK,  $Ca^{2+}$ -dependent  $Cl^-$  current, or T-type  $Ca^{2+}$  currents (Yue et al., 1997). Consistent with this observation, reductions in mRNA levels for Kv4.3, the  $\alpha_1$ -subunit of L-type  $Ca^{2+}$  channels, and the  $\alpha$ -subunit of cardiac  $Na^+$  channels were noted with no changes in mRNA levels for delayed rectifier  $K^+$  channel Kir2.1 or the  $Na^+/Ca^{2+}$  exchanger. Western blot analysis further confirmed a reduction in protein expression of Kv4.3 and  $Na^+$  channels, whereas that of the  $Na^+/Ca^{2+}$  exchanger was unchanged (Yue et al., 1999; Li et al., 2000). More importantly and consistent with data from the canine atrial fibrillation model, significant reductions in  $I_{TO}$  (encoded by Kv4.3) and ultrarapid delayed rectifier ( $IK_{ur}$ ) (encoded by Kv1.5) as well as L-type  $Ca^{2+}$  current densities were observed in atrial myocytes isolated from patients in chronic atrial fibrillation. Furthermore, quantitative Western blot analysis revealed that the expression of Kv1.5 protein was reduced by >50% in both the left and the right atrial appendages of atrial fibrillation (Van Wagoner et al., 1997, 1999). Although abnormalities of  $K^+$  channels may be fundamentally implicated in atrial fibrillation, other factors such as structural changes (Li et al., 1999) or heterogeneous alterations in atrial sympathetic innervation (Jayachandran et al., 2000) may also play critical roles in other forms of atrial fibrillation.

### C. Drug-Induced Long-QT Syndromes

Drug-induced precipitation of polymorphic ventricular dysrhythmia, the torsade de pointes, in susceptible individuals by certain  $H_1$  antagonists such as terfenadine has now been linked to the prolongation of the QT interval consequent to inhibition of the IKr channels encoded by the hERG gene (reviewed in Delpón et al., 1999; Tagliavolterra et al., 2000). These drugs have been shown to block hERG channels in a concentration range similar to that found in the plasma of subjects showing proarrhythmic effects. Similar interactions have been reported for antipsychotics such as sertindole (Rampe et al., 1998), tricyclic antidepressants, and certain antibiotics and anti-emetic agents. Inhibition of another cardiac delayed rectifier, Kv1.5, by  $H_1$  receptor antagonists such as loratadine (Lacerda et al., 1997) and rupatadine (Caballero et al., 1999) has also been suggested to contribute to drug-induced cardiac arrhythmias.

### D. Apoptosis and Oncogenesis

$K^+$  channel activities play important roles in signaling pathways leading to proliferation, differentiation, and cell fusion. Increases in  $K^+$  channel activity and enhanced  $K^+$  efflux are thought to sustain membrane hyperpolarization necessary to facilitate  $Ca^{2+}$  entry (Santella, 1998), although additional pathways, such as

control of cellular volume by K<sup>+</sup> channels, might also be involved in cell proliferation (Rouzaire-Dubois and Dubois, 1998; Vaur et al., 1998). A number of studies have suggested membrane hyperpolarization as an essential requirement for cell proliferation. For example, an increase in expression levels of a Ca<sup>2+</sup>-dependent K<sup>+</sup> channel with strong inward rectification was observed during the G<sub>1</sub> phase of HeLa cells, which progressively declined to a minimum in the S phase and then increased in the M phase (Takahashi et al., 1993). Inhibition of K<sup>+</sup> channels by pharmacological agents has been found to inhibit cell proliferation in normal human lymphocytes (Amigorena et al., 1990; Lin et al., 1993; Rader et al., 1996; Jensen et al., 1999), human melanoma cells (Nilius and Wohlrab, 1992; Lepple-Wienhues et al., 1996), small lung cancer cells (Pancrazio et al., 1993), breast cancer cells (Woodfork et al., 1995), and prostatic cells (Skryma et al., 1997). Changes in expression of an inward rectifying K<sup>+</sup> channel and a noninactivating delayed rectifier K<sup>+</sup> channel are associated with the time course of membrane fusion of myoblast to form multinucleated skeletal muscle fibers (Shin et al., 1997; Occhiodoro et al., 1998). Recently, a gene encoding the human EAG K<sup>+</sup> channel was cloned from myoblasts, localized to chromosome 1q32-41 and shown to be responsible, in part, for changes in membrane hyperpolarization during the myoblast fusion (Occhiodoro et al., 1998).

**1. Apoptosis.** Apoptosis, or programmed cell death, is a fundamental biological process involved in many physiological and pathological phenomena. This process is predominantly catabolic in nature where cellular macromolecules are broken down by distinct enzymes to be later recycled in healthy cells. Activities of enzymes, nucleases, and caspases that propagate and amplify death signals are K<sup>+</sup>-dependent (Bortner et al., 1997; Hughes and Cidlowski, 1999). Recent studies have shown that enhancement of K<sup>+</sup> current is directly involved in apoptosis (Yu et al., 1997, 1999) and oncogenesis (Pardo et al., 1999). In mouse neocortical neurons, a delayed rectifier and tetraethylammonium (TEA)-sensitive K<sup>+</sup> current responsible for neuronal apoptosis was enhanced by serum deprivation or staurosporine. Inhibition of outward K<sup>+</sup> currents with TEA or elevated extracellular K<sup>+</sup>, but not with blockers of Ca<sup>2+</sup>, Cl<sup>-</sup>, or other K<sup>+</sup> channels, reduced apoptosis. Exposure to the K<sup>+</sup> ionophore valinomycin or the K<sub>ATP</sub> channel opener cromakalim induced apoptosis (Yu et al., 1997). Thus, enhanced K<sup>+</sup> efflux through increase in expression of a specific TEA-sensitive and delayed rectifier K<sup>+</sup> channel may mediate certain forms of neuronal apoptosis in disease states. Thymocyte apoptosis induced by dexamethasone, etoposide,  $\gamma$ -irradiation, or ceramide has also been shown to be prevented by the K<sup>+</sup> channel blocker tetrapentylammonium (Dallaporta et al., 1999).

In addition to increased expression of K<sup>+</sup> currents, modulation of K<sup>+</sup> channel function is one of the mecha-

nisms used to induce programmed cell death by a variety of extrinsic and intrinsic signals. For example, the inhibition of Kv1.3 current by tyrosine kinase phosphorylation induced by Fas plays important roles in apoptosis, which is critical to the development of the immune system, and in the elimination of target cells expressing foreign antigens (Szabo et al., 1996). In *Drosophila*, *reaper*, *grim*, or *hid* gene expression triggers apoptosis in a caspase-dependent manner. The peptides encoded by these genes share a common feature in that their N termini are similar to those of the *Shaker* K<sup>+</sup> channel that block channel and lead to fast inactivation. Mutations that reduce the apoptotic activity of *reaper* also reduced the peptide's ability to induce channel inactivation. Thus, blocking a *Shaker* K<sup>+</sup> channel by peptides encoded by *reaper*, *grim*, or *hid* gene was suggested to be involved in apoptosis (Avdonin et al., 1998).

**2. Oncogenesis.** Modulation of K<sup>+</sup> channels is involved in Ras/Raf signal transduction in oncogenic transformation (Collin et al., 1990; Yatani et al., 1991; Huang and Rane, 1994; Decker et al., 1998). Recent studies have shown a high level of an intermediate conductance Ca<sup>2+</sup>-activated K<sup>+</sup> current (IK<sub>Ca</sub>) in Ras-transformed fibroblasts but not in the untransformed counterparts (Rane, 1991). High levels of expression of IK<sub>Ca</sub> have also been observed in rat prostate cancer cell lines, AT2.1 and MatLyLyu, suggesting hyperactivity of the Ras/MAPK pathway in prostatic cancer and that IK<sub>Ca</sub> plays important roles in regulating cell growth (Rane, 2000). Similarly, the hERG was shown to be sequentially expressed during neuronal development and to participate in the regulation of membrane potential in mammalian neuroblastoma cells (Arcangeli et al., 1995, 1997). The hERG, and the related *ether-a-go-go* K<sup>+</sup> channels are expressed in a variety of tumor cell lines (Bianchi et al., 1998; Pardo et al., 1999), the inhibition of which causes a significant reduction of cell proliferation. Moreover, the expression of rEAG favors tumor progression when transfected cells are injected into immunosuppressed mice, and overexpression of rEAG K<sup>+</sup> channels in Chinese hamster ovary or NIH 3T3 cells induces significant features characteristic of malignant transformation (Pardo et al., 1999). Taken together, these studies suggest that these K<sup>+</sup> channels play crucial roles in oncogenesis.

### E. Alzheimer's Disease

Alzheimer's disease is the most prevalent cause of progressive declining cognitive function, loss of memory, and late stage decreasing physical deterioration in the elderly. It is characterized pathologically by the presence of intracellular neurofibrillary tangles and extracellular neuritic plaques consisting of deposits of the  $\beta$ -amyloid (A $\beta$ ), a 39- to 43-amino acid peptide proteolytically derived from  $\beta$ -amyloid protein precursor ( $\beta$ -APP). In Alzheimer's disease, significant neuronal cell death is found in the temporal and parietal cortex,

hippocampus, amygdala, and basal forebrain cholinergic system. Several mechanisms have been linked to progressive neurodegenerative disorder, such as alterations in amyloid precursor protein metabolism, cholinergic transmission, calcium homeostasis, oxidative metabolism, and protein kinase C transduction systems (Mattson et al., 1993; Hensley et al., 1994; Ito et al., 1994; Yankner, 1996; Yu et al., 1998). As discussed below, dysfunction of  $K^+$  channels in both central nervous systems and peripheral tissues has been reported. It is plausible, however, that any association of  $K^+$  channel defects with the pathophysiology of Alzheimer's disease may be indirect or secondary in nature consequent to generalized degeneration associated with the disease.

1.  *$\beta$ -Amyloid.*  $K^+$  channel dysfunction in Alzheimer's disease was initially suggested by radioligand binding studies using apamin, the bee venom octadecapeptide that blocks small conductance  $Ca^{2+}$ -activated  $K^+$  channels responsible for afterhyperpolarization of neurons (Ikeda et al., 1991). In hippocampus, a reduction of  $^{125}I$ -apamin binding sites in the subiculum and CA1 regions was found in patients with Alzheimer's disease. The reduction of  $^{125}I$ -apamin binding sites in the subiculum correlated with cell density but not neuritic plaque density, indicating discrete loss of small conductance of  $Ca^{2+}$ -activated  $K^+$  channels within the hippocampal formation. In hippocampal neurons from neonatal rats,  $A\beta$  was shown to inhibit voltage-dependent fast-inactivating  $K^+$  currents (Good et al., 1996). This inhibition results in abnormally large increases in intracellular  $Ca^{2+}$  levels upon depolarization of the neuron leading to neurotoxicity (Good and Murphy, 1996).

Other evidence linking  $A\beta$ -induced abnormal  $K^+$  to the neuronal cell death was revealed by in vitro studies using a cholinergic septal cell line, SN56 (Colom et al., 1998). These cells exhibited a tetraethylammonium-sensitive outward  $K^+$  current with delayed rectifier characteristics. Addition of  $A\beta$  increased  $K^+$  current density some 44 to 66% and decreased cell viability by 25 to 39%. TEA (10 to 20 mM) or  $K^+$  depolarization inhibited outward currents, widened action potentials, elevated  $[Ca^{2+}]_i$ , and inhibited more than 68% of the  $A\beta$ -induced toxicity. These data suggest that a  $K^+$  channel with delayed rectifier characteristics may play an important role in  $A\beta$ -mediated toxicity in this septal cholinergic cell line (Colom et al., 1998).

In peripheral tissues,  $K^+$  channel dysfunction was initially identified in fibroblasts from patients with Alzheimer's disease where a 113-pS TEA-sensitive  $K^+$  channel was absent compared with normal human fibroblasts (Etcheberrigaray et al., 1993). This defect was mimicked in normal fibroblasts by the addition of  $\beta$ -amyloid protein (Etcheberrigaray et al., 1994). TEA depolarized and elevated intracellular  $Ca^{2+}$  levels in young and aged control fibroblasts but not in fibroblasts from Alzheimer's disease patients, supporting the dysfunction of TEA-sensitive  $K^+$  channels in the disease.

$Rb^+$  flux through apamin and charybdotoxin-sensitive  $Ca^{2+}$ -activated  $K^+$  channels was selectively impaired in fresh, noncultured platelets from patients with Alzheimer's-type dementia, although the  $\alpha$ -dendrotoxin-sensitive voltage-dependent  $K^+$  channel was not affected compared with nondemented controls (de Silva et al., 1998).  $\beta$ -Amyloid protein also enhanced phytohemagglutinin-induced  $Ca^{2+}$  rise in T-lymphocytes, consistent with the hypothesis that enhanced calcium responses serve as a general feature of  $\beta$ -amyloid neurotoxicity (Eckert et al., 1993). However, patch-clamp analysis indicated that T-lymphocyte  $K^+$  channels are not functionally deficient in Alzheimer's disease, and that  $\beta$ -amyloid protein does not mediate an alteration of their currents (Cohen et al., 1996), suggesting  $A\beta$  might induce toxicity through alternative pathways.

2.  *$\beta$ -Amyloid Protein Precursor.*  $\beta$ -APP, the source of the fibrillogenic  $A\beta$ , is a membrane-spanning and multifunctional protein that is widely expressed in the nervous system.  $\beta$ -APP is axonally transported and accumulates in presynaptic terminals and growth cones. A secreted form of  $\beta$ -APP (sAPP) is released from neurons in response to electrical activity and plays important roles in learning, memory, and cell survival (Roch et al., 1994; Mattson, 1997; Meziane et al., 1998; Dodart et al., 2000). In addition to  $A\beta$ -induced neurotoxicity via potential modulation of  $K^+$  channel function, a study revealed that sAPP can suppress action potential and hyperpolarize hippocampal neurons by activating large conductance  $Ca^{2+}$ -activated  $K^+$  channels leading to suppression of intracellular  $Ca^{2+}$  concentration (Furukawa et al., 1996). These results suggest that the effects of  $\beta$ -APP on synaptogenesis and synaptic plasticity might, in part, mediate through activation of  $Ca^{2+}$ -activated  $K^+$  channels and that the abnormalities in  $\beta$ -APP processing or sAPP might contribute to the neurodegenerative process in Alzheimer's disease.

3. *Presenilins.* The presenilins are proteins that contain multiple transmembrane domains and localize primarily to the endoplasmic reticulum and Golgi apparatus. Although the precise functions of presenilins are not totally understood, presenilins are involved in the proteolytic processing of  $\beta$ -amyloid precursor proteins and play important roles in the notch signaling during embryonic development and/or cellular differentiation (Kim and Tanzi, 1997; Chan and Jan 1999; Haass and De Strooper, 1999; Czech et al., 2000). Genetic linkage analysis showed that mutations in presenilin 1 (PS-1, mapped on chromosome 14) and presenilin 2 genes (PS-2 on chromosome 1) yielding abnormal release of amyloidogenic peptide from amyloid precursor protein have been linked to the autosomal dominant early onset of familial Alzheimer's disease (Clark et al., 1995; Rogaev et al., 1995; Schellenberg, 1995; Sherrington et al., 1995). Based on the multiple membrane-spanning topology, it was proposed that presenilins might function as, or as part of, a channel, transporter, or pore (Li and

Greenwald, 1996). Using *in vitro* expression in HEK-293 cells, a recent study has revealed that expression of wild-type PS-1 or PS-2 increases outward K<sup>+</sup> current densities. In HEK-293 cells transiently transfected with PS-1 (S290C) or PS-1 (G209V), two missense mutations associated with early onset Alzheimer's disease, mean outward K<sup>+</sup> current densities are also shown to be increased in HEK-293 cells expressing the S290C mutant but not with the G209V mutant. Expression of wild-type PS-1 in neonatal rat ventricular myocytes also results in increased outward K<sup>+</sup> currents, whereas no detectable effects on membrane currents were seen in COS-7 cells transfected with PS-1. These results suggest that the presenilins do not actually form K<sup>+</sup> channels, but rather that these proteins up-regulate functional K<sup>+</sup> channel expression (Malin et al., 1998). Thus, presenilins could regulate neuronal K<sup>+</sup> channel expression, and mutations in PS-1 or PS-2 can, in part, result in profound changes in neuronal excitability, which may contribute to the cognitive decline commonly associated with Alzheimer's disease to some extent.

#### F. Neuromuscular Disorders

Mutations in a variety of ion channels, including Na<sup>+</sup>, Ca<sup>2+</sup>, and Cl<sup>-</sup> channels, have been found to underlie various forms of human neuromuscular disorders. The defects of ion channels lead to the aberrant excitability of muscle fibers that gives rise to periodic paralysis or myotonia (for reviews see Cannon, 1996; Engel et al., 1998). In addition to inherited genetic diseases, diverse neuromuscular disorders are attributed to antibody-mediated autoimmunity where the extracellular domains of receptors or ion channels are the primary targets of autoantibodies. For example, myasthenia gravis is caused by autoantibodies to nicotinic acetylcholine receptors at the neuromuscular junction, which cause weakness of the skeletal muscle (Richman and Agius, 1994). The autoantibodies that interfere with neurotransmitter release by binding to presynaptic voltage-dependent Ca<sup>2+</sup> channels underlie the Lambert-Eaton myasthenic syndrome, which is often found in patients with small cell lung cancer (Kim and Neher, 1988; Pelucchi et al., 1993). In acquired neuromyotonia (Isaacs' syndrome), where hyperexcitability of peripheral motor nerves leads to muscle twitching during rest, cramps during muscle contraction, impaired muscle relaxation, and muscle weakness, antibodies directed against 4-aminopyridine or  $\alpha$ -dendrotoxin-sensitive K<sup>+</sup> channels in motor and sensory neurons were detected (Shil-lito et al., 1995; Hart et al., 1997). These antibodies mainly suppress voltage-gated K<sup>+</sup> channels (Kv1.1 and Kv1.6) with no change in gating kinetics and lead to peripheral nerve hyperexcitability (Nagado et al., 1999). In humans with hypokalemic periodic paralysis caused by mutations of the 1,4-dihydropyridine receptor of the voltage-gated calcium channel, diminished skeletal

muscle K<sub>ATP</sub> channel activity has also been reported (Tricarico et al., 1999).

### IV. Pharmacological Considerations

As discussed in the preceding sections, several genetically linked and acquired diseases involve alterations in the function of K<sup>+</sup> channels. Genetic linkage studies have been pivotal in elucidating the role of many K<sup>+</sup> channels in pathophysiologic and physiologic conditions. More importantly, these findings provide a basis to develop appropriate therapy for various diseases. Continuing pharmaceutical interest revolves around the discovery and development of selective organic modulators of various classes of K<sup>+</sup> channels (Colatsky, 1998; Curran, 1998; Kaczorowski and Garcia, 1999). Enthusiasm in the K<sup>+</sup> channel arena is driven by the realization that class III antiarrhythmic agents and antidiabetic sulfonylureas act as antagonists at specific K<sup>+</sup> channel classes and that a variety of K<sup>+</sup> channel inhibitors and openers offer significant therapeutic opportunities in areas ranging from cardiac, vascular, and nonvascular muscle, neuronal, immune, and secretory systems to modulation of hair follicle growth (Table 3). Gene delivery and selective targeting of channel proteins by antisense oligonucleotides represent emerging approaches. With advances in molecular biology and antisense technology, therapeutics based on gene delivery, with precise control of the level and distribution of ion channel expression into mammalian neuronal, cardiac, hair cells, and other cell types, are currently being investigated (Holt et al., 1999; Johns et al., 1999; Hoppe et al., 2000).

However, key hurdles in targeting K<sup>+</sup> channels remain to be resolved. Given the diversity of K<sup>+</sup> channel subunits and the potential to vary the constituents to form heteromeric channel complexes to alter expression, cellular targeting, and biophysical and pharmacological properties in native cell types, it is difficult to know the precise composition of channel complexes *in vivo*. The latter, together with information on tissue-specific localization and the availability of high-throughput *in vitro* assays predictive of *in vivo* drug activity and selectivity, is seldom available. This is an important issue, which has not been addressed to the full extent, as efforts are launched to design openers and/or blockers of various classes of potassium channel modulators. Nevertheless, over the past decade or so, intense medicinal chemistry efforts have focused on the synthesis and development of modulators of various voltage-gated K<sup>+</sup> channels, calcium-activated K<sup>+</sup> channels and ATP-sensitive K<sup>+</sup> channels (Figs. 3 and 4; Tables 3 and 4).

#### A. Voltage-Gated K<sup>+</sup> Channels

1. *Kv1.3 Channels.* The Kv1.3 channels, members of the voltage-gated K<sup>+</sup> channel family expressed predominantly in human lymphocytes, have been widely exploited as pharmacological targets for immunosuppressive

TABLE 3  
Potassium channel openers

Channel Family	Therapeutic Indication(s)	Compounds
KCNQ2/KCNQ3 BK <sub>Ca</sub>	Epilepsy	Retigabine (also GABA <sub>A</sub> agonist)
	Cerebral ischemia	BMS-204352 NS 004 (also inhibits other K <sup>+</sup> channels) NS 1608, NS1619 (also Ca <sup>2+</sup> channel inhibitor)
K <sub>ATP</sub>	Coronary disorders	NS8
	Antipsychotic	
	Urinary incontinence	
	Pollakisuria	
	Hypertension, ischemic heart disease, heart failure,	Pinacidil Diazoxide
	Asthma	Nicorandil Aprikalim (RP 52891) Bimakalim (EMD52692) Celikalim Cromakalim Emakalim NIP121 RO 316930 RWJ 29009 SDZ PCO 400 Rimakalim (HOE234) Symakalim (EMD 57283) YM-099, YM-934
	Myocardial ischemia	BMS180448 U 89232 (BMS 189365) (Mito K <sub>ATP</sub> ?)
	Alopecia	P1075, minoxidil
	Urinary incontinence	ZM244085, ZD6169, WAY133537, WAY151616, ZD0947
	Erectile dysfunction	PNU83757

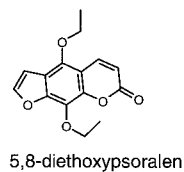
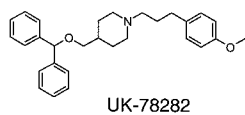
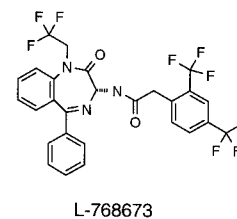
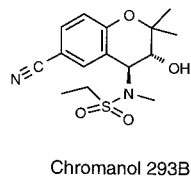
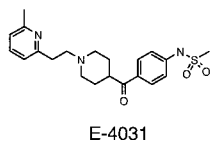
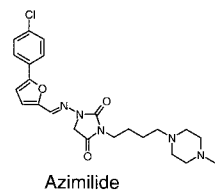
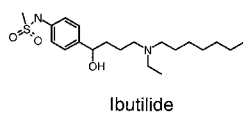
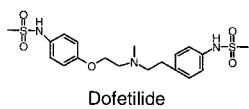
therapy. Selective blockers of these channels depolarize membrane to attenuate calcium influx and inhibition of T cell activation in vitro and immunosuppression in vivo (Cahalan and Chandy, 1997). Many peptides isolated from scorpion venoms and sea anemone potently block Kv1.3 channels and inhibit T-lymphocyte activation. Inhibition of these channels by margatoxin was initially shown to prevent T cell activation and attenuate immune responses in vivo (Koo et al., 1997). Several nonpeptide analogs, such as dihydroquinolines, WIN 17317-3 (Hill et al., 1995) and CP-339,818 (Nguyen et al., 1996), piperidines, UK 78,282, (Hanson et al., 1999), and certain alkoxyorsoralenes (Wulff et al., 1998) have been shown to block Kv1.3 channels and/or inhibit human T cell activation in vitro. Despite this in vitro evidence, there has been little in vivo demonstration until recently that blockade of Kv1.3 will attenuate immune responses, the latter possibly due to species differences, since in many rodent peripheral T cells these channels do not appear to set membrane potential. However, these channels appear to be present on peripheral T cells of minipigs, and Koo et al. (1999) have shown that the nortriterpene, correolide, and its analogs extracted from the tree *Spachea correae* can block Kv1.3 channels and inhibit delayed-type hypersensitivity response to tuberculin in minipigs (Koo et al., 1999). The Kv1.3 modulators described thus far could serve as tools for the further design of immunosuppressive agents because many of these compounds lack desirable potencies, selectivity, and pharmacokinetic profile. For example, a study with radiolabeled WIN 17317-3 has shown that this compound is also a potent blocker of brain type IIa sodium channels (Wanner et al., 1999).

**2. Cardiac Delayed Rectifier K<sup>+</sup> Channels.** The goal of developing a class III antiarrhythmic agent effective against ventricular arrhythmias while reducing hemodynamic liabilities remains to be realized, but should now be accelerated with the understanding of the molecular components of cardiac delayed rectifiers, i.e., IKs (KvLQT1-minK), IKr (hERG), and IK<sub>ur</sub> (Kv1.5) channels. The currently available class III drugs amiodarone (Kodama et al., 1999) and sotalol (Anderson and Prysowsky, 1999) possess properties beyond the realm of a pure class III effect (Roden, 1993; Nair and Grant, 1997; Sager, 1999).

Novel antiarrhythmic drugs belonging to the class III type have now become available that block a specific ionic current (e.g., dofetilide that blocks IKr) or block multiple ionic channels (e.g., ibutilide and azimilide) to prolong atrial and ventricular action potentials without unwanted pharmacological effects. Since IKr blockers increase action potential duration and refractoriness both in atria and ventricle without affecting conduction per se, theoretically they represent potentially useful agents for the treatment of arrhythmias, although they may have an enhanced risk of proarrhythmia at slow heart rates (Table 4).

As noted previously, cardiac tissues express rapidly activating delayed rectifier currents, designated IK<sub>ur</sub>, in contrast to the classical IKr and IKs channels. The Kv1.5 subunit is the major component of the cardiac ultrarapid delayed rectifier in human atria as revealed by localization (Mays et al., 1995) and antisense oligonucleotide studies in cultured adult human atrial myocytes (Feng et al., 1997). Association with Kvβ1.2

## A. Kv1.3

C. KvLQT1/minK (I<sub>K<sub>S</sub>)</sub>B. HERG (I<sub>K<sub>r</sub>)</sub>

## D. KvLQT2/KvLQT3 (M current)

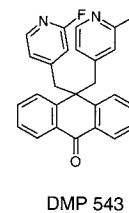
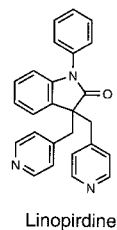
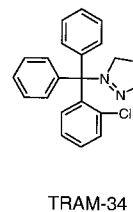
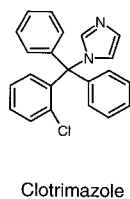
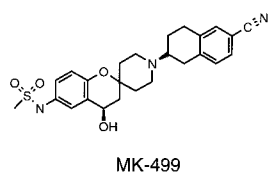
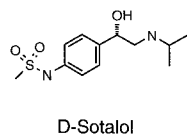
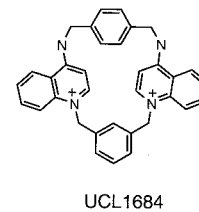
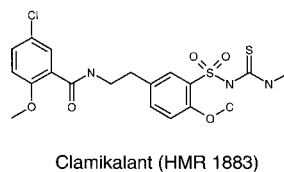
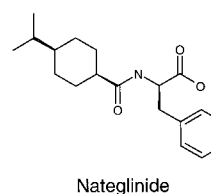
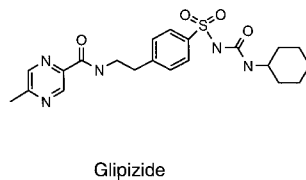
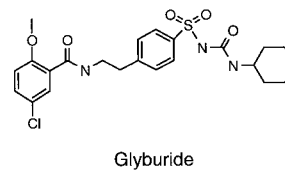
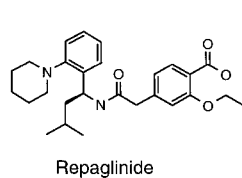
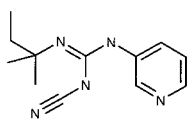
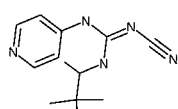
E. I<sub>K<sub>Ca</sub></sub>F. SK<sub>Ca</sub>G. K<sub>ATP</sub> channel

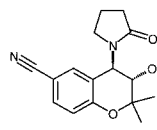
FIG. 3. K<sup>+</sup> channel blockers. Shown are blockers of voltage-gated, calcium-activated, and ATP-sensitive K<sup>+</sup> channels.

A.  $K_{ATP}$  channel

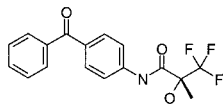
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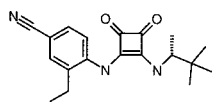
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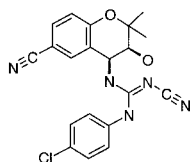
L-Cromakalim



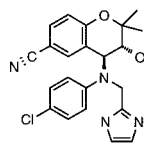
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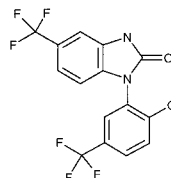
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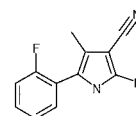
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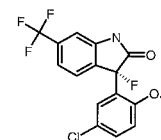
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B.  $BK_{Ca}$  channel

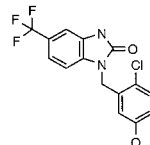
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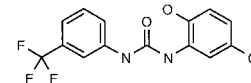
NS-8



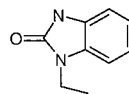
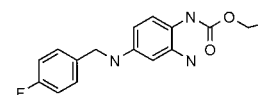
BMS-204352



BMS-189269



NS-1608

C.  $IK_{Ca}$  Channel1-ethyl-2-benzimidazoline  
(1-EBIO)D.  $KCNQ2/KCNQ3$ 

Retigabine

FIG. 4.  $K^+$  channel openers. Shown are openers of voltage-gated, calcium-activated, and ATP-sensitive  $K^+$  channels.TABLE 4  
*Potassium channel blockers*

Channel Family	Therapeutic Indication(s)	Compounds
Kv1.3	Immunosuppressant	CP308408, UK 78,282
Kv1.5	Atrial fibrillation	Fampridine (4-aminopyridine)
Kv (other)	Multiple sclerosis (axonal regeneration)	BIIA 0388
hERG/IKr	Epilepsy, ischemia	Dofetilide (Tikosyn)
	Atrial fibrillation/flutter	Ibutilide (Corvert injection) (also increases $Na^+$ current)
	Arrhythmia	Almokalant
		E4031
		MK 499
		Sematilide
		D-Sotalol
KvLQT1-minK/IK <sub>S</sub>	Arrhythmia	Chromanol 293B
		HMR1556
		E-0471
		L768673
IKr and IKs	Arrhythmia, angina	Ambasilide (LU 47710)
		Azimilide (NE 10064) (also L-type CaCh blocker)
		Tedisamil (also $Na^+$ channel blocker)
		Clofilium
		DMP543
I <sub>TO</sub>	Arrhythmia	HMR 1098, HMR 1883
KCNQ3/KCNQ4	Alzheimer's disease	Tolbutamide
K <sub>ATP</sub>	Ventricular arrhythmia, heart failure, cardiac arrest	Chlorpropamide
	Type II diabetes	Glibenclamide
		Glipizide
		Nategliniide
		Repagliniide

subunits can also alter functional properties of Kv1.5 channels (Majumder et al., 1995). Selective blockers of Kv1.5 channels could be potentially beneficial for the treatment of cardiac arrhythmias because such agents

could retard repolarization and prolong refractoriness selectively in cardiac myocytes (Nattel et al., 1999).

Gene transfer of delayed rectifier  $K^+$  channels represents an emerging strategy for the control of arrhythmias



triggered by altered cardiac repolarization. Myocytes isolated from adult rabbit ventricular myocytes in culture which demonstrate longer action potentials and frequent early-after depolarizations when maintained in culture, were reversed following adenoviral gene transfer of the hERG gene (Nuss et al., 1999). Infection with a recombinant adenovirus containing the hERG gene selectively enhanced the E-4031-sensitive currents without affecting the density of transient outward currents, suppressed early-after depolarizations, and lengthened the refractory period. Action potentials from failing dog hearts were also reversed after exposure to an adenovirus that overexpresses *Shaker* K<sup>+</sup> channels (Nuss et al., 1996). Further refinement of techniques to effectively control the level and to ensure homogenous distribution of transgene expression at the target organ is likely to be forthcoming (Hoppe et al., 2000).

As noted previously, it has also become increasingly important to avoid interactions of many noncardiovascular medicinal products with cardiac ion channels (reviewed in Pourrias et al., 1999). Certain H<sub>1</sub> antagonists, such as astemizole and terfenadine, and the prokinetic agent cisapride are capable of prolonging the QT interval and inducing torsade de pointes in susceptible individuals through inhibition of IKr channels encoded by hERG gene. Similar interactions have also been reported for certain antipsychotics such as sertindole (Rampe et al., 1998), tricyclic antidepressants, and some antibiotics. Inhibition of Kv1.5 channels by H<sub>1</sub> receptor antagonists such as loratadine (Lacerda et al., 1997) and rupatadine, a dual antagonist of H<sub>1</sub>, and platelet-activating factor receptors (Caballero et al., 1999) has also been suggested to contribute to drug-induced cardiac arrhythmias. Prolongation of cardiac repolarization reported with the 5HT<sub>3</sub> receptor antagonist, ondansetron, has been attributed to inhibition, albeit only 30%, of hERG channels (Kuryshv et al., 2000a). Needless to note, these pharmacologic misfortunes underscore the importance of evaluation of potential inhibition of these cardiac channels during the early developmental phase of novel compounds because drugs with minimal or no potential to block hERG or Kv1.5 channels are likely to possess cardiac safety advantages.

**3. KCNQ2/KCNQ3 Channels.** Unlike *KCNQ1*, *KCNQ2* and *KCNQ3* are present exclusively in the nervous system and coassemble to form heteromultimers that underlie the M-current (Wang et al., 1998) critical to neuronal excitability in the nervous system (Brown, 1988). The potential for targeting the KCNQ2/KCNQ3 combination as a drug target is underscored by the findings that compounds such as linopirdine [DuP 996, 3,3-bis(4-pyridinylmethyl)-1-phenylindolin-2-one] and XE991 developed as cognition enhancers are blockers of cloned KCNQ channels (Lamas et al., 1997; Eid and Rose, 1999). Linopirdine, a putative cognition enhancing drug, increases acetylcholine release in rat brain tissue and improves performance in animal models of learning and memory (Schnee and

Brown, 1998). Although clinical data with linopirdine were largely inconclusive, analogs such as XE991 and DMP543 with superior pharmacological and pharmacodynamic properties have entered development as orally active acetylcholine-releasing agents with potential in Alzheimer's disease (Zaczek et al., 1998). The KCNQ1/minK complex was 14- to 18-fold less sensitive to XE991 blockade compared with either KCNQ1 alone or neuronal KCNQ2/KCNQ3 combination, revealing a much desired degree of selectivity for this compound for neurotransmitter release over cardiac function (Wang et al., 2000). More recently, retigabine (D-23129), reportedly in phase II clinical studies for the treatment of epilepsy, has been shown to activate KCNQ2/KCNQ3 channels expressed in Chinese hamster ovary cells in a partially linopirdine-sensitive manner, suggesting that M-channel activation may be a novel mode of action for anticonvulsant drugs (Main et al., 2000; Rundfeldt and Netzer, 2000).

### B. Calcium-Activated K<sup>+</sup> Channels

The recent molecular cloning of various calcium-activated K<sup>+</sup> channels has renewed enthusiasm for the development of modulators for these channels. These channels, critically dependent on intracellular calcium for channel opening, were initially differentiated largely on the basis of biophysical (conductance, voltage dependence) and differential toxin sensitivity into large, intermediate, and small conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channels. Distinct genes are now known to encode the three subfamilies of calcium-activated K<sup>+</sup> channels, i.e., large conductance (BK<sub>Ca</sub>) ( $\alpha$ -subunit and its splice variants), small conductance (Sk1, Sk2, and Sk3), and intermediate conductance channels (reviewed in Vergara et al., 1998; Castle, 1999; Wallner et al., 1999b). The search for organic modulators of various Ca<sup>2+</sup>-activated K<sup>+</sup> channels with the potential to be developed as therapeutic agents has been actively explored by functional screening using many of the recombinant channels (Kaczorowski and Garcia, 1999).

**1. Large Conductance Channels.** The BK<sub>Ca</sub>  $\alpha$ -subunit cloned from either *Drosophila* (*Slo*) or mammalian (*mSlo*, *hSlo*), in combination with different  $\beta$ -subunits,  $\beta$ 1, and more recently  $\beta$ 2 to  $\beta$ 4, now extends diversity of BK<sub>Ca</sub> channels. Initial modulators reported include activators such as glycosylated triterpenes (dehydrosoyasaponin-I) and several indole diterpene blockers, such as paxilline, verruculogen, penitrem A, and aflatrem (Kaczorowski et al., 1996). Activators of BK<sub>Ca</sub> channels include the benzimidazolones, such as NS-1619 and NS-004. However, these compounds are, in general, not very potent or highly selective. More recently, openers of BK<sub>Ca</sub> channels have been developed as neuroprotective agents. One such compound, BMS-204352, is in advanced trials as a stroke neuroprotectant (Hewawasam et al., 2000). NS-8, a pyrrole derivative shown to activate BK<sub>Ca</sub> channels, is under investigation for the treatment of urinary incontinence (Tanaka et al., 1998). The potential for BK<sub>Ca</sub> modulators in

the treatment of erectile dysfunction has been underscored by recent studies with the BK<sub>Ca</sub> channel  $\alpha$ -subunit (Christ et al., 1998). Intracavernous injection of *hSlo* DNA was capable of altering nerve-stimulated penile erection and was associated with a significant elevation in intracavernous pressure at least until two months postinjection. Interestingly, the expression of the *hSlo* message was highest in the corpus cavernosum tissue and minimal in other tissues examined, raising the possibility that such localized delivery of K<sup>+</sup> channel genes may provide another avenue for achieving end organ selectivity.

**2. Intermediate Conductance Channels.** Blockers of the IK<sub>Ca</sub> channel have long been proposed for therapy in sickle cell anemia, diarrhea, and rheumatoid arthritis; clotrimazole, an inhibitor of the IK<sub>Ca</sub> channel in red blood cells, has been used for this purpose (Brugnara et al., 1995; de Franceschi et al., 1996). However, the inhibition of cytochrome P450 enzyme by clotrimazole limits its therapeutic applications. Recently, a more selective and potent inhibitor of IK<sub>Ca</sub> channel, TRAM-34 (1-[(2-chlorophenyl)diphenylmethyl]-1*H*-pyrazole), with no effect on cytochrome P450 activity, has been reported (Fig. 3) (Wulff et al., 2000). Although not highly specific, 1-ethyl-2-benzimidazolinone (1-EBIO) and the clinically used benzoxazoles, chlorzoxazone and zoxazolamine, are described as pharmacological activators of the IK<sub>Ca</sub> channel (Syme et al., 2000). Inhibitors of IK<sub>Ca</sub> may also be useful as immunosuppressive agents because these channels are up-regulated following antigenic or mitogenic stimulation (Khanna et al., 1999). IK<sub>Ca</sub> channels may also serve as an effector for mitogenic Ras/MAPK signaling in fibroblasts and other cell types, including prostate cancer cells (Rane, 2000). Openers of IK<sub>Ca</sub> channels may be therapeutically beneficial in cystic fibrosis and peripheral vascular disease, as well (Edwards, 1998).

**3. Small Conductance Channels.** The SK<sub>Ca</sub> channel, first identified in cultured rat skeletal muscle, was shown to be the receptor inhibited by the bee venom peptide apamin (Blatz and Magleby, 1986). Activation of apamin-sensitive SK<sub>Ca</sub> channels underlies a component of the after hyperpolarization current in neurons that parallels the rise and fall of intracellular calcium levels (Sah and Clements, 1999). Besides apamin, other blockers of SK<sub>Ca</sub> channels, albeit less selective, include tubocurarine and dequalinium. Many dequalinium analogs with varying potencies and selectivities for blocking IK<sub>Ca</sub> and SK<sub>Ca</sub> channels have been described (Malik-Hall et al., 2000). For example, the bisaminoquinolium cyclophane UCL 1684 is about 5000-fold more selective in inhibiting SK<sub>Ca</sub> channels compared with IK<sub>Ca</sub>-type channels. Recently, conditional overexpression of a small conductance K<sup>+</sup> channel, Sk3, induced abnormal breathing patterns during hypoxia and compromised parturition in mice by changes in uterine smooth muscle function (Bond et al., 2000). The availability of selective SK<sub>Ca</sub> modulators will permit evaluation of their poten-

tial role in epilepsy, sleep apnea, neurodegenerative, and smooth muscle disorders.

### C. ATP-Sensitive K<sup>+</sup> Channels

K<sub>ATP</sub> channels, a family of weak inward rectifiers inhibited by intracellular ATP that couple cellular energy metabolism to membrane electrical activity, have perhaps been the most widely explored K<sup>+</sup> channels in terms of therapeutic potential (Noma, 1983; Ashcroft and Ashcroft, 1990; Gopalakrishnan et al., 1993). First generation K<sup>+</sup> channel openers (KCOs), including cromakalim and pinacidil, have been known to activate glyburide-sensitive K<sub>ATP</sub> channels in a variety of vascular and nonvascular tissues (Edwards and Weston, 1993). A variety of structurally diverse KCOs, including benzopyran (cromakalim), cyanoguanidines (pinacidil), and nitroethylene analogs, have been evaluated as potential antihypertensive agents during the past 15 years, although only nicorandil, and to a lesser extent diazoxide, have been used in cardiovascular medicine, in part due to the availability of other classes of agents for these indications.

The recent cloning and expression of K<sub>ATP</sub> channel components has provided insight into the observed heterogeneity in the pharmacologic profile of KCOs (reviewed in Aguilar-Bryan et al., 1998). As noted previously, the K<sub>ATP</sub> channel expressed in pancreatic  $\beta$ -cells is a multimeric complex composed of Kir6.2 and the sulfonylurea receptor SUR1 (Clement et al., 1997; Lorenz et al., 1998). From expression studies using rat or mouse SUR subunits, it is thought that the molecular composition of the cardiac/skeletal muscle channel is SUR2A/Kir6.2, whereas SUR2B is thought to be one of the subunits constituting the smooth muscle type K<sub>ATP</sub> channels. More recently, SUR2 splice variants that lack either exon 14 or exon 17 have been identified by RNA analysis (Chutkow et al., 1999; Davis-Taber et al., 2000). With the emerging diversity of K<sub>ATP</sub> channel combinations, it could be anticipated that tissues may contain a predominance of certain isoforms involved in various functions ranging from transmitter release to ischemic protection and may be selectively targeted for development of tissue-selective compounds for the treatment of several cardiac and smooth muscle disorders.

Recent efforts have focused on the development of second generation openers of K<sub>ATP</sub> channels for nonvascular indications including bladder overactivity, irritative bowel syndrome, airway hyper-reactivity, erectile dysfunction, and as cardioprotective agents for the ischemic myocardium (Morley, 1994; Garlid et al., 1997). Compounds investigated for the treatment of bladder overactivity such as ZM-244085, ZD-6169, or WAY-133537 have been shown to activate K<sub>ATP</sub> channels, relax bladder smooth muscle, and exhibit modest in vivo selectivity (Howe et al., 1995; Wojdan et al., 1999; Gopalakrishnan et al., 1999). Analogs derived from the benzopyran nucleus, including BMS-180448 and BMS-191095, display selectivity for

cardioprotective over vasorelaxant effects relative to the nonselective KCO, cromakalim. BMS-180448 has been shown to have cardioprotective effects at concentrations that do not affect action potential shortening, indicative of activation of a K<sub>ATP</sub> channel other than the plasma membrane K<sub>ATP</sub> channel. The cardioprotective effects of the antianginal drug nicorandil have been shown to be via activation of mitochondrial K<sub>ATP</sub> channels (Sato et al., 2000). Mammalian cells transfected with K<sub>ATP</sub> channel subunits Kir6.2 and SUR1 showed resistance to hypoxia reoxygenation, and a therapeutic approach based on gene delivery of K<sub>ATP</sub> subunits in tissues vulnerable to hypoxia reoxygenation and damage has also been suggested (Jovanovic et al., 1998a,b). KCOs examined for airway hyperreactivity include SDZ 217-744, with reported improved selectivity of inhibition of airway hyperactivity relative to cromakalim (Williams et al., 1990). K<sub>ATP</sub> channel openers have also been investigated for the potential treatment of male erectile dysfunction. Pinacidil, cromakalim, and nicorandil or its analogs have shown increases in intracavernosal pressure by relaxing corporal smooth muscle, which leads to initiation and maintenance of erection (Moon et al., 1999; Vick et al., 2000), providing proof of principle that such compounds, if delivered directly into the corpus smooth muscle, could be a viable treatment option. The basis for the reported modest *in vivo* selectivity of second generation KCOs could, in principle, arise from interactions with distinct K<sub>ATP</sub> channel combinations or, more plausibly, from physiologic or pharmacokinetic factors. For instance, studies aimed at elucidating the basis for the cardioprotective effect of KCOs reveal a role for the mitochondrial K<sub>ATP</sub> channel, the molecular composition of which appears to be somewhat distinct from sarcolemmal K<sub>ATP</sub> channels (Garlid et al., 1997; Szewczyk and Marban, 1999).

Sulfonylureas such as glibenclamide and glipizide that block K<sub>ATP</sub> channels in pancreatic  $\beta$ -cells have been used for the treatment of type II diabetes for over 30 years, and newer agents with diminished propensity for sustained hypoglycemic potential continue to be developed. More recently, it has been demonstrated that transfection of SUR1 and Kir6.2 into an insulin-secreting cell line (NES 2Y  $\beta$ -cells) from PHHI patients can restore glucose-dependent insulin release. This opens up the potential for gene therapy to alleviate  $\beta$ -cell dysfunction in PHHI and diabetes (Dunne et al., 1997; Macfarlane et al., 2000). Blockers of K<sub>ATP</sub> channels such as PNU-37883A have also been evaluated as diuretics or as antiarrhythmic agents (Humphrey and Ludens, 1998). More recent focus continues in the identification of cardioselective K<sub>ATP</sub> channel blockers for the prevention of ischemia-induced ventricular fibrillation. This has been underscored by the notion that during acute myocardial infarction, activation of ATP-sensitive K<sup>+</sup> currents results in action potential duration shortening and elevation of interstitial [K<sup>+</sup>] accumulation that may contribute to reentry arrhythmias and cardiac death (Gögelein

et al., 1998). HMR 1883, a relatively cardioselective K<sub>ATP</sub> channel blocker with modest selectivity for cardiac K<sub>ATP</sub> over the pancreatic K<sub>ATP</sub>, prevented ventricular fibrillation in dogs at doses that did not affect plasma insulin or blood glucose. Such compounds may prove useful in the treatment of ventricular arrhythmias without pancreatic side effects or the liabilities of nonselective blockers under ischemic conditions.

#### D. Two-Pore K<sup>+</sup> Channels

The more recently identified two-pore K<sup>+</sup> channels, including TWIK, TREK, TASK, and TRAAK genes (Table 1), thought to function as background channels involved in the modulation of resting membrane potential in various cell types could emerge as attractive targets for discovering novel neuroprotective and anesthetic agents (Lesage and Lazdunski, 1999). The neuroprotective agent riluzole, currently in use for the treatment of amyotrophic lateral sclerosis, has been shown to be an activator of TREK-1 and TRAAK channels (Duprat et al., 2000). Volatile general anesthetics such as chloroform and isoflurane have also been shown to target TREK-1 channels (Patel et al., 1999). Further knowledge of the localization and regulation of these channels by cellular and extrinsic signals will be important in targeting specific two-pore channels for therapeutic intervention.

### V. Concluding Remarks

K<sup>+</sup> channels are increasingly being elucidated as molecular targets in a number of pathophysiologic states, and they continue to trigger considerable enthusiasm as drug targets. The pivotal role of K<sup>+</sup> channels in various physiological processes including neuronal signaling, vascular and nonvascular muscle contractility, cardiac pacing, auditory function, hormone secretion, immune function, and cell proliferation has been underscored by the recent flurry of discoveries linking K<sup>+</sup> channel mutations to various inherited disorders. Insight into the structure and function of channel proteins coupled with the knowledge of genetic and disease-induced regulation of K<sup>+</sup> channels could undoubtedly improve diagnosis and offer specific candidate genes for the development of appropriate therapies. On the assumption that defined K<sup>+</sup> channel mutations are linked to specific diseases, it may be feasible to conduct a molecular diagnosis to evaluate whether the patient will respond to a drug aimed at specific K<sup>+</sup> channels. It has been shown that differences in K<sup>+</sup> currents may underlie gender-based drug-induced cardiac arrhythmias; for example, women are at far greater risk of torsade de pointes following a variety of drugs including antihistamines, antibiotics, and antiarrhythmic agents (Makkar et al., 1993). Analysis of the differential contribution of K<sup>+</sup> currents contributing to cardiac repolarization could help improve screening methodologies for individuals at risk for

drug-induced arrhythmias and direct development of drugs with reduced incidence of inducing arrhythmias. Knowledge of specific mutations may also lead to validation of more suitable animal models of disease to help preclinical assessment of novel compounds. In the coming years, modulating K<sup>+</sup> channel gene expression in diseased tissues via various gene delivery approaches or antisense oligonucleotides could present an additional avenue to treat various diseases and/or, in combination with pharmacotherapy, to enhance the selectivity of K<sup>+</sup> channel modulators. Additionally, unraveling precise in situ channel combinations, localization, and channel regulation in disease pathologies could shed light on developing better therapeutic strategies. Targeting diverse auxiliary subunits or modulating the interactions of auxiliary subunits with the pore-forming subunit may also provide alternate avenues for identifying selective regulators of K<sup>+</sup> channel function. It is to be anticipated that these efforts could collectively enhance the development of selective compounds that modulate the various classes of K<sup>+</sup> channels with promising therapeutic and prophylactic utility.

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