

International Union of Pharmacology. LIV. Nomenclature and Molecular Relationships of Inwardly Rectifying Potassium Channels

YOSHIHIRO KUBO, JOHN P. ADELMAN, DAVID E. CLAPHAM, LILY Y. JAN, ANDREAS KARSCHIN, YOSHIHISA KURACHI, MICHEL LAZDUNSKI, COLIN G. NICHOLS, SUSUMU SEINO, AND CAROL A. VANDENBERG

Division of Biophysics and Neurobiology, Department of Molecular Physiology, National Institute for Physiological Sciences, Myodaiji, Okazaki, Aichi, Japan (Y.K.); Vollum Institute, Oregon Health Sciences University, Portland, Oregon (J.P.A.); Howard Hughes Medical Institute, Children's Hospital, Harvard Medical School, Boston, Massachusetts (D.E.C.); Howard Hughes Medical Institute, Department of Physiology and Biochemistry, University of California, San Francisco, San Francisco, California (L.Y.J.); Institute of Physiology, University of Würzburg, Würzburg, Germany (A.K.); Department of Pharmacology II, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan (Y.K.); Institut de Pharmacologie Moléculaire et Cellulaire, Centre National de la Recherche Scientifique-Unité Propre de Recherche 411, Valbonne, France (M.L.); Department of Cell Biology and Physiology, Washington University School of Medicine, St. Louis, Missouri (C.G.N.); Division of Cellular and Molecular Medicine, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan (S.S.); and Department of Molecular, Cellular and Developmental Biology, Neuroscience Research Institute, University of California, Santa Barbara, Santa Barbara, California (C.A.V.)

Introduction

Since the initial cDNA cloning of the first inward rectifiers $K_{ir}1.1$ (ROMK1) and $K_{ir}2.1$ (IRK1) in 1993, a succession of new members of this family have been identified, including the G protein-coupled $K_{ir}3$ and the ATP-sensitive $K_{ir}6$. These channels play an important physiological role in the function of many organs, including brain, heart, kidney, endocrine cells, ears, and retina. The phylogenetic tree shown in Fig. 1 illustrates the relationships between the seven K_{ir} subfamilies based on amino acid sequence alignments. No new members of this family have been identified since this tree appeared in the 2002 edition of *The IUPHAR Compendium of Voltage-Gated Ion Channels*, and it is unlikely that any other members remain to be discovered.

In the K_{ir} section of the 2002 edition, we cited a very limited number of original cDNA cloning papers (Kubo et al., 2002). The scope of these citations has been expanded herein so that inferences on the molecular architecture and functional and pharmacological aspects can be readily drawn. Some of the newer work cited in this article is outlined below. It is noteworthy that much of this work describes the identification of associating proteins and the link between particular K_{ir} genes and human diseases. These kinds of findings are expected to continue to increase:

Address correspondence to: Dr. Yoshihiro Kubo, Division of Biophysics and Neurobiology, Department of Molecular Physiology, National Institute for Physiological Sciences, Nishigoh-naka 38, Myodaiji, Okazaki, Aichi 444-8585, Japan.

The authors serve as the Subcommittee on K_{ir} channels of the Nomenclature Committee of the International Union of Pharmacology.

Article, publication date, and citation information can be found at <http://pharmrev.aspetjournals.org>.

doi:10.1124/pr.57.4.11.

- The interaction of $K_{ir}1.1$ with Na^+/H^+ exchange regulatory factor 2 in the postsynaptic density 95/disc-large/zona occludens (PDZ) complex was reported (Yoo et al., 2004).
- The assembly of $K_{ir}2.1$ channels with synapse-associated protein 97 (SAP97), calmodulin-dependent serine protein kinase (CASK), Veli, and Mint1 and their contribution to protein trafficking was shown (Leonoudakis et al., 2004).
- $K_{ir}4.1$ in glial cells and $K_{ir}2.2$ in muscle were shown to associate with the dystrophin-glycoprotein complex via α -syntrophin (Connors et al., 2004).
- $K_{ir}4.1$ has been associated with epilepsy in both causative and protective roles (Buono et al., 2004; Ferraro et al., 2004; Leonoudakis et al., 2004).
- It was shown that the loss of $K_{ir}4.1$ expression abolishes endocochlear potential and causes deafness in Pendred syndrome (Wangemann et al., 2004).
- The disruption of $K_{ir}6.1$ gene in mice was reported to cause phenotypes similar to those of vasospastic (Prinzmetal) angina (Miki et al., 2002).
- It was shown that an activating mutation of $K_{ir}6.2$ causes permanent neonatal diabetes (Gloyn et al., 2004).

Although it is not discussed herein, among the most exciting recent developments are those involving X-ray crystal structure analysis, including studies describing the structure of the cytoplasmic region of $K_{ir}3.1$ (Nishida and MacKinnon, 2002), the entire structure of the bacterial $K_{ir}1.1$ channel (Kuo et al., 2003), and the cytoplasmic region of $K_{ir}2.1$ (Pegan et al., 2005). These studies demonstrated that inward rectifier K^+ channels have a long cytoplasmic pore and confirmed the significance of negatively charged amino acids on the wall of the cytoplasmic pore that have been known to play critical roles for inward rectification. They also provided structure-based clues for the regulation mechanisms of gating by

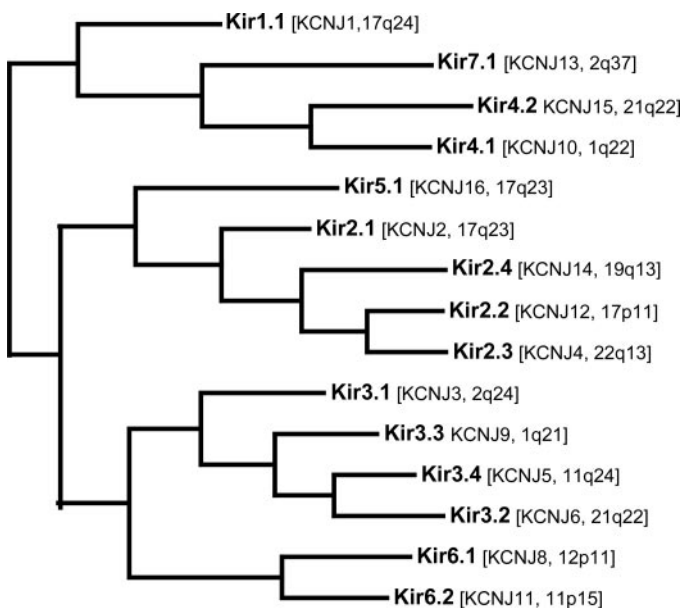


FIG. 1. Phylogenetic tree of K_{ir} channels. Amino acid sequence alignments and phylogenetic analysis for the 15 known members of the human K_{ir} family were generated as described in the legend for Fig. 1 of "LIII. Nomenclature and Molecular Relationships of Voltage-Gated Potassium Channels". No new channels have been added to this topology since it appeared in the earlier edition of this compendium. International Union of Pharmacology and HUGO Gene Nomenclature Committee names of the genes are shown together with their chromosomal localization.

ligands such as G proteins and phosphatidylinositol 4,5-bisphosphate. The information yielded by analysis of crystal structures is extremely valuable since it will enable more precise approaches to establishing structure-function relationships. Also noteworthy are published studies on the dynamic aspects of channel function using fluorescence resonance energy transfer analysis of fluorescent-labeled molecules (Riven et al., 2003). Knowledge of these dynamic aspects of K_{ir} channel function may also be expected to expand in the near future.

A great deal of additional knowledge on K_{ir} function, structure-function relationships, regulation of expression, and links with diseases has been accumulated. Since it is not possible to describe it in detail here, we refer the reader instead to several excellent recent re-

views (Stanfield et al., 2002; Bichet et al., 2003; Lu, 2004). See Tables 1 through 15 for K_{ir} 1 through K_{ir} 7.1.

Acknowledgments. We gratefully acknowledge the support of Drs. Atsushi Inanobe (Kurachi Lab), Wade Pearson (Nichols Lab), and Florian Lesage (Lazdunski Lab) and the contributions of Dr. Henry Lester (California Institute of Technology, Pasadena, CA) to the earlier edition of this compendium.

REFERENCES

- Bichet D, Haass FA, and Jan LY (2003) Merging functional studies with structures of inward rectifier K^+ channels. *Nat Rev Neurosci* **4**:957–967.
- Buono RJ, Lohoff FW, Sander T, Sperling MR, O'Connor MJ, Dlugos DJ, Ryan SG, den GT, Zhao H, Scattergood TM, et al. (2004) Association between variation in the human KCNJ10 potassium ion channel gene and seizure susceptibility. *Epilepsy Res* **58**:175–183.
- Connors NC, Adams ME, Froehner SC, and Kofuji P (2004) The potassium channel Kir4.1 associates with the dystrophin-glycoprotein complex via alpha-syntrophin in glia. *J Biol Chem* **279**:28387–28392.
- Ferraro TN, Golden GT, Smith GG, Martin JF, Lohoff FW, Gieringer TA, Zamboni D, Schwebel CL, Press DM, Kratzer SO, et al. (2004) Fine mapping of a seizure susceptibility locus on mouse chromosome 1: nomination of Kcnj10 as a causative gene. *Mamm Genome* **15**:239–251.
- Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, et al. (2004) Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med* **350**:1838–1849; erratum in *N Engl J Med* **351**:1470.
- Kubo Y, Adelman JP, Clapham DE, Jan LY, Karschin A, Kurachi Y, Lazdunski M, Lester HA, Nichols CG, et al. (2002) Kir potassium channels, in *The IUPHAR Compendium of Voltage-gated Ion Channels* (Catterall WA, Chandy KG, and Gutman G eds) pp 153–172, IUPHAR Media, Leeds, UK.
- Kuo A, Gulbis JM, Antcliff JF, Rahman T, Lowe ED, Zimmer J, Cuthbertson J, Ashcroft FM, Ezaki T, and Doyle DA (2003) Crystal structure of the potassium channel KirBac1.1 in the closed state. *Science (Wash DC)* **300**:1922–1926.
- Leonoudakis D, Conti LR, Anderson S, Radeke CM, McGuire LMM, Adams ME, Froehner SC, Yates JR 3rd, and Vandenberg CA (2004) Protein trafficking and anchoring complexes revealed by proteomic analysis of inward rectifier potassium channel (Kir2x)-associated proteins. *J Biol Chem* **279**:22331–22346.
- Lu Z (2004) Mechanism of rectification in inward rectifier K^+ channels. *Annu Rev Physiol* **66**:103–129.
- Miki T, Suzuki M, Shibasaki T, Uemura H, Sato T, Yamaguchi K, Koseki H, Iwanaga T, Nakaya H, and Seino S (2002) Mouse model of Prinzmetal angina by disruption of the inward rectifier Kir6.1. *Nat Med* **8**:466–472.
- Nishida M and MacKinnon R (2002) Structural basis of inward rectification: cytoplasmic pore of the G-protein-gated inward rectifier GIRK1 at 1.8 Å resolution. *Cell* **111**:957–965.
- Pegan S, Arrabit C, Zhou W, Kwiatkowski W, Collins A, Slesinger PA, and Choe S (2005) Cytoplasmic domain structures of Kir2.1 and Kir3.1 show sites for modulating gating and rectification. *Nat Neurosci* **8**:279–287.
- Riven I, Kalmanzon E, Segev L, and Reuveny E (2003) Conformational rearrangements associated with the gating of the G protein-coupled potassium channel revealed by FRET microscopy. *Neuron* **38**:225–235.
- Stanfield PR, Nakajima S, and Nakajima Y (2002) Constitutively active and G-protein coupled inward rectifier K^+ channels: Kir2.0 and Kir3.0. *Rev Physiol Biochem Pharmacol* **145**:47–179.
- Yoo D, Flagg TP, Olsen O, Raghuram V, Foskett JK, and Welling PA (2004) Assembly and trafficking of a multiprotein ROMK (Kir 1.1) channel complex by PDZ interactions. *J Biol Chem* **279**:6863–6873.
- Wangemann P, Itza EM, Albrecht B, Wu T, Jabba SV, Maganti RJ, Lee JH, Everett LA, Wall SM, Royaux IE, et al. (2004) Loss of KCNJ10 protein expression abolishes endocochlear potential and causes deafness in Pendred syndrome mouse model. *BMC Med* **2**:30.

TABLE 1
K_{ir}1.1 channels

Channel name	$K_{ir}1.1$
Description	Inwardly rectifying potassium channel $K_{ir}1.1$ subunit
Other names	$K_{ir}1.1$, ROMK, ROMK1
Molecular information	Human (KCNJ1): 391aa, Locus ID: 3758, GenBank: U12541, NM_000220, PMID: 7929082, ¹ chr. 11q24 Rat (Kcnj1): 391aa, Locus ID: 24521, GenBank: X72341, NM_017023, PMID: 7680431, ² chr. 8q21 Mouse (Kcnj1): 372aa, Locus ID: 56379, GenBank: AF012834 (see "Comments"), NM_019659, PMID: 7611454, ³ 89801344, ⁴ chr. 9A
Associated subunits	Na^+/H^+ exchange regulatory factor 2 (NHERF2) (not required for function ⁵)
Functional assays	Voltage-clamp
Current	Inwardly rectifying K^+ current
Conductance	47pS (285 mM K^+), 40pS (140 mM K^+)
Ion selectivity	K^+
Activation	Not established
Inactivation	Intracellular acidification
Activators	None
Gating inhibitors	None
Blockers	Nonselective: Ba^{2+} , Cs^+
Radioligands	None
Channel distribution	Kidney (apical membranes in cortex and outer medulla), RT-PCR shows transcripts in skeletal muscle, pancreas, spleen, brain, heart, and liver
Physiological functions	K^+ secretion ($K_{ir}1.1a$, $K_{ir}1.1c$, distal renal tubule), K^+ recycling ($K_{ir}1.1b$, thick ascending limb of loop of Henle)
Mutations and pathophysiology	Bartter's syndrome ⁶
Pharmacological significance	Not established
Comments	Six splice variants exist, denoted as $K_{ir}1.1a$, $K_{ir}1.1b$, $K_{ir}1.1c$, $K_{ir}1.1d$, $K_{ir}1.1e$, and $K_{ir}1.1f$

aa, amino acids; chr., chromosome; RT-PCR, reverse transcriptase-polymerase chain reaction.

1. Shuck ME, Bock JH, Benjamin CW, Tsai TD, Lee KS, Slightom JL, and Bienkowski MJ (1994) Cloning and characterization of multiple forms of the human kidney ROM-K potassium channel. *J Biol Chem* **269**:24261–24270.

2. Ho K, Nichols CG, Lederer WJ, Lytton J, Vassilev PM, Kanazirska MV, and Hebert SC (1993) Cloning and expression of an inwardly rectifying ATP-regulated potassium channel. *Nature (Lond)* **362**:31–38.

3. Boim MA, Ho K, Shuck ME, Bienkowski MJ, Block JH, Slightom JL, Yang Y, Brenner BM, and Hebert SC (1995) ROMK inwardly rectifying ATP-sensitive K^+ channel. II. Cloning and distribution of alternative forms. *Am J Physiol* **268**:F1132–F1140.

4. Kondo C, Isomoto S, Matsumoto S, Yamada M, Horio Y, Yamashita S, Takemura-Kameda K, Matsuzawa Y, and Kurachi Y. (1996) Cloning and functional expression of a novel isoform of ROMK inwardly rectifying ATP-dependent K^+ channel, ROMK6 ($K_{ir}1.1f$). *FEBS Lett* **399**:122–126.

5. Yoo D, Flagg TP, Olsen O, Raghuram V, Foskett JK, and Welling PA (2004) Assembly and trafficking of a multiprotein ROMK ($K_{ir}1.1$) channel complex by PDZ interactions. *J Biol Chem* **279**:6863–6873.

6. Schwalbe RA, Bianchi L, Accili EA, and Brown AM (1998) Functional consequences of ROMK mutants linked to antenatal Bartter's syndrome and implications for treatment. *Hum Mol Genet* **7**:975–980.

TABLE 2
K_{ir}2.1 channels

Channel name	K _{ir} 2.1
Description	Inwardly rectifying potassium channel K _{ir} 2.1 subunit
Other names	IRK1
Molecular information	Human (KCNJ2): 427aa, Locus ID: 3759, GenBank: U12507, NM_000891, PMID: 7696590, ¹ chr. 17q23.1-24.2 Rat (Kcnj2): 427aa, Locus ID: 29712, GenBank: L48490, NM_017296, PMID: 7603835, ² chr. 10q32.1 Mouse (Kcnj2): 428aa, Locus ID: 16518, GenBank: X73052, NM_008425, PMID: 7680768, ³ chr. 11E2, 11, 68.0 centimorgans
Associated subunits	K _{ir} 2.2, K _{ir} 4.1, PSD-95, ⁴ SAP97, ⁵ AKAP79 ⁶
Functional assays	Voltage-clamp
Current	I _{K1} in the heart with other K _{ir} 2 subunits
Conductance	23pS (in 140 mM K ⁺) ³
Ion selectivity	K ⁺³
Activation	Unblocking of polyamines ^{7,8}
Inactivation	Not established
Activators	Phosphorylation by PKA and ATP hydrolysis, ⁹ PIP ₂ ^{10,11}
Inhibitors	PKA phosphorylation, ¹² tyrosine kinase phosphorylation ¹³
Blockers	Cs ⁺ , Rb ⁺ , ¹⁴ Ba ²⁺ , ¹⁵ intracellular Mg ²⁺ (IC ₅₀ = 17 μM at +40 mV), putrescine (IC ₅₀ = 7.5 μM at +40 mV), spermidine (IC ₅₀ = 8.0 nM at +40 mV), spermine (IC ₅₀ = 0.9 nM at +40 mV) ¹⁶
Radioligands	None
Channel distribution	Forebrain, heart, skeletal muscle, aortic endothelial cells, macrophage cells, ³ olfactory tubercle, dentate gyrus granule cells, caudate putamen, nucleus accumbens, superior colliculus, anterior pretectal nucleus, deep mesencephalic nucleus ¹⁷
Physiological functions	Maintenance of a resting membrane potential, repolarization of cardiac action potential
Mutations and pathophysiology	Andersen's syndrome ¹⁸
Pharmacological significance	Not established

aa, amino acids; chr., chromosome; PKA, protein kinase A.

1. Raab-Graham KF, Radeke CM, and Vandenberg CA (1994) Molecular cloning and expression of a human heart inward rectifier potassium channel. *NeuroReport* **5**:2501–2505.
2. Wischmeyer E, Lentjes KU, and Karschin A (1995) Physiological and molecular characterization of an IRK-type inward rectifier K⁺ channel in a tumor mast cell line. *Pflueg Arch Eur J Physiol* **429**:809–819.
3. Kubo Y, Baldwin TJ, Jan YN, and Jan LY (1993) Primary structure and functional expression of a mouse inward rectifier potassium channel. *Nature (Lond)* **362**:127–133.
4. Nehring RB, Wischmeyer E, Doring F, Veh RW, Sheng M, and Karschin A (2000) Neuronal inwardly rectifying K⁺ channels differentially couple to PDZ proteins of the PSD-95/SAP90 family. *J Neurosci* **20**:156–162.
5. Leonoudakis D, Mailliard W, Wingerd K, Clegg D, and Vandenberg C (2001) Inward rectifier potassium channel Kir2.2 is associated with synapse-associated protein SAP97. *J Cell Sci* **114**:987–998.
6. Dart C and Leyland ML (2001) Targeting of an A-kinase anchoring protein, AKAP79, to an inwardly rectifying potassium channel, Kir2.1. *J Biol Chem* **276**:20499–20505.
7. Lopatin AN, Makhina EN, and Nichols CG (1994) Potassium channel block by cytoplasmic polyamines as the mechanism of intrinsic rectification. *Nature (Lond)* **372**:366–369.
8. Ishihara K, Hiraoka M, and Ochi R (1996) The tetravalent organic cation spermine causes the gating of the IRK1 channel expressed in murine fibroblast cells. *J Physiol* **419**:297–320.
9. Fakler B, Brandle U, Glowatzki E, Zenner HP, and Ruppersberg JP (1994) Kir2.1 inward rectifier K⁺ channels are regulated independently by protein kinases and ATP hydrolysis. *Neuron* **13**:1413–1420.
10. Huang CL, Feng S, and Hilgemann DW (1998) Direct activation of inward rectifier potassium channels by PIP₂ and its stabilization by Gβγ. *Nature (Lond)* **391**:803–806.
11. Soom M, Schonherr R, Kubo Y, Kirsch C, Klinger R, and Heinemann SH (2001) Multiple PIP₂ binding sites in Kir2.1 inwardly rectifying potassium channels. *FEBS Lett* **490**:49–53.
12. Wischmeyer E and Karschin A (1996) Receptor stimulation causes slow inhibition of IRK1 inwardly rectifying K⁺ channels by direct protein kinase A-mediated phosphorylation. *Proc Natl Acad Sci USA* **93**:5819–5823.
13. Wischmeyer E, Doring F, and Karschin A (1998) Acute suppression of inwardly rectifying Kir2.1 channels by direct tyrosine kinase phosphorylation. *J Biol Chem* **273**:34063–34068.
14. Abrams CJ, Davies NW, Shelton PA, and Stanfield PR (1996) The role of a single aspartate residue in ionic selectivity and block of a murine inward rectifier K⁺ channel Kir2.1. *J Physiol* **493**:643–649.
15. Alagem N, Dvir M, and Reuveny E (2001) Mechanism of Ba²⁺ block of a mouse inwardly rectifying K⁺ channel: differential contribution by two discrete residues. *J Physiol* **534**:381–393.
16. Yang J, Jan YN, and Jan LY (1995) Control of rectification and permeation by residues in two distinct domains in an inward rectifier K⁺ channel. *Neuron* **14**:1047–1054.
17. Karschin C, Dissmann E, Stumer W, and Karschin A (1996) IRK(1–3) and GIRK(1–4) inwardly rectifying K⁺ channel mRNAs are differentially expressed in the adult rat brain. *J Neurosci* **16**:3559–3570.
18. Plaster NM, Tawi R, Tristani-Firouzi M, Canun S, Bendahhou S, Tsunoda A, Donaldson MR, Iannaccone ST, Brunt E, Barohn R, et al. (2001) Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. *Cell* **105**:511–519.

TABLE 3
 $K_{ir2.2}$ channels

Channel name	$K_{ir2.2}$
Description	Inwardly rectifying potassium channel $K_{ir2.2}$ subunit
Other names	IRK2, RB-IRK2, MB-IRK2, hIRK
Molecular information	Human (KCNJ12): 427aa, Locus ID: 3768, GenBank: L36069, NM_021012, PMID: 7859381, ¹ chr. 17p11.1 ² Rat (Kcnj12): 427aa, Locus ID: 117052, GenBank: X78461, NM_053981, PMID: 8137958, ³ chr. 10q22 Mouse (Kcnj12): 427aa, Locus ID: 16515, GenBank: X80417, NM_010603, PMID: 8083233, ⁴ chr. 11, 34.15 centimorgans <i>Drosophila melanogaster</i> : GenBank: NM_170076, PMID: 10731132, ⁵ chr. 95A1-95A1
Associated subunits	$K_{ir2.1}$ and $K_{ir2.3}$ to form heteromeric channel, auxiliary subunit: SAP97, Veli-1, Veli-3, ⁶ PSD-95, Chapsyn-110, SAP102, CASK, Dlg2, Dlg3, Pals2, actin-binding LIM protein, $\alpha 1$, $\beta 1$, and $\beta 2$ syntrophin, dystrophin, Dp71, α -dystrobrevin-1, and α -dystrobrevin-2 ⁷
Functional assays	Voltage-clamp
Current	I_{K1} in the heart with other K_{ir2} subunits
Conductance	34.2pS ($K_{ir2.2}$ homomeric channel) in 140 mM symmetric K^+ ⁴ 30.0pS ($K_{ir2.2}$ - $K_{ir2.1}$ concatemer) in 145 mM symmetric K^+ ⁸ 30.1pS ($K_{ir2.1}$ - $K_{ir2.2}$ concatemer) in 145 mM symmetric K^+ ⁸
Ion selectivity	K^+
Activation	Voltages negative to E_K , ³ intercellular alkalization, $pK = 6.2^9$
Inactivation	Voltages positive to E_K , ³ intercellular acidification, $pK = 6.2^9$
Activators	Not established
Gating inhibitors	Not established
Blockers	Ba^{2+} (IC_{50} to $K_{ir2.2}$ homomeric channel, 0.5 μM ; to $K_{ir2.1}/K_{ir2.2}$ heteromeric channel, 0.64 μM ; to either $K_{ir2.1}$ - $K_{ir2.2}$ or $K_{ir2.2}$ - $K_{ir2.1}$ concatemer, 0.68 μM ; to either $K_{ir2.2}$ - $K_{ir2.3}$ or $K_{ir2.3}$ - $K_{ir2.2}$ concatemer, 1.73 μM ; to $K_{ir2.2}/K_{ir2.3}$ heteromeric channel, 1.94 μM , ⁸ intracellular Mg^{2+} ($K_i = 11 \mu M^{10}$), intracellular polyamines (IC_{50} for spermine, 3 nM ¹⁰)
Radioligands	None
Channel distribution	Cerebellum, skeletal muscle, kidney, heart, forebrain
Physiological functions	Maintenance of a resting membrane potential, repolarization of cardiac action potential, modulation of cell excitability
Mutations and pathophysiology	$K_{ir2.2}$ knockout mice show 50% reduction in I_{K1} , and $K_{ir2.1}$ knockout mice lack a detectable I_{K1} at 4 mM external K^+ , suggesting that a large population of $K_{ir2.2}$ behaves as a heteromeric channel with $K_{ir2.1}$ to form I_{K1} ¹¹
Pharmacological significance	Not established

aa, amino acids; chr., chromosome.

1. Wible BA, De Biasi M, Majumder K, Tagliatela M, and Brown AM (1995) Cloning and functional expression of an inwardly rectifying K^+ channel from human atrium. *Circ Res* **76**: 343–350.
2. Hugnot JP, Pedetour F, Le Calvez C, Grosgeorge J, Passage E, Fontes M, and Lazdunski M (1997) The human inward rectifying K^+ channel Kir 2.2 (KCNJ12) gene: gene structure, assignment to chromosome 17p11.1, and identification of a simple tandem repeat polymorphism. *Genomics* **39**:113–116.
3. Koyama H, Morishige K, Takahashi N, Zanelli J, Fass DN, and Kurachi Y (1994) Molecular cloning functional expression and localization of a novel inward rectifier potassium channel in the rat brain. *FEBS Lett* **341**:303–307.
4. Takahashi N, Morishige K, Jahangir A, Yamada M, Findlay I, Koyama H, and Kurachi Y (1994) Molecular cloning and functional expression of cDNA encoding a second class of inward rectifier potassium channel. *J Biol Chem* **269**:23274–23279.
5. Adams MD, Celniker SE, Holt RA, Evans CA, Gocayne JD, Amanatides PG, Scherer SE, Li PW, Hoskins RA, Galle RF, et al (2000) The genome sequence of *Drosophila melanogaster*. *Science* **287**:2185–2195.
6. Leonoudakis D, Conti LR, Radeke CM, McGuire LMM, and Vandenberg CA (2004) A multiprotein trafficking complex composed of SAP97, CASK, Veli, and Mint1 is associated with inward rectifier Kir2 potassium channels. *J Biol Chem* **279**:19051–19063.
7. Leonoudakis D, Conti LR, Anderson S, Radeke CM, McGuire LMM, Adams ME, Froehner SC, Yates III JR, and Vandenberg CA (2004) Protein trafficking and anchoring complexes revealed by proteomic analysis of inward rectifier potassium channel (Kir2x)-associated proteins. *J Biol Chem* **279**:22331–22346.
8. Preisig-Müller R, Schlichthörl G, Goerge T, Heinen S, Brüggemann A, Rajan S, Derst C, Veh R, and Daut J (2002) Heteromerization of Kir2x potassium channels contributes to the phenotype of Andersen's syndrome. *Proc Natl Acad Sci USA* **99**:7774–7779.
9. Collins A and Larson M (2002) Differential sensitivity of inward rectifier K^+ channels to metabolic inhibitors. *J Biol Chem* **277**:35815–35818.
10. Yamashita T, Horio Y, Yamada M, Takahashi N, Kondo C, and Kurachi Y (1996) Competition between Mg^{2+} and spermine for a cloned IRK 2 channel expressed in a human cell line. *J Physiol* **493**:143–156.
11. Zaritsky JJ, Redell JB, Tempel BL, and Schwarz TL (2001) The consequences of disrupting cardiac inwardly rectifying K^+ current (I_{K1}) as revealed by the targeted deletion of the murine *Kir2.1* and *Kir2.2* genes. *J Physiol* **533**:697–710.

TABLE 4
K_{ir}2.3 channels

Channel name	K _{ir} 2.3
Description	Inwardly rectifying potassium channel K _{ir} 2.3 subunit
Other names	IRK3, HIR, HRK1, BIRK2, BIR11, hIRK2, MB-IRK3, CCD-IRK3, mK _{ir} 2.3
Molecular information	Human (KCNJ4): 445aa, Locus ID: 3761, GenBank: U07364, S72503, NM_152868, ¹⁻³ PMID: 8016146, ¹ chr. 22q13.10 Rat (Kcnj4): 446aa, Locus ID: 116649, GenBank: X83580, ⁴ U27582, ⁵ NM_053870, PMID: 7874445, ⁴ chr. 7q34 Mouse (Kcnj4): 445aa, Locus ID: 16520, GenBank: S71382, NM_008427, PMID: 8013643, ^{6,7} chr. 15, 46.7 centimorgans Guinea pig (Kcnj4): GenBank: AF18787, ⁴ PMID: 11283229 ⁸
Associated subunits	K _{ir} 2.1 and K _{ir} 2.2 to form heteromeric channel, auxiliary subunit: PSD-95, ⁹ Chapsyn-110/PSD-93, ¹⁰ syntrophin, α -dystrobrevin-2, Dp71 (dsyntrophin protein 71), SAP97, CASK, Veli-3 ¹¹
Functional assays	Voltage-clamp
Current	I _{K1} in the heart with other K _{ir} 2 subunits; small conductance channel at basolateral membrane of renal cortical correcting duct
Conductance	13pS in 140 mM symmetric K ⁺ ⁶
Ion selectivity	K ⁺
Activation	Voltages negative to E _K ⁶
Inactivation	Voltages positive to E _K ⁶
Activators	Intracellular alkalinization (pK = 6.76 ¹²), extracellular alkalinization (pK = 7.4 ^{13,14}), PIP ₂ , arachidonic acid (EC ₅₀ 0.4 μ M at -100 mV ¹⁵), tenidap (EC ₅₀ 0.4–1.3 μ M ¹⁶)
Inhibitors	None
Gating inhibitors	ATP (K _i = 1.47 mM ¹⁷), G protein $\beta\gamma$ subunits (K _i , not established ¹⁸), intracellular acidification (pK = 6.76 ¹²), extracellular acidification (pK = 7.4 ^{13,14}), reactive oxygen (K _i , not established ¹⁹), intracellular Mg ²⁺ (K _i , not established ²⁰)
Blockers	Ba ²⁺ (IC ₅₀ to K _{ir} 2.3 homomeric channel, 10.3 μ M; to K _{ir} 2.1/K _{ir} 2.3 heteromeric channel, 6.32 μ M; to either K _{ir} 2.1–K _{ir} 2.3 or K _{ir} 2.3–K _{ir} 2.1 concatemer, 3.39 μ M; to either K _{ir} 2.2–K _{ir} 2.3 or K _{ir} 2.3–K _{ir} 2.2 concatemer, 1.73 μ M; to K _{ir} 2.2/K _{ir} 2.3 heteromeric channel, 1.94 μ M ²¹) Cs ⁺ (IC ₅₀ to K _{ir} 2.3 homomeric channel, 30 μ M ²) Internal tetraethylammonium ion (K _i = 62 μ M ²) Intracellular Mg ²⁺ (K _i , not established), intracellular polyamines (K _i , not established) ²² SCH23390; 34% inhibition at 100 μ M ²³
Radioligands	None
Channel distribution	Forebrain (after embryonic day 22 ²⁴), olfactory bulb, hippocampus, cortex, basal ganglia, reactive astrocyte, ²⁵ microvilli of Schwann cells, ²⁶ postsynaptic membrane at excitatory synapse, ¹⁰ heart (not rodent), kidney
Physiological functions	Maintenance of a resting membrane potential, repolarization of cardiac action potential, modulation of cell excitability; specific distribution at postsynaptic membrane suggests that K _{ir} 2.3 participates in keeping a deep resting membrane potential at the postsynaptic region, which is a determinant for the activity of ionotropic glutamate receptors and a <i>N</i> -methyl-D-aspartate- and α -aminomethylphosphonic acid-sensitive receptor ¹⁰ ; although it depends on the species, K _{ir} 2.3 in the heart may form channels in complexes with other K _{ir} 2 subunits, contributing a small fraction of I _{K1}
Mutations and pathophysiology	Not established
Pharmacological significance	Not established

aa, amino acids; chr., chromosome; SCH23390, *R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride.

1. Périer F, Radeke CM, and Vandenberg CA (1994) Primary structure and characterization of a small-conductance inwardly rectifying potassium channel from human hippocampus. *Proc Natl Acad Sci USA* **91**:6240–6244.

2. Makhina EN, Kelly AJ, Lopatin AN, Mercer RW, and Nichols CG (1994) Cloning and expression of a novel human brain inward rectifier potassium channel. *J Biol Chem* **269**:20468–20474.

3. Tang W and Yang X-C (1994) Cloning a novel human brain inward rectifier potassium channel and its functional expression in *Xenopus* oocytes. *FEBS Lett* **348**:239–243.

4. Bond CT, Pessia M, Xia XM, Lagrutta A, Kavanaugh MP, and Adelman JP (1994) Cloning and expression of a family of inward rectifier potassium channels. *Receptor Channels* **2**:183–194.

5. Bredt DS, Wang TL, Cohen NA, Guggino WB, and Snyder SH (1995) Cloning and expression of two brain-specific inwardly rectifying potassium channels. *Proc Natl Acad Sci USA* **92**: 6753–6757.

6. Morishige K, Takahashi N, Jahangir A, Yamada M, Koyama H, Zanelli JS, and Kurachi Y (1994) Molecular cloning and functional expression of a novel brain-specific inward rectifier potassium channel. *FEBS Lett* **346**:251–256.

7. Lesage F, Duprat F, Fink M, Guillemare E, Coppola T, Lazdunski M, and Hugnot JP (1994) Cloning provides evidence for a family of inward rectifier and G-protein coupled K⁺ channels in the brain. *FEBS Lett* **353**:37–42.

8. Liu GX, Derst C, Schlichter G, Heinen S, Seebohm G, Bruggemann A, Kummer W, Veh RW, Daut J, and Preisig-Muller R (2001) Comparison of cloned Kir2 channels with native inward rectifier K⁺ channels from guinea-pig cardiomyocytes. *J Physiol* **531**:115–126.

9. Cohen NA, Brenman JE, Snyder SH, and Bredt DS (1996) Binding of the inward rectifier K⁺ channel Kir2.3 to PSD-95 regulated by protein kinase A phosphorylation. *Neuron* **17**:759–767.

10. Inanobe A, Fujita A, Ito M, Tomoike H, Inagada K, and Kurachi Y (2002) Inwardly rectifier K⁺ channel Kir2.3 is localized at the postsynaptic membrane of excitatory synapses. *Am J Physiol Cell Physiol* **282**:C1396–C1403.

11. Leonoudakis D, Conti LR, Anderson S, Radeke CM, McGuire LMM, Adams ME, Froehner SC, Yates JR III, and Vandenberg CA (2004) Protein trafficking and anchoring complexes revealed by proteomic analysis of inward rectifier potassium channel (Kir2x)-associated proteins. *J Biol Chem* **279**:22331–22346.

12. Qu Z, Yang Z, Cui N, Zhu G, Liu C, Xu H, Chanchevalap S, Shen W, Wu J, Li Y, et al. (2000) Gating of inward rectifier K⁺ channels by protein-mediated interactions of N- and C-terminal domains. *J Biol Chem* **275**:31573–31580.

13. Coulter KL, Périer F, Radeke CM, and Vandenberg CA (1995) Identification and molecular localization of a pH-sensing domain for the inward rectifier potassium channel HIR. *Neuron* **15**: 1157–1168.

14. Zhu G, Chanchevalap S, Cui N, and Jiang C. (1999) Effects of intra- and extracellular acidifications on single channel Kir2.3 currents. *J Physiol* **516**:699–710.
15. Liu Y, Liu D, Heath L, Meyers DM, Krafe DS, Wagoner PK, Silvia CP, Yu W and Curran ME. (2001) Direct activation of an inwardly rectifying potassium channel by arachidonic acid. *Mol Pharmacol* **59**:1061–1068.
16. Liu Y, Liu D, Printzenhoff D, Coghlan MJ, Harris R, and Krafe DS (2002) Tenidap, a novel anti-inflammatory agent, is an opener of the inwardly rectifying K^+ channel hKir2.3. *Eur J Pharmacol* **435**:153–160.
17. Collins A, German MS, Jan YN, Jan LY, and Zhao B (1996) A strong inwardly rectifying K^+ channel that is sensitive to ATP. *J Neurosci* **16**:1–9.
18. Cohen NA, Brenman JE, Snyder SH, and Brecht DS (1996) Binding of the inward rectifier K^+ channel Kir 2.3 to PSD-95 is regulated by protein kinase A phosphorylation. *Neuron* **17**:759–767.
19. Douprat F, Guillemare E, Romey G, Fink M, Lesage F, Lazdunski M, and Honore E (1995) Susceptibility of cloned K^+ channels to reactive oxygen species. *Proc Natl Acad Sci USA* **92**:11796–11800.
20. Chuang H, Jan YN, and Jan LY (1997) Regulation of inward rectifier K^+ channel by m1 acetylcholine receptor and intracellular magnesium. *Cell* **89**:1121–1132.
21. Preisig-Müller R, Schlichthörl G, Goerge T, Heinen S, Brüggemann A, Rajan S, Derst C, Veh RW, and Daut J (2002) Heteromerization of Kir2x potassium channels contributes to the phenotype of Andersen's syndrome. *Proc Natl Acad Sci USA* **99**:7774–7779.
22. Lopatin AN, Makhina EN, and Nichols CG. (1995) The mechanism of inward rectification of potassium channels: "long-pore plugging" by cytoplasmic polyamines. *J Gen Physiol* **106**:923–955.
23. Kuzhikandathil EV and Oxford GS (2002) Classic D1 dopamine receptor antagonist *R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2345-tetrahydro-1*H*-3-benzazepine-hydrochloride (SCH23390) directly inhibits G protein-coupled inwardly rectifying potassium channels. *Mol Pharmacol* **62**:119–126.
24. Karschin C and Karschin A (1997) Ontogeny of gene expression of Kir channel subunits in the rat. *Mol Cell Neurosci* **10**:131–148.
25. Perillán PR, Li X, Potts EA, Chen M, Brecht DS, and Simard JM (2000) Inwardly rectifying K^+ channel Kir2.3 (IRK3) in reactive astrocytes from adult rat brain. *Glia* **31**: 181–192.
26. Mi H, Deerinck TJ, Jones M, Ellisman MH, and Schwarz TL (1996) Inwardly rectifying K^+ channels that may participate in K^+ buffering are localized in microvilli of Schwann cells. *J Neurosci* **16**:2421–2429.

TABLE 5
 $K_{ir2.4}$ channels

Channel name	$K_{ir2.4}$
Description	Inwardly rectifying potassium channel $K_{ir2.4}$ subunit
Other names	IRK4
Molecular information	Human (KCNJ14): 434aa, Locus ID: 3770, GenBank: AF181988, AF081466, NM_013348, NM_170720, PMID: 10723734, ¹ chr. 19q13.1-13.3 Rat (Kcnj14): 434aa, Locus ID 276720, AJ003065, NM_170718, PMID: 9592090, ² chr. 1q22 Mouse (Kcnj14): 434aa, Locus ID 211480, GenBank: NM_145963, PMID: 10942728, ³ 12477932, ⁴ chr. 7
Associated subunits	Can form heteromers with $K_{ir2.1}$
Functional assays	Voltage-clamp, Western blot
Current	Not established
Conductance	15pS (in 140 mM K^+)
Ion selectivity	K^+
Activation	Not established
Inactivation	Not established
Activators	Extracellular alkalization
Gating inhibitors	Extracellular Na^+ ions, extracellular acidification ($pK_a = 7.14$ human)
Blockers	Nonselective: Ba^{2+} ($IC_{50} = 72\text{--}116 \mu\text{M}$ at $-120 \text{ mV}^{3,5}$), Cs^+ ($IC_{50} = 40 \mu\text{M}^3$)
Radioligands	None
Channel distribution	Neuronal cells in heart, brain (restricted to cholinergic neurons in striatum and cranial motor nerve nuclei), retina
Physiological functions	Setting the membrane potential near E_K
Mutations and pathophysiology	Not established
Pharmacological significance	Not established

aa, amino acids; chr., chromosome.

1. Töpert C, Döring F, Derst C, Daut J, Grzeschik KH, and Karschin A (2000) Cloning structure and assignment to chromosome 19q13 of the human Kir2.4 inwardly rectifying potassium channel gene (*KCNJ14*). *Mamm Genome* **11**:247–249.
2. Töpert C, Döring F, Wischmeyer E, Karschin C, Brockhaus J, Ballanyi K, Derst C, and Karschin A (1998) Kir2.4: a novel brain K^+ inward rectifier predominantly expressed in motoneurons of cranial nerve nuclei. *J Neurosci* **18**:4096–4105.
3. Schram G, Melnyk P, Pourrier M, Wang Z, and Nattel S (2002) Kir2.4 and Kir2.1 K^+ channel subunits co-assemble: a potential new contributor to inward rectifier current heterogeneity. *J Physiol* **544**:337–349.
4. Strausberg RL, Feingold EA, Grouse H, Derge JG, Klausner RD, Collins FS, Shenmen CM, Schuler GD, Altshul SF, Zeeberg B, et al. (2002) Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences: Mammalian Gene Collection Program Team. *Proc Natl Acad Sci USA* **99**:16899–16903.
5. Hughes BA, Kumar G, Yuan Y, Swaminathan A, Yan D, Sharma A, Plumley L, Yang-Feng T, and Swaroop A (2000) Cloning and functional expression of human retinal Kir2.4, a pH-sensitive inwardly rectifying K^+ channel. *Am J Physiol* **279**:C771–C784.

TABLE 6
K_{ir}3.1 channels

Channel name	K _{ir} 3.1
Description	G protein-gated, inwardly rectifying potassium channel K _{ir} 3.1 subunit
Other names	GIRK1, KGA
Molecular information	Human (KCNJ3): 501aa, Locus ID: 3760, GenBank: U50964, NM_002239, PMID: 8804710, ¹ chr. 2q24.1 Rat (Kcnj3): 501aa, Locus ID: 50599, GenBank: Y12259, NM_031610, PMID: 8642402, ² chr. 3 Mouse (Kcnj3): 501aa, Locus ID: 16519, GenBank: L25264, U01071, NM_008426, PMID: 8355805, ³ 8234283, ⁴ chr. 2c1.1
Associated subunits	K _{ir} 3.2, K _{ir} 3.4, K _{ir} 3.5, ⁵ K _{ir} 3.1, is not functional by itself (see "Comments")
Functional assays	Voltage-clamp
Current	I _{GIRK}
Conductance	43pS (in 140 mM K ⁺ in oocytes ³) [see detail in section for K _{ir} 3.2 (Table 7)]
Ion selectivity	K ⁺
Activation	G _{βγ} subunits ^{6–8}
Inactivation	Voltage- and RGS protein-dependent ⁹
Activators	G _{βγ} subunits (1–50 nM); modified by PIP ₂ , sodium; K _{ir} 3.1/K _{ir} 3.2 and K _{ir} 3.1/K _{ir} 3.4 modified by ethanol [see details in section for K _{ir} 3.2 (Table 7)]
Inhibitors	G _α subunits (by binding G _{βγ} subunits), ¹⁰ protein kinase C ^{11,12}
Blockers	Nonselective: Ba ²⁺ , Cs ⁺ [see details in section for K _{ir} 3.2 (Table 7)]
Radioligands	None
Channel distribution	Olfactory bulb (piriform cortex), neocortex (layers 2–6), hippocampus (dentate gyrus granule cells), basal ganglia (habenula), thalamus midbrain (inferior colliculus), cerebellum (granule cell layer), brainstem (pontine nucleus), atrium ^{3,13}
Physiological functions	Receptor-dependent hyperpolarization of membrane potential
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	K _{ir} 3.1 is not functional by itself; in the heart, the major form is K _{ir} 3.1/3.4 heteromultimer ¹⁴ —in the brain, it is K _{ir} 3.1/3.2 ¹⁵ ; the functional expression of K _{ir} 3.1 alone in <i>Xenopus</i> oocytes is due to the coassembly with the endogenous <i>Xenopus</i> K _{ir} 3 subunit (K _{ir} 3.5) ⁵

aa, amino acids; chr., chromosome.

- Schoots O, Yue KT, MacDonald JF, Hampson DR, Nobrega JN, Dixon LM, and Van Tol HH (1996) Cloning of a G-protein activated inwardly rectifying potassium channel from human cerebellum. *Brain Res Mol Brain Res* **39**:23–30.
- Karschin C, Dissmann E, Stühmer W, and Karschin A (1996) IRK1–3 and GIRK1–4 inwardly rectifying K⁺ channels are differentially expressed in the adult and developing rat CNS. *J Neurosci* **16**: 3559–3571.
- Kubo Y, Reuveny E, Slesinger PA, Jan YN, and Jan LY (1993) Primary structure and functional expression of a rat G protein coupled muscarinic potassium channel. *Nature (Lond)* **364**:802–806.
- Dascal N, Schreibmayer W, Lim NF, Wang W, Chavkin C, Dimangno L, Labarca C, Kieffer BL, Gaveriaux-Ruff C, Trollinger D, et al. (1993) Atrial G protein-activated K⁺ channel: expression cloning and molecular properties. *Proc Natl Acad Sci USA* **90**:10235–10239.
- Hedin KE, Lim NF, and Clapham DE (1996) Cloning of a *Xenopus laevis* inwardly rectifying K⁺ channel subunit that permits GIRK1 expression of IKACH currents in oocytes. *Neuron* **16**:423–429.
- Reuveny E, Slesinger PA, Inglese J, Morales JM, Iniguez-Lluhi JA, Lefkowitz RJ, Bourne HR, Jan YN, and Jan LY (1994) Activation of the cloned muscarinic potassium channel by G protein βγ subunits. *Nature (Lond)* **370**:143–146.
- Wickman KD, Iniguez-Lluhi JA, Davenport PA, Taussig R, Krapivinsky GB, Linder ME, Gilman AG, and Clapham DE (1994) Recombinant G-protein βγ-subunits activate the muscarinic-gated atrial potassium channel. *Nature (Lond)* **368**:255–257.
- Kurachi Y (1995) G protein regulation of cardiac muscarinic potassium channel. *Am J Physiol* **269**:C821–C830.
- Saitoh O, Masuho I, Terakawa I, Nomoto S, Asano T, and Kubo Y (2001) Regulator of G protein signaling 8 (RGS8) requires its NH₂ terminus for subcellular localization and acute desensitization of G protein-gated K⁺ channels. *J Biol Chem* **276**:5052–5058.
- Schreibmayer W, Dessauer CW, Vorobiov D, Gilman AG, Lester HA, Davidson N, and Dascal N (1996) Inhibition of an inwardly rectifying K⁺ channel by G-protein α-subunits. *Nature (Lond)* **380**:624–627.
- Hill JJ and Peralta EG (2001) Inhibition of a G_i-activated potassium channel (GIRK1/4) by the G_q-coupled m1 muscarinic acetylcholine receptor. *J Biol Chem* **276**:5505–5510.
- Mao J, Wang X, Chen F, Wang R, Rojas A, Shi Y, Piao H, and Jiang C (2004) Molecular basis for the inhibition of G protein-coupled inward rectifier K⁺ channels by protein kinase C. *Proc Natl Acad Sci USA* **101**:1087–1092.
- Karschin C, Dissmann E, Stumer W, and Karschin A (1996) IRK(1–3) and GIRK(1–4) inwardly rectifying K⁺ channel mRNAs are differentially expressed in the adult rat brain. *J Neurosci* **16**: 3559–3570.
- Krapivinsky G, Gordon E, Wickman K, Velimirovic B, Krapivinsky L, and Clapham DE (1995) The G protein-gated atrial K⁺ channel IKACH is a heteromultimer of two inwardly rectifying K⁺ channel proteins. *Nature (Lond)* **374**:135–141.
- Lesage F, Guillemare E, Fink M, Duprat F, Heurteaux C, Fosset M, Romey G, Barhanin J, and Lazdunski M (1995) Molecular properties of neuronal G-protein-activated inwardly rectifying K⁺ channels. *J Biol Chem* **270**:28660–28667.

TABLE 7
 $K_{ir,3.2}$ channels

Channel name	$K_{ir,3.2}$
Description	G-protein gated, inwardly rectifying potassium channel $K_{ir,3.2}$ subunit
Other names	GIRK2, hiGIRK2
Molecular information	Human (KCNJ6): 423aa, Locus ID: 3763, GenBank: U24660, U52153, NM_002240, PMID: 7592809, ¹ 10659995, ² chr. 21q22.13-q22.2 Rat (Kcnj6): 414aa, Locus ID: 25743, GenBank: AB073753, NM_013192, PMID: 11883954, ³ chr. 11q21 Mouse (Kcnj6): 414aa, Locus ID: 16522, GenBank: U37253, NM_010606, PMID: 7499385, ⁴ chr. 16, 68.75 centimorgans
Associated subunits	$K_{ir,3.1}$, $K_{ir,3.3}$, and $K_{ir,3.4}$ to form heteromeric channels; no auxiliary subunit is reported
Functional assays	Voltage-clamp
Current	I_{GIRK}
Conductance	30pS for $K_{ir,3.2c}$ homomeric channel in 150 mM symmetric K^+ , ⁵ 32pS for $K_{ir,3.2d}$ in 140 mM symmetric K^+ , ⁶ 35–37pS for $K_{ir,3.2}/K_{ir,3.1}$ heteromeric channel in 150 mM symmetric K^+ , ⁵ 31pS for $K_{ir,3.2}/K_{ir,3.3}$ in 140 mM symmetric K^+ ⁷
Ion selectivity	K^{+8}
Activation	G protein $\beta\gamma$ subunits EC_{50} : 53 nM for $K_{ir,3.2}/K_{ir,3.3}$ ⁷
Inactivation	Voltage- and RGS protein-dependent ^{9,10}
Activators	G protein $\beta\gamma$ subunits (EC_{50} , not established), PIP_2 (EC_{50} , not established ¹¹), sodium (EC_{50} to $K_{ir,3.2c}$ homomeric channel, 37 mM; EC_{50} to $K_{ir,3.2c}/K_{ir,3.1}$, 27 mM ¹²), ethanol ($K_{ir,3.2}$ -containing K_{ir} channel is reported to be sensitive to ethanol compared with the others (100 mM ethanol increases the basal current amplitude of either $K_{ir,3.2}$ or $K_{ir,3.2}/K_{ir,3.1}$ by about 40% ^{13,14})
Gating inhibitors	G protein α subunits by binding G protein $\beta\gamma$ subunits ¹⁵
Blockers	Ba^{2+} (not established), Cs^+ (not established), tertiapin (IC_{50} to $K_{ir,3.2d}$, 7 nM; to $K_{ir,3.1}/K_{ir,3.2d}$, 5.4 nM ¹⁶), halothane (IC_{50} to $K_{ir,3.2}$, 60 μM ¹⁷), 1-chloro-1,2,2-trifluorocyclobutane (IC_{50} not assigned by the authors ¹⁸), bupivacaine (K_i to $K_{ir,3.2}$, 500 μM ; K_i to $K_{ir,3.1}/K_{ir,3.2}$, 107 μM ¹⁹), antipsychotic drug (IC_{50} to $K_{ir,3.1}/K_{ir,3.2}$ for haloperidol, 75.5 μM ; for thioridazine, 57.6 μM ; for pimozide, 2.96 μM ; for clozapine, 179 μM ²⁰), fluoxetine (Prozac) (IC_{50} to $K_{ir,3.2}$, 89.5 μM ; to $K_{ir,3.1}/K_{ir,3.2}$, 16.9 μM ²¹), SCH23390; IC_{50} to $K_{ir,3.1}/K_{ir,3.2}$, 7.8 μM ; to $K_{ir,3.2}$, 83 μM ²²), Verapamil (IC_{50} to $K_{ir,3.1}/K_{ir,3.2}$, 120 μM ²³), MK-801 (IC_{50} to $K_{ir,3.1}/K_{ir,3.2}$, 200 μM ²³), QX-314 (IC_{50} to $K_{ir,3.1}/K_{ir,3.2}$, 200 μM ²³)
Radioligands	None
Channel distribution	Distribution of $K_{ir,3.2}$ is related to the expression of the isoforms; at least seven exons contribute to produce alternative splicing variants ^{6,24,25} ; at least four splice variants are known (numbers in parentheses are GenBank accession numbers and PMID accession numbers, respectively); $K_{ir,3.2a}$ (rat: AB07375, ⁴ 11883954 ³ ; mouse: U11859, 7926018 ⁴) is specifically expressed in brain ²⁶ and exists as a channel in heterologous complex with either $K_{ir,3.1}$ (throughout the brain ²⁷) or $K_{ir,3.2c}$ (dopaminergic neurons in substantia nigra ²⁸); $K_{ir,3.2b}$ (rat: AB07375, ⁶ 11883954 ³ ; mouse: D86040, 8573147 ²⁹) is ubiquitously expressed; $K_{ir,3.2c}$ (human: U24660, 7592809, ¹ rat: AB07375, ³ 11883954 ³ ; mouse: U37253, 7499385 ³⁰) is expressed in the brain and exists as a heterologous channel in the complex with either $K_{ir,3.1}$ (throughout the brain ²⁷) or $K_{ir,3.2a}$ (dopaminergic neurons in substantia nigra ²⁸); in pancreatic α -cells, $K_{ir,3.2c}$ coexpresses with $K_{ir,3.4}$ ³¹ ; $K_{ir,3.2d}$ (mouse: AB02950, ² 10562331 ⁶) shows specific expression in testis and behaves as a homomeric channel ⁶ ; in the brain, some parts of $K_{ir,3.2}$ isoforms exist as a complex not only with $K_{ir,3.1}$ but also with $K_{ir,3.3}$ ^{7,32} and $K_{ir,3.4}$ ³⁰
Physiological functions	$K_{ir,3.2}$ participates in the formation of the slow inhibitory postsynaptic potential ^{28,33} and probably in the presynaptic inhibition in the brain; in the endocrine organs, neurotransmitters induce hyperpolarization of the membrane potential and lead to the inhibition of hormone secretion ^{31,34} ; $K_{ir,3.2d}$ possibly involves in spermatogenesis ⁶
Mutations and pathophysiology	Weaver (WV) mouse has been isolated to have a natural mutation at a glycine to serine at residue 156 ³⁵ ; the mutant channel permits ion flow for both potassium and sodium ions ⁸ and reduces the sensitivity to G protein $\beta\gamma$ subunit ³⁶ ; $K_{ir,3.2}$ -null mice show the spontaneous tonic-clonic seizures ³³ ; an immunocytochemical study suggested that expression of the mutated channel is not a sufficient condition to induce cell death in the ventral mesencephalon of the <i>wv/wv</i> mice ³⁷
Pharmacological significance	Not established

aa, amino acids; chr., chromosome; SCH23390, *R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride; MK-801, (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzol*a,d*cyclohepten-5,10-imine; QX-314, *N*-(2,6-dimethylphenyl)carbamoylmethyltriethylammonium.

1. Ferrer J, Nichols CG, Makhina EN, Salkoff L, Bernstein J, Gerhard D, Wasson J, Ramanadham S, and Permutt A (1995) Pancreatic islet cells express a family of inwardly rectifying K^+ channel subunits which interact to form G-protein-activated channels. *J Biol Chem* **270**:26086–26091.

2. Schoots O, Wilson JM, Ethier N, Bigras E, Hebert T, and Val Tol HH (1999) Co-expression of human Kir3 subunits can yield channels with different functional properties. *Cell Signal* **11**: 871–883.

3. Suda S, Nibuya M, Suda H, Takamatsu K, Miyazaki T, Nomura S, and Kawai N (2002) Potassium channel mRNAs with AU-rich elements and brain specific expression. *Biochem Biophys Res Commun* **291**:1265–1271.

4. Lesage F, Duprat F, Fink M, Guillemare E, Coppola T, Lazdunski M, and Hugnot JP (1994) Cloning provides evidence for a family of inward rectifier and G-protein coupled K^+ channels in the brain. *FEBS Lett* **353**:37–42.

5. Kofuji P, Davidson N, and Lester HA (1995) Evidence that neuronal G-protein-gated inwardly rectifying K^+ channels are activated by $G\beta\gamma$ subunits and function as heteromultimers. *Proc Natl Acad Sci USA* **92**:6542–6546.

6. Inanobe A, Horio Y, Fujita A, Tanemoto M, Hibino H, Inageda K, and Kurachi Y (1999) Molecular cloning and characterization of a novel splicing variant of the Kir3.2 subunit predominantly expressed in mouse testis. *J Physiol* **521**:19–30.

7. Jelacic TM, Kennedy ME, Wickman K, and Clapham DE (2000) Functional and biochemical evidence for G-protein-gated inwardly rectifying K⁺ channels composed of GIRK2 and GIRK3. *J Biol Chem* **275**:36211–36216.
8. Slesinger PA, Patil N, Liao YJ, Jan YN, Jan LY, and Cox DR (1996) Functional effects of the mouse *weaver* mutation on G protein-gated inwardly rectifying K⁺ channels. *Neuron* **16**:321–331.
9. Doupnik CA, Davidson N, Lester HA, and Kofuji P (1997) RGS proteins reconstitute the rapid gating kinetics of Gβγ-activated inwardly rectifying K⁺ channels. *Proc Natl Acad Sci USA* **94**:10461–10466.
10. Saitoh O, Kubo Y, Miyatani Y, Asano T, and Nakata H (1997) RGS8 accelerates G-protein-mediated modulation of K⁺ currents. *Nature (Lond)* **390**:525–529.
11. Huang C-L, Feng S, and Hilgemann DW (1998) Direct activation of inward rectifier potassium channels by PIP₂ and its stabilization by Gβγ. *Nature (Lond)* **391**:803–806.
12. Ho IH and Murrell-Lagnado RD (1999) Molecular determinants for sodium-dependent activation of G protein-gated K⁺ channels. *J Biol Chem* **274**:8639–8648.
13. Lewohl JM, Wilson WR, Mayfield RD, Brozowski SJ, Morrisett RA, and Harris RA (1999) G-protein-coupled inwardly rectifying potassium channels are targets of alcohol action. *Nat Neurosci* **2**:1084–1090.
14. Kobayashi T, Ikeda K, Kojima H, Niki H, Yano R, Yoshioka T, and Kumanishi T (1999) Ethanol opens G-protein-activated inwardly rectifying K⁺ channels. *Nat Neurosci* **2**:1091–1097.
15. Peleg S, Varon D, Ivanina T, Dessauer CW, and Dascal N (2002) Gα_i controls the gating of the G protein-activated K⁺ channel GIRK. *Neuron* **33**:87–99.
16. Matsushita K, Fujita A, Makino Y, Fujita S, Tanemoto M, and Kurachi Y (2000) Effect of bee toxin tertiapin on cloned inwardly rectifying potassium channels. *Jpn J Pharmacol* **82**(Suppl. 1):130P.
17. Weigl LG and Schreiber W (2001) G protein-gated inwardly rectifying potassium channels are targets for volatile anesthetics. *Mol Pharmacol* **60**:282–289.
18. Yamakura T, Lewohl JM, and Harris RA (2001) Differential effects of general anesthetics on G protein-coupled inwardly rectifying and other potassium channels. *Anesthesiology* **95**:144–153.
19. Zhou W, Arrabit C, Choe S, and Slesinger PA (2001) Mechanism underlying bupivacaine inhibition of G protein-gated inwardly rectifying K⁺ channels. *Proc Natl Acad Sci USA* **98**:6482–6487.
20. Kobayashi T, Ikeda K, and Kumanishi T (2000) Inhibition by various antipsychotic drugs of the G-protein-activated inwardly rectifying K⁺ (GIRK) channels expressed in *Xenopus* oocytes. *Br J Pharmacol* **129**:1716–1722.
21. Kobayashi T, Washiyama K, and Ikeda K (2003) Inhibition of G protein-activated inwardly rectifying K⁺ channels by fluoxetine (Prozac). *Br J Pharmacol* **138**:1119–1128.
22. Kuzhikandathil EV and Oxford GS (2002) Classic D1 dopamine receptor antagonist R-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390) directly inhibits G protein-coupled inwardly rectifying potassium channels. *Mol Pharmacol* **62**:119–126.
23. Kofuji P, Hofer M, Millen KJ, Millonig JH, Davidson N, Lester HA, and Hatten ME (1996) Functional analysis of the *weaver* mutant GIRK2 K⁺ channel and rescue of *weaver* granule cells. *Neuron* **16**:941–952.
24. Wei J, Hodes ME, Piva R, Feng Y, Wang Y, Ghetti B, and Dlouhy SR (1998) Characterization of murine *Girk2* transcript isoforms: structure and differential expression. *Genomics* **51**:379–390.
25. Wickman K, Pu WT, and Clapham DE (2002) Structural characterization of the mouse *Girk* genes. *Gene* **284**:241–250.
26. Murer G, Adelbrecht C, Lauritzen I, Lesage F, Lazdunski M, Agid Y, and Raisman-Vozari R (1997) An immunocytochemical study on the distribution of two G-protein-gated inward rectifier potassium channels (GIRK2 and GIRK4) in the adult rat brain. *Neuroscience* **80**:345–357.
27. Liao YJ, Jan YN, and Jan LY (1996) Heteromultimerization of G-protein-gated inwardly rectifying K⁺ channel proteins GIRK1 and GIRK2 and their altered expression in *weaver* brain. *J Neurosci* **16**:7137–7150.
28. Inanobe A, Yoshimoto Y, Horio Y, Morishige K, Hibino H, Matsumoto S, Tokunaga Y, Maeda T, Hata Y, Takai Y, et al. (1999) Characterization of G-protein-gated K⁺ channels composed of Kir3.2 subunits in dopaminergic neurons of the substantia nigra. *J Neurosci* **19**:1006–1017.
29. Isomoto S, Kondo C, Takahashi N, Matsumoto S, Yamada M, Takumi T, Horio Y, and Kurachi Y (1996) A novel ubiquitously distributed isoform of GIRK2 (GIRK2B) enhances GIRK1 expression of the G-protein-gated K⁺ current in *Xenopus* oocytes. *Biochem Biophys Res Commun* **218**:286–291.
30. Lesage F, Guillemare E, Fink M, Duprat F, Heurteaux C, Fosset M, Romey G, Barhanin J, and Lazdunski M (1995) Molecular properties of neuronal G-protein-activated inwardly rectifying K⁺ channels. *J Biol Chem* **270**:28660–28667.
31. Yoshimoto Y, Fukuyama Y, Horio Y, Inanobe A, Gotoh M, and Kurachi Y (1999) Somatostatin induces hyperpolarization in pancreatic islet α cells by activating a G protein-gated K⁺ channel. *FEBS Lett* **444**:265–269.
32. Torrecilla M, Marker CL, Cintora SC, Stoffel M, Williams JT, and Wickman K (2002) G-protein-gated potassium channels containing Kir3.2 and Kir3.3 subunits mediate the acute inhibitory effects of opioids on locus ceruleus neurons. *J Neurosci* **22**:4328–4334.
33. Signorini S, Liao YJ, Duncan SA, Jan LY, and Stoffel M (1997) Normal cerebellar development but susceptibility to seizures in mice lacking G protein-coupled inwardly rectifying K⁺ channel GIRK2. *Proc Natl Acad Sci USA* **94**:923–927.
34. Morishige K, Inanobe A, Yoshimoto Y, Kurachi H, Murata Y, Tokunaga Y, Maeda T, Maruyama Y, and Kurachi Y (1999) Secretagogue-induced exocytosis recruits G protein-gated K⁺ channels to plasma membrane in endocrine cells. *J Biol Chem* **274**:7969–7974.
35. Patil N, Cox DR, Bhar D, Faham M, Myers RM, and Peterson AS (1995) A potassium channel mutation in *weaver* mice implicates membrane excitability in granule cell differentiation. *Nat Genet* **11**:126–129.
36. Navarro B, Kennedy ME, Velimirović B, Bhat D, Peterson AS, and Clapham DE (1996) Nonselective and Gβγ-insensitive *weaver* K⁺ channels. *Science* **272**:1950–1953.
37. Adelbrecht C, Murer MG, Lauritzen I, Lesage F, Lazdunski M, Agid Y, and Raisman-Vozari R (1997) An immunocytochemical study of a G-protein-gated inward rectifier K⁺ channel (GIRK2) in the *weaver* mouse mesencephalon. *NeuroReport* **8**:969–974.

TABLE 8
K_{ir}3.3 channels

Channel name	$K_{ir}3.3$
Description	G-protein gated, inwardly rectifying potassium channel $K_{ir}3.3$ subunit
Other names	GIRK3
Molecular information	Human (KCNJ9): 393aa, Locus ID: 3765, GenBank: AF193615, NM_004983, PMID: 8575783, ¹ chr. 1q21-23 Rat (Kcnj9): 393aa, Locus ID: 116560, GenBank: L77929, NM_053834, PMID: 8670302, ² chr. 13q24 Mouse (Kcnj9): 393aa, Locus ID: 16524, GenBank: AF130860, NM_008429, PMID: 7926018, ³ 10341034 ⁴
Associated subunits	$K_{ir}3.1$, $K_{ir}3.2$
Functional assays	Voltage-clamp
Current	I_{GIRK}
Conductance	39pS for $K_{ir}3.3/K_{ir}3.1$; 31pS for $K_{ir}3.3/K_{ir}3.2$
Ion selectivity	K^+
Activation	$G_{\beta\gamma}$ subunits at 1 to 50 nM
Inactivation	Not established
Activators	$G_{\beta\gamma}$ subunits, modified by PIP_2 , sodium
Gating inhibitors	G_{α} subunits by binding $G_{\beta\gamma}$ subunits
Blockers	None
Radioligands	None
Channel distribution	Brain
Physiological functions	Receptor-dependent hyperpolarization of membrane potential
Mutations and pathophysiology	Candidate gene for type 2 diabetes mellitus
Pharmacological significance	Not established

aa, amino acids; chr., chromosome.

1. Lesage F, Fink M, Barhanin J, Lazdunski M, and Matti MG (1995) Assignment of human G-protein-coupled inward rectifier K^+ channel homolog GIRK3 gene to chromosome 1q21-q23. *Genomics* **29**:808–809.

2. Dissmann E, Wischmeyer E, Spauschus A, Karschin C, and Karschin A (1996) Cloning and functional expression and cellular localization of a rat brain G protein-activated K^+ inward rectifier GIRK3. *Biochem Biophys Res Commun* **223**:474–479.

3. Lesage F, Duprat F, Fink M, Guillemare E, Coppola T, Lazdunski M, and Hugnot JP (1994) Cloning provides evidence for a family of inward rectifier and G-protein coupled K^+ channels in the brain. *FEBS Lett* **353**:37–42.

4. Jelacic T, Stephen SM, and Clapham DE (1999) Functional expression and characterization of G-protein-gated inwardly rectifying K^+ channels containing GIRK3. *J Membr Biol* **169**:123–129.

TABLE 9
K_{ir}3.4 channels

Channel name	K _{ir} 3.4
Description	G-protein gated, inwardly rectifying potassium channel K _{ir} 3.4 subunit
Other names	GIRK4
Molecular information	Human (KCNJ5): 419aa, Locus ID: 3762, GenBank: L47208, NM_000890, PMID: 8558261, ¹ chr. 11q24 Rat (Kcnj5): 419aa, Locus ID: 29713, GenBank: L35771, NM_017297, PMID: 7877685, ² chr. 8q21 Mouse (Kcnj5): 419aa, Locus ID: 16521, GenBank: U33631, NM_010605, PMID: 7499385, ³ chr. 11q23
Associated subunits	K _{ir} 3.1, K _{ir} 3.2, K _{ir} 3.3, K _{ir} 3.5 ⁴
Functional assays	Voltage-clamp
Current	I _{GIRK}
Conductance	35pS (in symmetrical 140 mM K ⁺)
Ion selectivity	Highly K ⁺ -selective
Activation	G _{βγ} subunits at 1 to 50 nM
Inactivation	Voltage- and RGS protein-dependent
Activators	K _{ir} 3.4 and K _{ir} 3.4-containing GIRK channels are activated by direct binding to the G _{βγ} subunits of PTX-sensitive G proteins; modified by PIP ₂ , sodium
Gating inhibitors	G _α subunits (by binding G _{βγ} subunits)
Blockers	Nonselective: Ba ²⁺ , Cs ⁺ , tetraethylammonium, 4-aminopyridine
Radioligands	None
Channel distribution	Heart atria and other pacemaking tissues, ventricles in human; restricted areas of the brain: islands of Calleja, cerebellum, habenula, cortex, hippocampal pyramidal cells, less in skeletal muscle, urinary bladder, lungs, eyes; for a distribution in rat brain see ref. 5
Physiological functions	Mediates vagal-induced slowing of heart rate by muscarinic acetylcholine M ₂ and G _{α_i} -coupled adenosine and somatostatin receptors; in brain, possibly activated by muscarinic acetylcholine, GABA _B , dopamine D ₂ , 5-HT _{1A} , adenosine, somatostatin, and enkephalin receptors and β ₂ -adrenoceptors
Mutations and pathophysiology	Not established
Pharmacological significance	Atropine blocks M ₂ receptor-mediated activation in heart; adenosine activation is used in the treatment of supraventricular tachycardias
Comments	The <i>Xenopus</i> homolog (U42207) of mammalian K _{ir} 3.4 has been given the nomenclature K _{ir} 3.5 ⁴

aa, amino acids; chr., chromosome; PTX, picrotoxin; 5-HT, 5-hydroxytryptamine.

1. Spauschus A, Lentjes KU, Wischmeyer E, Dissmann E, Karschin C, and Karschin A (1996) A G protein-activated inwardly rectifying K⁺ channel GIRK4 from human hippocampus associates with other GIRK channels. *J Neurosci* **16**:930–942.

2. Krapivinsky G, Gordon E, Wickman K, Velimirovic B, Krapivinsky L, and Clapham DE (1995) The G protein-gated atrial K⁺ channel IKACH is a heteromultimer of two inwardly rectifying K⁺ channel proteins. *Nature (Lond)* **374**:135–141.

3. Lesage F, Guillemare E, Fink M, Duprat F, Heurteaux C, Fosset M, Romey G, Barhamin J, and Lazdunski M (1995) Molecular properties of neuronal G-protein-activated inwardly rectifying K⁺ channels. *J Biol Chem* **270**:28660–28667.

4. Hedin K, Lim N, and Clapham DE (1996) Cloning of *Xenopus laevis* inwardly rectifying K⁺ channel subunit that permits GIRK1 expression of IKACH currents in oocytes. *Neuron* **16**: 423–429.

5. Murer G, Adelbrecht C, Lauritzen I, Lesage F, Lazdunski M, Agid Y, and Raisman-Vozari R (1997) An immunocytochemical study on the distribution of two G-protein-gated inward rectifier potassium channels (GIRK2 and GIRK4) in the adult rat brain. *Neuroscience* **80**:345–357.

TABLE 10
 $K_{ir4.1}$ channels

Channel name	$K_{ir4.1}$
Description	Glial ATP-dependent inward rectifier potassium channel, subfamily J, member 10
Other names	$K_{ir1.2}$, ¹ K_{AB-2} , ² BIR10, ³ BIRK-10, BIRK-1, ⁴ KCNJ13-PEN
Molecular information	Human (KCNJ10): 379aa, Locus ID: 3766, GenBank: U52155, NM_002241, PMID: 8995301, ¹ chr. 1q22-q2 Rat (Kcnj10): 379aa, Locus ID: 29718, GenBank: X83585, X86818, NM_031602, PMID: 7608203, ² 7874445, ³ chr. 13q24 Mouse (Kcnj10): 379aa, Locus ID: 16513, GenBank: AF322631, NM_020269, PMID: 11169792, ⁵ chr. 1, 93.5 centimorgans
Associated subunits	$K_{ir4.2}$, ¹ $K_{ir5.1}$, ⁶ and $K_{ir2.1}$ ⁷ to form heteromeric channels; no auxiliary subunit is reported
Interacting proteins	CIPP, ⁸ α -syntrophin, ⁹ possibly laminin and insulin, ¹⁰ PKA, PKC (C. Lossin and Y. Kurachi, unpublished data)
Functional assays	Voltage-clamp
Current	$I_{Kir4.1}$
Conductance	Various subconductances in homomeric and heteromeric channels; main conductance expression system-dependent: \approx 20pS in 152 mM symmetric K^+ in mammalian cells (C. Lossin and Y. Kurachi, unpublished data), \approx 40pS in oocytes, ¹¹ 40pS for mouse $K_{ir4.1/5.1}$ heteromers in 145 mM symmetric K^+ ¹²
Ion selectivity	K^+
Activation	Constitutively open; enhanced by ATP ²
Inactivation	Voltage-dependent, blocked by Mg^{2+} ⁷ and polyamines ¹³ (putrescine, spermine, and spermidine) at positive potentials
Activators	ATP, PIP_2 (in $K_{ir4.1/5.1}$ heteromers) ¹⁴
Gating inhibitors	None
Blockers	Ba^{2+} (IC_{50} at -100 mV), ¹⁵ human $K_{ir4.1}$: 3 μ M, human 4.1/5.1: 8 μ M; Cs^+ (IC_{50} at -100 mV), ¹⁶ human $K_{ir4.1}$: 460 μ M, human 4.1/5.1: 650 μ M, intracellular H^+ (pK_a as specified below), $K_{ir4.1}$: pK_a 6.0, ¹³ $K_{ir4.1/5.1}$: pK_a 7.5 ¹⁴
Radioligands	None
Channel distribution	Glial, enriched around blood vessels and synapses, ¹⁷ retina, ^{10,18} ear, ¹⁹ kidney ²⁰
Physiological functions	$K_{ir4.1}$ function has been implicated in glial K^+ buffering in the brain in general ¹⁸ and in K^+ homeostasis in the inner ear and the kidney ²¹ ; colocalization with aquaporin-4 proposes a role in water homeostasis ²² ; also suggested is a contribution to oligodendrocyte development and myelination ²³ ; heteromeric $K_{ir4.1/5.1}$ channels have been proposed to act as brainstem CO_2 sensors ¹⁴
Mutations and pathophysiology	Knockout of $K_{ir4.1}$ results in retinal defects, ²⁴ loss of the endocochlear potential ²⁵ with an otherwise normal phenotype; various studies have identified <i>KCNJ10</i> as a possible epilepsy locus conferring susceptibility ²⁶ or resistance ²⁷ to hyperexcitability
Pharmacological significance	Not established
Comments	The salmon homolog (D83537) of mammalian $K_{ir4.1}$ has been given the nomenclature $K_{ir4.3}$ ²⁸

aa, amino acids; chr., chromosome; PKA, protein kinase A; protein kinase C.

- Shuck ME, Piser TM, Bock JH, Slightom JL, Lee KS, and Bienkowski MJ (1997) Cloning and characterization of two K^+ inward rectifier (Kir) 1.1 potassium channel homologs from human kidney (Kir1.2 and Kir1.3). *J Biol Chem* **272**:586–593.
- Takumi T, Ishii T, Horio Y, Morishige K, Takahashi N, Yamada M, Yamashita T, Kiyama H, Sohmiya K, Nakanishi S, and Kurachi Y (1995) A novel ATP-dependent inward rectifier potassium channel expressed predominantly in glial cells. *J Biol Chem* **270**:16339–16346.
- Bond CT, Pessia M, Xia XM, Lagrutta A, Kavanaugh MP, and Adelman JP (1994) Cloning and expression of a family of inward rectifier potassium channels. *Receptors Channels* **2**:183–191.
- Bredt DS, Wang TL, Cohen NA, Guggino WB, and Snyder SH (1995) Cloning and expression of two brain-specific inwardly rectifying potassium channels. *Proc Natl Acad Sci USA* **92**:6753–6757.
- Li L, Head V, and Timpe LC (2001) Identification of an inward rectifier potassium channel gene expressed in mouse cortical astrocytes. *Glia* **33**:57–71.
- Pearson WL, Dourado M, Schreiber M, Salkoff L, and Nichos CG (1999) Expression of a functional Kir4 family inward rectifier K^+ channel from a gene cloned from mouse liver. *J Physiol* **514**:639–653.
- Fakler B, Bond CT, Adelman JP, and Ruppersberg JP (1996) Heterooligomeric assembly of inward-rectifier K^+ channels from subunits of different subfamilies: Kir2.1 (IRK1) and Kir4.1 (BIR10). *Pflug Arch Eur J Physiol* **433**:77–83.
- Kurschner C, Mermelstein PG, Holden WT, and Surmeier DJ (1998) CIPP, a novel multivalent PDZ domain protein, selectively interacts with Kir4.0 family members, NMDA receptor subunits, neurexins, and neuroligins. *Mol Cell Neurosci* **11**:161–172.
- Connors NC, Adams ME, Froehner SC, and Kofuji P (2004) The potassium channel Kir4.1 associates with the dystrophin-glycoprotein complex via α -syntrophin in glia. *J Biol Chem* **279**:28387–28392.
- Ishii M, Horio Y, Tada Y, Hibino H, Inanobe A, Ito M, Yamada M, Gotow T, Uchiyama Y, and Kurachi Y (1997) Expression and clustered distribution of an inwardly rectifying potassium channel $K_{AB-2}/Kir4.1$ on mammalian retinal Müller cell membrane: their regulation by insulin and laminin signals. *J Neurosci* **17**:7725–7735.
- Pessia M, Tucker SJ, Lee K, Bond CT, and Adelman JP (1996) Subunit positional effects revealed by novel heteromeric inwardly rectifying K^+ channels. *EMBO J* **15**:2980–2987.
- Lourdel S, Paulais M, Cluzeaud F, Bens M, Tanemoto M, Kurachi Y, Vandewalle A, and Teulon J (2002) An inward rectifier K^+ channel at the basolateral membrane of the mouse distal convoluted tubule: similarities with Kir4.1-Kir5.1 heteromeric channels. *J Physiol* **538**:391–404.
- Lopatin AN, Makhina EN, and Nichols CG (1994) Potassium channel block by cytoplasmic polyamines as the mechanism of intrinsic rectification. *Nature (Lond)* **372**:366–369.
- Yang Z, Xu H, Cui N, Qu Z, Chanchevalap S, Shen W, and Jiang C (2000) Biophysical and molecular mechanisms underlying the modulation of heteromeric Kir4.1-Kir5.1 channels by CO_2 and pH. *J Gen Physiol* **116**:33–45.
- Hagiwara S, Miyazaki S, Moody W, and Patlak J (1978) Blocking effects of barium and hydrogen ions on the potassium current during anomalous rectification in the starfish egg. *J Physiol* **279**:167–185.
- Hagiwara S, Miyazaki S, and Rosenthal NP (1976) Potassium current and the effect of cesium on this current during anomalous rectification of the egg cell membrane of a starfish. *J Gen Physiol* **67**: 621–638.
- Higashi K, Fujita A, Inanobe A, Tanemoto M, Doi K, Kubo T, and Kurachi Y (2001) An inwardly rectifying K^+ channel, Kir4.1, expressed in astrocytes surrounds synapses and blood vessels in brain. *Am J Physiol Cell Physiol* **281**:C922–C931.

18. Brew H, Gray PT, Mobbs P, and Attwell D (1986) End feet of retinal glial cells have higher densities of ion channels that mediate K^+ buffering. *Nature (Lond)* **324**:466–468.
19. Hibino H, Horio Y, Fujita A, Inanobe A, Doi K, Gotow T, Uchiyama Y, Kubo T, and Kurachi Y (1999) Expression of an inwardly rectifying K^+ channel, Kir4.1, in satellite cells of rat cochlear ganglia. *Am J Physiol* **277**:C638–C644.
20. Ito M, Inanobe A, Horio Y, Hibino H, Isomoto S, Ito H, Mori K, Tonosaki A, Tomoike H, and Kurachi Y (1996) Immunolocalization of an inwardly rectifying K^+ channel K_{AB-2} (Kir4.1), in the basolateral membrane of renal distal tubular epithelia. *FEBS Lett* **388**:11–15.
21. Fujita A, Horio Y, Higashi K, Mouri T, Hata F, Takeguchi N, and Kurachi Y (2002) Specific localization of an inwardly rectifying K^+ channel, Kir4.1, at the apical membrane of rat gastric parietal cells; its possible involvement in K^+ recycling for the H^+ - K^+ -pump. *J Physiol* **540**:85–92.
22. Nagelhus EA, Horio Y, Inanobe A, Fujita A, Haug FM, Nielsen S, Kurachi Y, and Ottersen OP. Immunogold evidence suggests that coupling of K^+ siphoning and water transport in rat retinal Müller cells is mediated by a coenrichment of Kir4.1 and AQP4 in specific membrane domains. *Glia* **26**:47–54.
23. Neusch C, Rozengurt N, Jacobs RE, Lester HA, and Kofuji P (2001) Kir4.1 potassium channel subunit is crucial for oligodendrocyte development and in vivo myelination. *J Neurosci* **21**:5429–5438.
24. Kofuji P, Ceelen P, Zahs KR, Surbeck LW, Lester HA, and Newman EA (2000) Genetic inactivation of an inwardly rectifying potassium channel (Kir4.1 subunit) in mice: phenotypic impact in retina. *J Neurosci* **20**:5733–5740.
25. Wangemann P, Itza EM, Albrecht B, Wu T, Jabba SV, Maganti RJ, Lee JH, Everett LA, Wall SM, Royaux IE, et al. (2004) Loss of KCNJ10 protein expression abolishes endocochlear potential and causes deafness in Pendred syndrome mouse model. *BMC Med* **2**:30.
26. Ferraro TN, Golden GT, Smith GG, Martin JF, Lohoff FW, Gieringer TA, Zamboni D, Schwebel CL, Press DM, Kratzer SO, et al. (2004) Fine mapping of a seizure susceptibility locus on mouse chromosome 1: nomination of Kcnj10 as a causative gene. *Mamm Genome* **15**:239–251.
27. Buono RJ, Lohoff FW, Sander T, Sperling MR, O'Connor MJ, Dlugos DJ, Ryan SG, Golden GT, Zhao H, Scattergood TM, et al. (2004) Association between variation in the human KCNJ10 potassium ion channel gene and seizure susceptibility. *Epilepsy Res* **58**:175–83.
28. Kubo Y, Miyashita T, and Kubokawa K (1996) A weakly inward rectifying potassium channel of the salmon brain. *J Biol Chem* **271**:15729–15735.

TABLE 11
K_{ir}4.2 channels

Channel name	$K_{ir}4.2$
Description	Inwardly rectifying potassium channel $K_{ir}4.2$ subunit
Other names	$K_{ir}1.3$, IRKK
Molecular information	Human (KCNJ15): 375aa, Locus ID: 3772, GenBank: Y10745, NM_002243, PMID: 8995301, ¹ chr. 21q22.2 Rat (Kcnj15): 375 or 405aa, Locus ID: 170847, GenBank: AY028455, NM_133321, PMID: 11804844, ² chr. 11q11 Mouse (Kcnj15): 375aa, Locus ID: 16516, GenBank: AF085696, NM_019664, PMID: 9882736, ³ chr. 16, 69.1 centimorgans
Associated subunits	Reported to interact with $K_{ir}1.1$ (inhibits) and $K_{ir}5.1$ (forms novel channels) when coexpressed in heterologous expression systems
Functional assays	Voltage-clamp
Current	Inwardly rectifying K^+ current
Conductance	25.2pS (120 mM K^+) ⁴
Ion selectivity	K^+
Activation	Not established
Inactivation	Intracellular acidification
Activators	None
Gating inhibitors	None
Blockers	Nonselective: Ba^{2+} , Cs^+
Radioligands	None
Channel distribution	Kidney (cortex), pancreas, liver (hepatocyte basolateral membrane), lung, testes
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Two splice variants have been identified in rat: $K_{ir}4.2$ (375aa) and $K_{ir}4.2a$ (405aa)

aa, amino acids; chr., chromosome.

1. Shuck ME, Piser TM, Bock JH, Slightom JL, Lee KS, and Bienkowski MJ (1997) Cloning and characterization of two K^+ inward rectifier (Kir) 11 potassium channel homologs from human kidney (Kir1.2 and Kir1.3). *J Biol Chem* **272**:586–593.

2. Hill CE, Briggs MM, Liu J, and Magtanong L (2002) Cloning expression and localization of a rat hepatocyte inwardly rectifying potassium channel. *Am J Physiol Gastrointest Liver Physiol* **282**:G233–G240.

3. Pearson WL, Dourrado M, Schreiber M, Salkoff L, and Nichols CG (1999) Expression of a functional Kir4 family inward rectifier K^+ channel from a gene cloned from mouse liver. *J Physiol* **514**:639–653.

4. Pessia M, Imbrici P, D'Adamo MC, Salvatore L, and Tucker SJ (2001) Differential pH sensitivity of Kir4.1 and Kir4.2 potassium channels and their modulation by heteropolymerisation with Kir5.1. *J Physiol* **532**:359–367.

TABLE 12
K_{ir}5.1 channels

Channel name	$K_{ir}5.1$
Description	Inwardly rectifying potassium channel $K_{ir}5.1$ subunit
Other names	BIR 9 ¹
Molecular information	Human (KCNJ16): 418aa, Locus ID: 3773, GenBank: AF179353, NM_018658, chr. 17q23.1-24.2 Rat (Kcnj16): 419aa, Locus ID: 29719, GenBank: X83581, AF249676, NM_053314, PMID: 7874445, ¹ 10764726, ² chr. 10q32.1 Mouse: 418aa, Locus ID: 16517, GenBank: AB016197, NM_010604, PMID: 9806850, ³ chr. 11, 71.0 centimorgans
Associated subunits	$K_{ir}4.1$, $K_{ir}4.2$ ⁴ associates with PSD-95 to form functional homomeric channels ⁵
Functional assays	Voltage-clamp in <i>Xenopus</i> oocytes, HEK293 cells
Current	Inwardly rectifying K^+ current
Conductance	54pS when coexpressed with $K_{ir}4.2$ (120 mM K^+) ⁴
Ion selectivity	K^+
Activation	Not established
Inactivation	Not established
Activators	None
Gating inhibitors	Protein kinase A phosphorylation ⁵
Blockers	Nonselective: Ba^{2+} , Cs^+ ; intracellular H^+ for $K_{ir}5.1/K_{ir}4.1$
Radioligands	None
Channel distribution	Convulved tubule cells of the kidney, pancreatic acinar and ductal cells, thyroid gland, ⁶ Müller cells and GABAergic amacrine cells of the retina, ⁷ spiral ligament of the cochlear lateral wall, ⁸ spleen, adrenal gland, liver, testis, ¹ and regions of the brain including forebrain and olfactory astrocytes, ⁹ brainstem nuclei; locus coeruleus, mesencephalic trigeminal nucleus, hypoglossal nucleus ¹⁰ and pontine nucleus ¹¹
Physiological functions	pH sensing ²
Mutations and pathophysiology	Not established
Pharmacological significance	Not established

aa, amino acids; chr., chromosome; HEK, human embryonic kidney.

1. Bond CT, Pessia M, Xia XM, Lagrutta A, Kavanaugh MP, and Adelman JP (1994) Cloning and expression of a family of inward rectifier potassium channels. *Receptors Channels* **2**:183–191. [Erratum in *Receptors Channels* (1994) **2**:following 350.]

2. Tucker SJ, Imbrici P, Salvatore L, D'Adamo MC, and Pessia M (2000) pH dependence of the inwardly rectifying potassium channel Kir5.1 and localization in renal tubular epithelia. *J Biol Chem* **275**:16404–16407.

3. Mouri T, Kittaka N, Horio Y, Copeland NG, Gilbert DJ, Jenkins NA, and Kurachi Y (1998) Assignment of mouse inwardly rectifying potassium channel kcnj16 to the distal region of mouse chromosome 11. *Genomics* **54**:181–182.

4. Pessia M, Imbrici P, D'Adamo MC, Salvatore L, and Tucker SJ (2001) Differential pH sensitivity of Kir4.1 and Kir4.2 potassium channels and their modulation by heteropolymerisation with Kir5.1. *J Physiol* **532**:359–367.

5. Tanemoto M, Fujita A, Higashi K, and Kurachi Y (2002) PSD-95 mediates formation of a functional homomeric Kir5.1 channel in the brain. *Neuron* **34**:387–397.

6. Liu Y, McKenna E, Figueroa DJ, Blevins R, Austin CP, Bennett PB, and Swanson R (2000) The human inward rectifier K^+ channel subunit Kir5.1 (KCNJ16) maps to chromosome 17q25 and is expressed in kidney and pancreas. *Cytogenet Cell Genet* **90**:60–63.

7. Ishii M, Fujita A, Iwai K, Kusaka S, Higashi K, Inanobe A, Hibino H, and Kurachi Y (2003) Differential expression and distribution of Kir5.1 and Kir4.1 inwardly rectifying K^+ channels in retina. *Am J Physiol Cell Physiol* **285**:C260–C267.

8. Hibino H, Higashi-Shingai K, Fujita A, Iwai K, Ishii M, and Kurachi Y (2004) Expression of an inwardly rectifying K^+ channel Kir5.1 in specific types of fibrocytes in the cochlear lateral wall suggests its functional importance in the establishment of endocochlear potential. *Eur J Neurosci* **19**:76–84.

9. Hibino H, Fujita A, Iwai K, Yamada M, and Kurachi Y (2004) Differential assembly of inwardly rectifying K^+ channel subunits Kir4.1 and Kir5.1 in brain astrocytes. *J Biol Chem* **279**:44065–44073.

10. Wu J, Xu H, Shen W, and Jiang C (2004) Expression and coexpression of CO_2 -sensitive Kir channels in brainstem neurons of rats. *J Membr Biol* **197**:179–191.

11. Derst C, Karschin C, Wischmeyer E, Hirsch JR, Preisig-Muller R, Rajan S, Engel H, Grzeschik K, Daut J, and Karschin A (2001) Genetic and functional linkage of Kir5.1 and Kir2.1 channel subunits. *FEBS Lett* **491**:305–311.

TABLE 13
K_{ir}6.1 channels

Channel name	K _{ir} 6.1
Description	ATP-sensitive potassium channel K _{ir} 6.1 subunit, NDP-dependent potassium channel K _{ir} 6.1 subunit
Other names	uKATP-1
Molecular information	Human (KCNJ8): 424aa, Locus ID: 3764, GenBank: D50315, NM_004982, PMID: 8595887, ¹ chr. 12p11.23 Rat (Kcnj8): 424aa, Locus ID: 25472, GenBank: D42145, NM_017099, PMID: 8595887, ² chr. 4q44 Mouse (Kcnj8): 424aa, Locus ID: 16523, GenBank: D88159, NM_008428, PMID: 9130167, ³ chr. 6G3; 6, 70.0 centimorgans
Associated subunits	SUR1, SUR2A, and SUR2B in reconstituted systems; SUR2B in native tissues
Functional assays	Voltage-clamp
Current	I _{K(NDP)}
Conductance	33 to 40pS (in 140 mM K ⁺)
Ion selectivity	K ⁺
Activation	Nucleoside diphosphates
Inactivation	Not established
Activators	NDP, diazoxide, pinacidil, nicorandil (for associated SUR subunits)
Gating inhibitors	None
Blockers	Glibenclamide (for associated SUR subunits)
Radioligands	[³ H]Glibenclamide (for associated SUR subunits)
Channel distribution	Vascular smooth muscle
Physiological functions	Regulation of vascular smooth muscle tone
Mutations and pathophysiology	Mouse lacking K _{ir} 6.1 is a model of vasospastic (Prinzmetal) angina ⁴
Pharmacological significance	SUR2B is a target for antihypertensive agents and coronary vasodilators

aa, amino acids; chr., chromosome; NDP, nucleotide diphosphate; SUR, sulfonylurea receptor.

1. Inagaki N, Inazawa J, and Seino S (1995) cDNA sequence, gene, structure and chromosomal localization of the human ATP-sensitive potassium channel u-K(ATP)-1 gene (KCNJ8). *Genomics* **30**:102–104.

2. Inagaki N, Tsuura Y, Namba N, Masuda K, Gono T, Horie M, Seino Y, Mizuta M, and Seino S (1995) Cloning and functional characterization of a novel ATP-sensitive potassium channel ubiquitously expressed in rat tissues including pancreatic islets pituitary skeletal muscle and heart. *J Biol Chem* **270**:5691–5694.

3. Yamada M, Isomoto S, Matsumoto S, Kondo C, Shindo T, Horio Y, and Kurachi Y (1997) Sulphonylurea receptor 2B and Kir 6.1 form a sulphonyl urea-sensitive but ATP insensitive K⁺ channel. *J Physiol* **499**:715–720.

4. Miki T, Suzuki M, Shibasaki T, Uemura H, Sato T, Yamaguchi K, Koseki H, Iwanaga T, Nakaya H, and Seino S (2002) Mouse model of Prinzmetal angina by disruption of the inward rectifier Kir6.1. *Nat Med* **8**: 466–472.

TABLE 14
 $K_{ir,6.2}$ channels

Channel name	$K_{ir,6.2}$
Description	ATP-sensitive potassium channel $K_{ir,6.2}$ subunit
Other names	BIR
Molecular information	Human (KCNJ11): 390aa, Locus ID: 3767, GenBank: NM_000525, chr. 11p15.1 Rat (Kcnj11): 390aa, Locus ID: 83535, GenBank: D86039, NM_031358, PMID: 8798681, ¹ chr. 1q22 Mouse (Kcnj11): 390aa, Locus ID: 16514, GenBank: D50581, NM_010602, PMID: 7502040, ² 8549751, ³ chr. 7B3, 7, 41.0 centimorgans
Associated subunits	SUR1, SUR2A, and SUR2B in native tissues
Functional assays	Voltage-clamp
Current	$I_{K(ATP)}$
Conductance	65 to 80pS (in 140 mM K^+)
Ion selectivity	K^+
Activation	MgADP
Inactivation	ATP
Activators	MgADP, diazoxide, pinacidil, cromokalim, nicorandil (for associated SUR subunits)
Gating inhibitors	ATP
Blockers	Sulfonylureas, benzamide derivatives, glinides (for associated SUR subunits)
Radioligands	[³ H]glibenclamides, [¹²⁵ I]iodoglibenclamides (for associated SUR subunits)
Channel distribution	Pancreatic β -cell, heart, skeletal muscle, brain
Physiological functions	Regulation of insulin secretion in pancreatic β -cells, ⁴ oxygen and glucose sensor in brain, ⁵ cytoprotection during cardiac and brain ischemia, ^{6,7} glucose uptake in skeletal muscle and adipose tissue ⁸
Mutations and pathophysiology	Mutations of $K_{ir,6.2}$ or SUR1 are implicated in PHHI of infancy ⁹ ; mutations of SUR1 and $K_{ir,6.2}$ are implicated in a certain form of diabetes ¹⁰
Pharmacological significance	$K_{ir,6.2}$ is a target for the K_{ATP} channel blocker phentolamine; SUR1 is a target for both sulfonylureas and benzamide derivatives used in the treatment of diabetes and diazoxide in the treatment of PHHI

aa, amino acids; chr., chromosome; SUR, sulfonylurea receptor; PHHI, persistent hyperinsulinemic hypoglycemia.

1. Isomoto S, Kondo C, Yamada M, Matsumoto S, Higashiguchi O, Horio Y, Matsuzawa Y, and Kurachi Y (1996) A novel sulphonylurea receptor forms with BIR (Kir6.2) a smooth muscle type ATP-sensitive K^+ channel. *J Biol Chem* **271**:24321–24324.

2. Inagaki N, Gono T, Clement JP, Namba N, Inazawa J, Gonzalez G, Aguilar-Bryan L, Seino S, and Bryan J (1995) Reconstitution of IKATP: an inward rectifier subunit plus the sulfonylurea receptor. *Science* **270**:1166–1170.

3. Sakura H, Ammala C, Smith PA, Gribble FM, and Ashcroft, FM (1995) Cloning and functional expression of the cDNA encoding a novel ATP-sensitive potassium channel subunit expressed in pancreatic beta cells brain heart and skeletal muscle. *FEBS Lett* **377**:338–344.

4. Miki T, Nagashima K, Tashiro F, Kotake K, Yoshitomi H, Tamamoto A, Gono T, Iwanaga T, Miyazaki J, and Seino S (1998) Defective insulin secretion and enhanced insulin action in K_{ATP} channel-deficient mice. *Proc Natl Acad Sci USA* **95**:10402–10406.

5. Miki T, Liss B, Minami K, Shiuchi T, Saraya A, Kashima Y, Horiuchi M, Ashcroft F, Minokoshi Y, Roeper J, and Seino S. (2001) ATP-sensitive K^+ channels in the hypothalamus are essential for the maintenance of glucose homeostasis. *Nat Neurosci* **4**:507–512.

6. Suzuki M, Sasaki N, Miki T, Sakamoto N, Ohmoto-Sekine Y, Tamagawa M, Seino S, Marbán E, and Nakaya H (2002) Role of sarcolemmal K_{ATP} channels in cardioprotection against ischemia/reperfusion injury in mice. *J Clin Invest* **109**:509–516.

7. Yamada K, Ji JJ, Yuan H, Miki T, Sato S, Horimoto N, Shimizu T, Seino S, and Inagaki N (2001) Protective role of ATP-sensitive potassium channels in hypoxia-induced generalized seizure. *Science* **292**:1543–1546.

8. Miki T, Minami K, Zhang L, Morita M, Gono T, Shiuchi T, Minokoshi Y, Renaud J-M, and Seino S (2002) ATP-sensitive potassium channels participate in glucose uptake in skeletal muscle and adipose tissue. *Am J Physiol Endocrinol Metab* **283**:1178–1184.

9. Nestorowicz A, Inagaki N, Gono T, Schoor KP, Wilson BA, Glaser B, Landau H, Stanley CA, Thornton PS, et al. (1997) A nonsense mutation in the inward rectifier potassium channel gene Kir6.2 is associated with familial hyperinsulinism. *Diabetes* **46**:1743–1748.

10. Gloyd AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, et al. (2004) Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med* **350**:1838–1849 [Erratum in *N Engl J Med* (2004) **351**:1470].

TABLE 15
K_{ir}7.1 channels

Channel name	K _{ir} 7.1
Description	Inwardly rectifying potassium channel K _{ir} 7.1 subunit
Other names	K _{ir} 1.4
Molecular information	Human (KCNJ13): 360aa, Locus ID: 3769, GenBank: AF061118, AJ006128, AJ007557, NM_002242, PMID: 9620703, ¹ 9786970, ² 9738472, ³ chr. 2q37 ⁴ Rat (Kcnj13): 360aa, Locus ID: 94341, GenBank: AJ006129, NM_053600, PMID: 9786970, ² chr. 9q35 Mouse: sequence not in the database
Associated subunits	None reported
Functional assays	Voltage-clamp
Current	I _{Kir7.1}
Conductance	50fS to 1pS (in 140 mM K ⁺), 2pS (recombinant and in bovine retinal epithelial cells) ⁵
Ion selectivity	Rb ⁺ ≫ K ⁺ > Na ⁺ > Cs ⁺ > Li ⁺
Activation	Activated at voltages lower than -130 mV; activation is faster than 1 ms at all voltages
Inactivation	Essentially noninactivating
Activators	None
Gating inhibitors	None
Blockers	Low sensitivity to Ba ²⁺ (IC ₅₀ = 1 mM) and Cs ⁺ (IC ₅₀ ~30 mM), relatively insensitive to block by tetraethylammonium (>10 mM), 4-aminopyridine (IC ₅₀ ~10 mM)
Radioligands	None
Channel distribution	Purkinje cells of the cerebellum, pyramidal cells of the hippocampus, choroid plexus, retinal pigment epithelium, thyroid gland, kidney (basolateral membrane of epithelial cells of the proximal tubule), small intestine, stomach, prostate, testis, lung ^{6,7}
Physiological functions	Contributes to resting membrane potential of neurons and epithelial cells, transepithelial potassium transport, K ⁺ excretion
Mutations and pathophysiology	The M125R mutation increases conductance to ~1pS and sensitivity to block by Ba ²⁺ ⁸
Pharmacological significance	Possible site of side effects for calcium channel blockers
Comments	Functional coupling to Na ⁺ ,K ⁺ -ATPase in apical membranes

aa, amino acids; chr., chromosome.

1. Krapivinsky G, Medina I, Eng L, Krapivinsky L, Yang Y, and Clapham DE (1998) A novel inward rectifier K⁺ channel with unique pore properties. *Neuron* 20:995–1005.
2. Döring F, Derst C, Wischmeyer E, Schneggenburger R, Karschin C, Daut J, and Karschin A (1998) The epithelial inward rectifier channel Kir7.1 displays unusual K⁺ permeation properties. *J Neurosci* 18: 8625–8636.
3. Partiseti M, Collura V, Agnel M, Culouscou J-M, and Graham D (1998) Cloning and characterization of a novel human inwardly rectifying potassium channel predominantly expressed in small intestine. *FEBS Lett* 434:171–176.
4. Derst C, Döring F, Preisig-Müller R, Daut J, Karschin A, Jeck N, Weber S, Engel H, and Grzeschik K-H (1998) Partial gene structure and assignment to chromosome 2q37 of the human inwardly rectifying K⁺ channel (Kir7.1) gene (*KCNJ13*). *Genomics* 54: 560–563.
5. Shimura M, Yuan Y, Chang JT, Zjang S, Campochiaro PA, Zack DJ, and Hughes BA (2001) Expression and permeation properties of the K⁺ channel Kir7.1 in the retinal pigment epithelium. *J Physiol* 531:329–346.
6. Nakamura N, Suzuki Y, Sakuta H, Ookata K, and Kawahara K (1999) Inwardly rectifying K⁺ channel Kir7.1 is highly expressed in thyroid follicular cells, intestinal epithelial cells, and choroid plexus epithelial cells: implication for a functional coupling with Na⁺,K⁺-ATPase. *Biochem J* 342:329–336.
7. Kusaka S, Inanobe A, Fujita A, Makino Y, Tanemoto M, Matsushita K, Tano Y, and Kurachi Y (2001) Functional Kir7.1 channels localized at the root of apical processes in rat retinal pigment epithelium. *J Physiol* 531:27–36.
8. Wischmeyer E, Döring F, and Karschin A (2000) Stable cation coordination at a single outer pore residue defines permeation properties in Kir channels. *FEBS Lett* 466:115–120.