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

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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 phylogenic 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:

- 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

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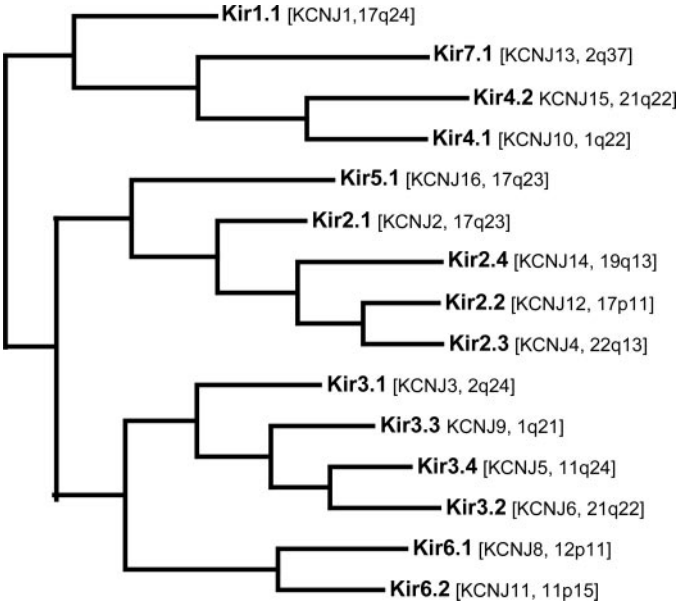

FIG. 1. Phylogenetic tree of K_{ir} channels. Amino acid sequence alignments and phylogenetic analysis for the 15 known members of the human K_{ir} family were generated as described in the legend for Fig. 1 of "LIII. Nomenclature and Molecular Relationships of Voltage-Gated Potassiuim Channels". No 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 reviews (Stanfield et al., 2002; Bichet et al., 2003; Lu, 2004). See Tables 1 through 15 for $K_{ir}1$ through $K_{ir}7.1$.

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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.

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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.

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TABLE 3
K_{ir}2.2 channels

Channel name	K_{ir}2.2
Description	Inwardly rectifying potassium channel K_{ir}2.2 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 *Drosophila melanogaster*: GenBank: NM_170076, PMID: 10731132,[5] chr. 95A1-95A1
Associated subunits	K_{ir}2.1 and K_{ir}2.3 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, α1, β1, and β2 syntrophin, dystrophin, Dp71, α-dystrobrevin-1, and α-dystrobrevin-2[7]
Functional assays	Voltage-clamp
Current	I_{K1} in the heart with other K_{ir}2 subunits
Conductance	34.2pS (K_{ir}2.2 homomeric channel) in 140 mM symmetric K^+ [4] 30.0pS (K_{ir}2.2–K_{ir}2.1 concatemer) in 145 mM symmetric K^+ [8] 30.1pS (K_{ir}2.1–K_{ir}2.2 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_{ir}2.2 homomeric channel, 0.5 μM; to K_{ir}2.1/K_{ir}2.2 heteromeric channel, 0.64 μM; to either K_{ir}2.1–K_{ir}2.2 or K_{ir}2.2–K_{ir}2.1 concatemer, 0.68 μM; to either K_{ir}2.2–K_{ir}2.3 or K_{ir}2.3–K_{ir}2.2 concatemer, 1.73 μM; to K_{ir}2.2/K_{ir}2.3 heteromeric channel, 1.94 μM,[8] intracellular Mg^{2+} (K_i = 11 μM[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_{ir}2.2 knockout mice show 50% reduction in I_{K1}, and K_{ir}2.1 knockout mice lack a detectable I_{K1} at 4 mM external K^+, suggesting that a large population of K_{ir}2.2 behaves as a heteromeric channel with K_{ir}2.1 to form I_{K1}[11]
Pharmacological significance	Not established

aa, amino acids; chr., chromosome.

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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 (dsystrophin 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^+[1]
Activation	Voltages negative to E_K[6]
Inactivation	Voltages positive to E_K[6]
Activators	Intracellular alkalization (pK = 6.76[12]), extracellular alkalization (pK = 7.4[13,14]), PIP_2, arachidonic acid (EC_{50} 0.4 μM at −100 mV[15]), tenidap (EC_{50} 0.4–1.3 μM[16])
Inhibitors	None
Gating inhibitors	ATP (K_i = 1.47 mM[17]), G protein βγ 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 μM; to K_{ir}2.1/K_{ir}2.3 heteromeric channel, 6.32 μM; to either K_{ir}2.1–K_{ir}2.3 or K_{ir}2.3–K_{ir}2.1 concatemer, 3.39 μM; to either K_{ir}2.2–K_{ir}2.3 or K_{ir}2.3–K_{ir}2.2 concatemer, 1.73 μM; to K_{ir}2.2/K_{ir}2.3 heteromeric channel, 1.94 μM[21])
	Cs^+ (IC_{50} to K_{ir}2.3 homomeric channel, 30 μM[2])
	Internal tetraethylammonium ion (K_i = 62 μM[2])
	Intracellular Mg^{2+} (K_i, not established), intracellular polyamines (K_i, not established)[22]
	SCH23390; 34% inhibition at 100 μM[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 *N*-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.

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TABLE 5
K_{ir}2.4 channels

Channel name	K_{ir}2.4
Description	Inwardly rectifying potassium channel K_{ir}2.4 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_{ir}2.1
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} = 72–116 μM at −120 mV[3,5]), Cs^+ (IC_{50} = 40 μM[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.

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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	$G_{\beta\gamma}$ subunits[6–8]
Inactivation	Voltage- and RGS protein-dependent[9]
Activators	$G_{\beta\gamma}$ 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 $G_{\beta\gamma}$ 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 *Xenopus* oocytes is due to the coassembly with the endogenous *Xenopus* K_{ir}3 subunit (K_{ir}3.5)[5]

aa, amino acids; chr., chromosome.

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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 *wv*/*wv* 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*-dibenzo[*a*,*d*]cyclohepten-5,10-imine; QX-314, *N*-(2,6-dimethylphenylcarbamoylmethyl)triethylammonium.

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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.

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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	$G_{\beta\gamma}$ 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 $G_{\beta\gamma}$ subunits of PTX-sensitive G proteins; modified by PIP_2, sodium
Gating inhibitors	G_α subunits (by binding $G_{\beta\gamma}$ 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 $G\alpha_i$-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 *Xenopus* 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.

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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_{ir}4.1 channels

Channel name	K_{ir}4.1
Description	Glial ATP-dependent inward rectifier potassium channel, subfamily J, member 10
Other names	K_{ir}1.2,[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_{ir}4.2,[1] K_{ir}5.1,[6] and K_{ir}2.1[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: ≈ 20pS in 152 mM symmetric K^+ in mammalian cells (C. Lossin and Y. Kurachi, unpublished data), ≈ 40pS in oocytes,[11] 40pS for mouse K_{ir}4.1/5.1 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_{ir}4.1/5.1 heteromers)[14]
Gating inhibitors	None
Blockers	Ba^{2+} (IC_{50} at −100 mV),[15] human K_{ir}4.1: 3 μM, human 4.1/5.1: 8 μM; Cs^+ (IC_{50} at −100 mV),[16] human K_{ir}4.1: 460 μM, human 4.1/5.1: 650 μM, intracellular H^+ (pK_a as specified below), K_{ir}4.1: pK_a 6.0,[13] K_{ir}4.1/5.1: 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_{ir}4.1 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_{ir}4.1/5.1 channels have been proposed to act as brainstem CO_2 sensors[14]
Mutations and pathophysiology	Knockout of K_{ir}4.1 results in retinal defects,[24] loss of the endocochlear potential[25] with an otherwise normal phenotype; various studies have identified *KCNJ10* 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_{ir}4.1 has been given the nomenclature K_{ir}4.3[28]

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

1. 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.
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11. 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.
12. 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.
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14. 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.
15. 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.
16. 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.
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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.
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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.
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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 *Xenopus* 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	Convoluted 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.

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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.

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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.

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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.

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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	$Rb^+ \gg K^+ > Na^+ > Cs^+ > Li^+$
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.

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