

Potassium Channels

Key References

- Castle, N.A. et al. "Toxins in the characterization of potassium channels." *Trends Neurosci.* **12**, 59-65 (1989).
- Chandy, K.G., Gutman, G.A. "Voltage-gated potassium channel genes." in *Handbook of Receptors and Channels: Ligand and Voltage-Gated Ion Channels* R.A. North (Ed.) 1, pp. 1-71, CRC, Boca Raton, FL (1995).
- Doyle, D.A. et al. "The structure of the potassium channel: Molecular basis of K⁺ conduction and selectivity." *Science* **280**, 69-77 (1998).
- Huang, C.-L. et al. "Direct activation of inward rectifier potassium channels by PIP₂ and its stabilization by Gβγ." *Nature* **391**, 803-806 (1998).
- Jan, L.Y., Jan, Y.N. "Cloned potassium channels from eukaryotes and prokaryotes." *Annu. Rev. Neurosci.* **20**, 91-123 (1997).
- Kaczorowski, G.J., Garcia, M.L. "Pharmacology of voltage-gated and calcium-activated potassium channels." *Curr. Opin. Chem. Biol.* **3**, 448-458 (1999).
- Rauer, H. et al. "Structure-guided transformation of charybdotoxin yields an analog that selectively targets Ca²⁺-activated over voltage-gated K⁺ channels." *J. Biol. Chem.* **275**, 1201-1208 (2000).
- Rogawski, M.A. "KCNQ2/KCNQ3 K⁺ channels and the molecular pathogenesis of epilepsy: Implications for therapy." *Trends Neurosci.* **23**, 393-398 (2000).
- Sirois, J.E. et al. "The TASK-1 two-pore domain K⁺ channel is a molecular substrate for neuronal effects of inhalational anesthetics." *J. Neurosci.* **20**, 6347-6354 (2000).
- Vandenberg, J.I. "HERG K⁺ channels: Friend and foe." *Trends Pharmacol. Sci.* **22**, 240-246 (2001).
- Wang, H.S. et al. "KCNQ2 and KCNQ3 potassium channel subunits: Molecular correlates of the M-channel." *Science* **282**, 1890-1893 (1998).
- Wulff, H. et al. "Design of a potent and selective inhibitor of the intermediate-conductance Ca²⁺-activated K⁺ channel, IKCa1: A potent immunosuppressant." *Proc. Natl. Acad. Sci. USA* **97**, 8151-8156 (2000).

Overview

Potassium channels contribute to the control of cell volume, membrane potential, neuronal excitability, and the secretion of salt, hormones and neurotransmitters. Their activities may be regulated by the electrical potential across the cell membrane, calcium or ATP in the cytoplasm, kinases and phosphatases, and other second messengers mobilized by neurotransmitters and hormones.

Several factors contribute to the complexity of potassium channel pharmacology. Several closely related channel subunits can form homomultimeric or heteromultimeric channels with similar properties. Thus, potassium channels of a given type may arise from different genes and/or different alternatively spliced transcripts and exhibit a range of pharmacological properties. Also, potassium channels of different electrophysiological properties are structurally related. For these reasons, it is not uncommon for reagents to affect multiple potassium channel types.

The newest advancements have come with the discovery of new potassium channel gene families and our understanding of the structure and function of potassium channels. Potassium channels are comprised of four pore-lining α subunits and additional auxiliary β subunits that may regulate channel function or targeting. One large family includes α subunits with six transmembrane segments, S1-S6, with the H5 or P loop between S5 and S6. Included in this family are voltage-gated potassium channels (Kv channels), *ether-a-gogo* related potassium channels (HERG channels), and calcium-activated potassium channels (K_{Ca} channels). The BK subfamily of K_{Ca} channels contains a seventh

transmembrane segment termed S₀ that comes before the six transmembrane segments found in other members of this family. Another large family of potassium channels is the inwardly-rectifying potassium channels whose α subunits each contain two transmembrane segments, M1 and M2, with the P loop in between. These include the cardiac and neuronal inward rectifiers that show strong inward rectification and the weakly inwardly rectifying ATP-sensitive potassium channels of the pancreas, smooth muscle, heart, brain and skeletal muscles. A new branch has recently been added to the potassium channel family tree to include the tandem pore potassium channels. These channels contain four (or eight) transmembrane segments and two P loops and resemble two inward rectifiers linked together. Their properties suggest that members of this family may mediate background potassium currents.

Along with the identification of new potassium channels has come an increasing repertoire of drugs and toxins that modulate potassium channels. Many peptide toxins from venomous species, together with several drugs act as blockers by plugging the channel pore. Other drugs work by shifting the sensitivity of channels to voltage, calcium concentrations, or other modulating factors. The potency of the drug can be strongly influenced by the β subunit, e.g. potassium channel openers activate ATP-sensitive potassium channels through the sulfonylurea receptor and the block of HERG channels by methane-sulfonanilide drugs is markedly enhanced when coexpressed with MiRP1.

In the future, the discovery and design of potassium channel drugs will be aided by

the X-ray crystal structure of the bacterial potassium channel, KcsA. Mutational analyses have identified specific residues that are important for the action of certain potassium channel activators or inhibitors. Mapping those residues onto the KcsA structure may provide insight into the selectivity displayed by some drugs or peptide toxins, and may guide efforts to design pharmacological agents that are specific for certain potassium channel subtypes.

There is significant therapeutic potential for drugs that modulate potassium channels. Mutations of voltage-sensitive potassium channels have been associated with epilepsy, cardiac arrhythmias, episodic ataxia/myokymia, and congenital deafness. Blockers of Kv1.3 and IK_{Ca} channels have been pursued as potential immunosuppressive agents, and blockers of IK_{Ca} channels may also benefit patients with sickle cell anemia. Mutations of inwardly rectifying potassium channels are known to cause persistent hyperinsulinemic hypoglycemia of infancy and kidney diseases leading to hypertension. Finally, tandem pore potassium channels may mediate the effects of inhalational anesthetics.

Potassium Channels

TYPES	INWARD RECTIFIER (Kir) ^a	ATP-SENSITIVE ^b	TANDEM PORE ^c	VOLTAGE-GATED (Kv) ^d	Ca ²⁺ -ACTIVATED ^e		KCNQ ^f	HERG	
SUBTYPES	Kir1.x Kir2.x Kir3.x Kir4.x Kir5.x Kir7.x	Kir6.x	TREK TRAAK TASK TWIK TOK THIK	Kv1.x Kv2.x Kv3.x Kv4.x Kv5.x Kv6.x	Large conductance (maxi, BK)	Intermediate conductance (IK)	Small conductance (SK)	KCNQ1 KCNQ2 KCNQ3 KCNQ4 KCNQ5	
EFFECT OF Ca²⁺	Insensitive	Insensitive	Insensitive	Insensitive	Variable K _d for Ca ²⁺	Highly sensitive	Highly sensitive	Sensitive	Sensitive
EFFECT OF VOLTAGE	Strong, inward rectification	Weak, inward rectification	Weak, outward rectification	Sensitive	Sensitive	Insensitive	Insensitive	Sensitive	Sensitive
EFFECT OF ATP	Insensitive	Inhibits channel opening	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive
ACTIVATORS ^l	PI(4,5)P ₂ (P 9763)	Minoxidil (M 4145) Diazoxide (D 9035) Pinacidil (P-154) Cromakalim (C 1055) Nicorandil Aprikalim ZD 6169 Bimakalim BRL 55834 Levcromakalim BMS-180448 RP 66471	Halothane (H 1283) Isoflurane Sevoflurane	None	NS1619 (N-170) NS004 SCA40 DHS-1 NS1608 Maxi-K diol CGS7184	None	None	Retigabine	

a Based on sequence homology, the inwardly rectifying potassium channels can be divided into at least seven distinct subfamilies. Accordingly, inward rectifiers are typically designated as Kira.*b* where *a* specifies the subfamily and *b* the individual channel.

b ATP-sensitive inward rectifier potassium channels are formed by the co-assembly of the Kir6.x channel, which constitutes the pore-forming unit, with the sulfonylurea receptor (SUR).

c Tandem pore potassium channels are also referred to by the family name KCNKX.

d The designations for voltage-sensitive potassium channels are quite imprecise. Molecular biological evidence demonstrates that both inactivating (A-type) and non-inactivating (delayed rectifier) channels belong to the same molecular family and represent at least four homologous gene products in both *Drosophila* and rodents. Since each functional channel appears to consist of four, probably different, subunits, the possibility exists that there may be hundreds of different voltage-sensitive potassium channels, depending on their subunit composition.

e Large conductance "maxi" or "BK" (big K) calcium-activated potassium channels display single channel conductances of 100-300 pS. The K_d for calcium varies with membrane potential and thus their activation is voltage-dependent. Maxi calcium-activated potassium channels appear to be involved in action potential repolarization. The voltage-insensitive, small conductance ("SK") calcium-activated potassium channel has a single channel conductance of < 20 pS and is activated by residual intracellular calcium during spike trains, thereby generating hyperpolarizing afterpotentials.

f Members of this family may combine to form the potassium current known as the M-current.

g Low potency and specificity.

h Calcium-dependent outward currents and afterpotentials in mammalian hippocampal neurons appear to be due to small conductance, voltage-insensitive potassium channels that are insensitive to apamin.

i and other Old World scorpion toxins.

j and other New World scorpion toxins.

k Block of HERG channels is not a general property of H₁ histamine receptor antagonists.

l Potency and specificity of the agents listed may vary according to subtype.

FOOTNOTES

Potassium Channels

TYPES	INWARD RECTIFIER (Kir) ^a	ATP-SENSITIVE ^b	TANDEM PORE ^c	VOLTAGE-GATED (Kv) ^d	Ca ²⁺ -ACTIVATED ^e	KCNQ ^f	HERG	
BLOCKERS ^l	Gaboon viper venom (V 4875) Terikalant LY-97241 δ -Dendrotoxin (D 0439) Tertiapin (T 8316) Tertiapin-Q (T 1567)	TEA (T 2265) Glibenclamide (G 0639) (Glyburide) Tolbutamide (T 0891) TMB-8 (86, 180-4) 5-Hydroxydecanoate (H-135) Efaroxan (E 3263) Phentolamine (P 7547) Guanethidine (G 8520) ZM 181,037 U-37883A Ciclazindol Troglitazone Englitazone	—	4-Aminopyridine (A 0152) ⁹ TEA (T 2265) ⁹ α -Dendrotoxin (D 9667) ⁱ β -Dendrotoxin (D 4438) Charybdotoxin (C 7802) Efaroxan (E 3263) Noxiustoxin (N 0659) Agitoxin-2 (A 9219) Margatoxin (M 8278) κ -Conotoxin Hanatoxin-1 (H 8534) Hanatoxin-2 (H 8659) Hongotoxin Correolide WIN 17317-3 UK 78282	TEA (T 2265) ⁹ Charybdotoxin (C 7802) (C 7802) Iberiotoxin (I 2141) Kaliotoxin Aflatrem Paxilline (P 2928) Tityustoxin-K α (T-154) ^j Penitrem A (P 3053) Paspalitre C Verruculogen (V 7755) Limbatoxin	Charybdotoxin Clotrimazole (C 6019) TRAM-34 Carbocyanine Nitrendipine (N-144)	Apamin (A 9459) ^h TEA (T 2265) ^g Scyllatoxin Linopirdine (L-134) XE991	E-4031 (M 5060) MK-499 Dofetilide Sotalol (S 0278) Ibutilide Terfenadine ^k (T 9652) Astemizole ^k (A 6424)
RADIOLIGANDS OF CHOICE		[³ H]-Glibenclamide [³ H]-P-1075 [¹²⁵ I]-Glibenclamide		[¹²⁵ I]-Charybdotoxin [¹²⁵ I]- α -Dendrotoxin	[¹²⁵ I]-Charybdotoxin [¹²⁵ I]-Charybdotoxin	[¹²⁵ I]-Charybdotoxin [¹²⁵ I]-Apamin		

ABBREVIATIONS

BRL 55834: 1-[(3S,4R)-3,4-Dihydro-3-hydroxy-2,2-dimethyl-6-(pentafluoroethyl)-2H-1-benzopyran-4-yl]-2-piperidinone

CGS7184: 1-[[[(4-Chlorophenyl)amino]carbonyl]-2-hydroxy-6-(trifluoromethyl)-1H-indole-3-carboxylic acid ethyl ester

DHS-1: Dihydrosoyasaporin-1

E-4031: 1-[2-(6-Methyl-2-pyridyl)ethyl]-4-(methylsulfonyl-aminobenzoyl)piperidine

HERG: Human *ether-à-go-go* related gene

LY-97241: N-Ethyl-N-heptyl-4-nitrobenzenebutanamine

MK-499: (+)-N-[1'-(6-Cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxy-2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide monohydrochloride

NS004: 5-Trifluoromethyl-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benzimidazole-2-one

NS1608: N-(3-(Trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl)urea

NS1619: 1,3-Dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-benzimidazol-2-one

P-1075: N-Cyano-N'-(1,1-dimethylpropyl)-N''-3-pyridylguanidine

RP 66471: 2-(Benzoyloxy)-N-methyl-1-(3-pyridinyl)-, (1S-trans)-cyclohexanecarbothioamide

SCA40: 6-Bromo-8-(methylamino)imidazo[1,2-a]pyrazine-2-carbonitrile

TEA: Tetraethylammonium

TMB-8: 8-(Diethylamino)octyl 3,4,5-trimethoxybenzoate

TRAM-34: 1-[2-(2-Chlorophenyl)diphenylmethyl]-1H-pyrazole

U-37883A: 4-Morpholinecarboximidine-N-1-adamantyl-N'-1-cyclohexyl

UK 78282: 4-[(Diphenylmethoxy)methyl]-1-[3-(4-methoxyphenyl)propyl]-piperidine

WIN 17317-3: (1-Benzyl-7-chloro-4-n-propylimino-1,4-dihydroquinoline

XE991: 10,10-bis(4-Pyridinylmethyl)-9-(10H)-anthracenone

ZD 6169: (S)-N-(4-Benzoyl-phenyl)-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide

ZM 181,037: (R*,R*)-2-[2-[2-(Dimethylamino)-1-[5-(1,1-dimethylethyl)-2-methoxyphenyl]-1-hydroxypropyl]phenoxy]-acetamide