

Potassium Channels

Key References

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Overview

Potassium channels are essential in both excitable and non-excitable cells for the control of membrane potential, regulation of cell volume, and the secretion of salt, neurotransmitters and hormones. They are integral membrane proteins that allow the selective, diffusional passage of potassium ions across biological membranes, and are capable of up to 10,000-fold selectivity of potassium over sodium. With the sequencing of the human genome, over 80 potassium channel genes have now been identified, and can be grouped into several classes based on their transmembrane topologies. A vast pharmacology exists for potassium channels, including many peptide toxins isolated from venoms of various animals, as well as therapeutically more useful small organic compounds. Many of these agents act on multiple potassium channel subtypes, on account of the conserved structural elements among potassium channels, while others show potent specificity for a single channel subtype.

The inwardly-rectifying potassium channels have two transmembrane segments flanking the highly conserved P loop, which confers potassium selectivity, and assemble as tetramers. The two-P domain, or KCNK channels, consist of two inward rectifier-type domains linked together, and function as dimers. The voltage-gated and calcium-activated potassium channels have an inward rectifier-type topology preceded by four transmembrane domains (five, in the case of BK channels). A highly charged fourth transmembrane segment functions as the voltage sensor in the voltage-gated channels.

The N- and C-terminal domains of potassium channels are cytoplasmic and can regulate channel electrophysiological

properties and trafficking, and can be a platform for phosphorylation, channel-lipid interactions, and co-assembly with other proteins. In addition to these pore-forming, or α -subunits, a number of cytosolic and transmembrane proteins co-assemble with potassium channels and can alter channel sensitivity to various ligands or to voltage, and can regulate subcellular localization of the channel complex.

While best known for their role in repolarizing the membrane of neurons and cardiomyocytes during an action potential, potassium channels are, in fact, expressed in all mammalian cell types, and even in lower organisms such as yeast, bacteria and viruses. They play a critical role in salt balance across epithelial cells, particularly in the kidney and colon. Two potassium channels, $\text{K}_v1.3$ and IKCa , are important for T cell signaling, proliferation and cytokine release, and the BK calcium-activated channel has recently been shown to be critical for neutrophil microbicidal activity. The ATP-inhibited, inwardly-rectifying potassium channel KATP , modulates insulin release by pancreatic β cells and is a major therapeutic target for treating type 2 diabetes.

In addition to KATP , a growing number of potassium channels are potential targets for treatment of diseases. For example, missense mutations in KCNQ2 or KCNQ3 that reduce M-channel current cause an autosomal dominant form of epilepsy, benign neonatal familial convulsions. In some forms of cancer, there is a correlation between overexpression of EAG or TASK3 and tumor cell proliferation.

The last six years have brought high-resolution structures of several bacterial potassium channels, as well as cytoplasmic

domains and β subunits of several mammalian channels. The determination of the structure of KcsA in 1998 showed the atomic details of potassium coordination by the selectivity filter. While the KcsA channel shows a channel in the closed state, the structure of the calcium-activated MthK revealed the conformation of an open channel. A structure of the voltage-gated potassium channel KvAP was published in 2003, but there is still much debate regarding the organization of transmembrane helices of this class of channels and the conformational changes involved in voltage gating. The increasing use of structural biology as a tool for studying ion channels will allow for more detailed understanding of disease-causing mutations, as well as the interactions between channels and the drugs that modulate them.

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TYPE	INWARD RECTIFIER	ATP-SENSITIVE ^a	2-P DOMAIN	VOLTAGE-GATED (K _v) ^b
SUBTYPES	K _{ir} 1.1 (ROMK;KCNJ1), K _{ir} 2.1-2.4 (IRK;KCNJ 2, 12, 4, 14), K _{ir} 3.1-3.4 (GIRK1-4;KCNJ 3, 6, 9, 5), K _{ir} 4.1-4.2 (KCNJ 10, 15), K _{ir} 5.1 (KCNJ 16), K _{ir} 7.1 (KCNJ 13)	K _{ir} 6.1-2 (KCNJ 8, 11)	KCNK1 (TWIK-1), KCNK2 (TREK-1), KCNK3 (TASK-1), KCNK4 (TRAAK), KCNK5 (TASK-2), KCNK6 (TWIK-2), KCNK7, KCNK9 (TASK-3), KCNK10 (TREK-2), KCNK12 (TALK-1), KCNK13 (TALK-2), KCNK15 (TASK-5), KCNK16 (THIK-2), KCNK17 (THIK-1)	K _v 1.1-1.8 (KCNA1-8), K _v 2.1-2.2 (KCNB1-2), K _v 3.1-3.4 (KCNC1-4), K _v 4.1-4.3 (KCND1-3), K _v 5.1 (KCNF1), K _v 6.1-6.3 (KCNG1-3), K _v 8.1 (KCNB3), K _v 9.1-9.3 (KCNS1-3)
EFFECT OF CA²⁺	Insensitive	Insensitive	Insensitive	Insensitive
EFFECT OF VOLTAGE	Strong, inward, rectification	Weak, inward, rectification	Weak, outward or open rectification	Sensitive
EFFECT OF ATP	Insensitive	Sensitive	Insensitive	Insensitive
ACTIVATORS^f	PI(4,5)P ₂ , dipalmitoyl PI(4,5)P ₂ , dioctanoyl (P3584), PI(4,5)P ₂ (P9763)	Nicorandil, Minoxidil (M4145), ZM 226600, Diazoxide (D9035) P-1075, Cromakalim (C1055), Levcromakalim (L0540), Pinacidil (P154), Aprikalim, ZD 6169, Bimakalim, BRL 55834, BMS-180448, RP 66471, A-312110	Halothane (B4388), Isoflurane, Riluzole (R116), Arachidonic acid (A9673)	
BLOCKERS^f	δ-Dendrotoxin (D0439), Lq2 (L1915), Tertiapin (T8316), Tertiapin-Q (T1567), E-4031 (M5060), Terikalant, SCH 23390 (D054)	Glibenclamide (G0639), Efaroxan (E3263), Glipizide (G117), SKF-525A (P1061), Adenylyl-imidodiphosphate (A2647), Tolbutamide, (T0891) TMB-8, 5-Hydroxydecanoate (H135), Phentolamine (P7547), Guanethidine (G8520), ZM 181,037, PNU-37883A (P0248), Ciclazindol, Troglitazone (T2573), Englitazone	Quinidine (Q5001), Bupivacaine (B5274), Lidocaine (L7757), Mepivacaine (M3189), Ruthenium red (R2751), Sipatrigine, Anandamide (A0580), Hanatoxins, CP 339818, Quinidine (Q5001),	4-Aminopyridine (A78403), Dendrotoxins, (Kv1) (D9667 , D4438 , D0439 , D4688 , D4813 , D4563), Maurotoxin, Kaliotoxin, BgK, Charybdotoxin (C7802), Hongotoxin (H0287), Correolide, UK 78,282, Margatoxin (M8278), Tamulustoxin, BDS-I (B9554), -BDS II (B9679), Phrixotoxins (P3495), Heteropodatoxins (H3163), Flecainide (F6777), K-Conotoxin, Aa1 (A6603), Agitoxins (A5229 , A9219 , A5476), Noxiustoxin (N0659), Stromatoxin (S1570), Tityustoxin (T154), AM 92016, Mepivacaine (M3189), Psora-4 (P9872), Pandinotoxin-Kα (P222), Stichodactyla Toxin
RADIOLIGANDS OF CHOICE	Not known	[³ H]-Glibenclamide, [³ H]-P-1075, [¹²⁵ I]-Glibenclamide, [¹²⁵ I]-A-312110	Not known	[¹²⁵ I]-Charybdotoxin, [¹²⁵ I]-α-Dendrotoxin
TISSUE EXPRESSION^g	Heart, CNS, pancreas, ubiquitous	CNS, pancreas, muscle, heart	Ubiquitous	Brain, skeletal muscle, vascular smooth muscle, lymphocytes, heart, pancreas, liver, spleen
PHYSIOLOGICAL FUNCTION	Electrolyte balance, cardiac electrical activity, resting membrane	Insulin secretion, vascular smooth muscle tone	Neuronal excitability, cold sensation, hypoxia/acidosis sensation	Action potential shaping, spike frequency oxygen sensing T cell proliferation and cytokine production,
DISEASE RELEVANCE	Bartter's syndrome, Andersen-Tawil syndrome	Type II diabetes, persistent hyperinsulinemic, hypoglycemia of infancy	Cancer	Episodic ataxia, myokymia multiple sclerosis, hypertension

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TYPE	CALCIUM-ACTIVATED ^c		KCNQ ^d	HERG	
SUBTYPES	Large Conductance, BK (Slo1/Maxi-K) Slack/Slo2 Slo3	Intermediate Conductance IK (KCNN4)	Small conductance SK1-3 (KCNN1-3)	KCNQ1-5 (K _v 7.1-7.5)	KCNH1-8 (HERG, EAG, ELK)
EFFECT OF CA²⁺	Highly sensitive ^e	Highly sensitive	Highly sensitive	Sensitive	Sensitive
EFFECT OF VOLTAGE	Sensitive	Insensitive	Insensitive	Sensitive	Sensitive
EFFECT OF ATP	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive
ACTIVATORS^f	NS1619 (N170), NS004, Maxi-k diol, CGS7184, Pimaric acid (I6783), S(+)-Niguldipine (N135)	1-Ethyl-2-Benzimidazolinone, Chlorzoxazone (C4397), Zoxazolamine (A45807), NS309 (N8161)	1-Ethyl-2-Benzimidazolinone, Chlorzoxazone (C4397), NS309 (N8161)	DIDS (D3514), Retigabine, BMS-204352, Niflumic Acid (N0630)	NS 1643 RPR 260243
BLOCKERS^f	Iberiotoxin (I5904), Charybdotoxin (C5856), Slotoxin (S0944), Paxilline (P2928), Verruculogen (V7755), Penitrem A (P3053), BmBKTx1, Neuropeptide Y (N5017)	Charybdotoxin (C5856), Clotrimazole (C6019), TRAM-34 (T6700), Trifluoroperazine (T8516), Haloperidol (H1512), Bicuculline	Apamin (A9459), Scyllatoxin, Dequalinium (D3768), UCL 1684 (U8881), (+)-Tubocurarine (T2379), methiodide (B6889), BmSKTx1 Astemizole (A6424), LY-97241	Chromanol 293B (C2615), Linopirdine (L134), XE 991, Clofilium (C2365) MK-499, Ibutilide, Terfenadine (T9652),	rBeKm-1 (B6934), E-4031 (M5060), Ergtoxin (E9904), Amitriptyline (A8404), Imipramine (I0899), Dofetilide, Sotalol (S0278),
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-Charybdotoxin	[¹²⁵ I]-Charybdotoxin	[¹²⁵ I]-Apamin	Not known	[¹²⁵ I]-BeKm-1
TISSUE EXPRESSION^g	Smooth muscle, pancreas, leukocytes, inner ear, brain, olfactory bulb	Erythrocytes, lymphocytes, vascular smooth muscle, skeletal muscle, lung, placenta, colon, enteric neurons	Eye, brain, heart, adrenal gland, skeletal muscle, mast cells	Heart, ear, colon, lung, kidney, pituitary, placenta, CNS, testis, spleen, skeletal muscle	Heart, neuroblastoma cells, smooth muscle, neuroendocrine cells, CNS
PHYSIOLOGICAL FUNCTION	Vascular tone, neuronal excitability, hormone secretion, cochlear hair, cell tuning, leukocyte microbicidal activity	T cell proliferation and cytokine production, myogenesis	Neuronal afterhyperpolarization (AHP), spike frequency adaptation, hormone secretion	Cardiac action potential, Cl ⁻ absorption in colon, K ⁺ recycling in inner ear, neuronal excitability, neuroprotection	Cell cycle regulation, resting membrane potential, cardiac action potential, oxygen sensing
DISEASE RELEVANCE	Deafness, hypertension, cerebral ischemia sclerosis	Sickle cell anemia, multiple	Alzheimer's disease, epilepsy, myotonic muscular dystrophy	Long-QT syndrome-arrhythmia, Jervell and Lange-Nielsen syndrome (JLNS)-deafness, Beckwith-Wiedemann syndrome, atrial fibrillation, benign familial neonatal convulsions (BFNC), epilepsy nonsyndromic autosomal dominant deafness-2 (DFNA2)	Long QT syndrome (LQT-2), cancer

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Abbreviations

A-312110: (9R)-9-(4-Fluoro-3-iodophenyl)-2,3,5,9-tetrahydro-4H-pyrano[3,4-b]thieno [2,3-e]pyridin-8(7H)-one-1,1-dioxide
BMS-180448: (3S-trans)-N-(4-Chlorophenyl)-N'-cyano-N''-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)
BMS-204352: (3S)-(+)-(5-Chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one
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
CP 339818: 1-Benzyl-4-pentylimino-1,4-dihydroquinoline
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)-hydroxyspiro(2H-1-benzopyran-2,4'-piperidin)-6-yl]methanesulfonamide monohydrochloride
NS004: 5-Trifluoromethyl-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benzimidazole-2-one
NS309: 3-Oxime-6,7-dichloro-1H-indole-2,3-dione
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
NS1643: N,N'-bis[2-Hydroxy-5-(trifluoromethyl)phenyl]-urea
P-1075: N-Cyano-N'-(1,1-dimethylpropyl)-N''-3-pyridylguanidine
PNU-37883A: N-(1-adamantyl)-N'-cyclohexyl-4-morpholinecarboxamidine hydrochloride
RP 66471: 2-(Benzoyloxy)-N-methyl-1-(3-pyridinyl)-, (1S-trans)-cyclohexanecarbothioamide
RPR260243: (3R,4R)-4-[3-(6-Methoxyquinolin-4-yl)-3-oxo-propyl]-1-[3-(2,3,5-trifluoro-phenyl)-propyl-2-ynyl]-piperidine-3-carboxylic acid
SCA40: 6-Bromo-8-(methylamino)imidazo[1,2-a]pyrazine-2-carbonitrile
SCH 23390: R(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride
SKF-525A: 2-Diethylaminoethyl-2,2-diphenylvalerate hydrochloride, Proadifen hydrochloride
TMB-8: 8-(Diethylamino)octyl 3,4,5-trimethoxybenzoate
TRAM-34: 1-[2-Chlorophenyl]diphenylmethyl]-1H-pyrazole
U-37883A: 4-Morpholinecarboximidine-N-1-adamantyl-N'-1-cyclohexyl
UCL 1684: 6,10-Diaza-3(1,3),8(1,4)-dibenzena-1,5(1,4)-diquinolinacyclodecaphane
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
ZM 226600: N-(4-Phenylsulphonylphenyl)-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide

FOOTNOTES

- ATP-sensitive inward rectifier potassium channels are formed by the co-assembly of the $K_{ir}6.x$ channel, which constitutes the pore-forming unit, with the sulfonylurea receptor (SUR).
- 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. Since functional channels consist of four potentially different α subunits, the possibility exists that there may be hundreds of different voltage-sensitive potassium channels, depending on their subunit composition.
- Large I_{K1} for calcium varies with membrane potential and thus their activation is voltage-dependent. The voltage-insensitive I_{K1} has a conductance of < 20 pS and 20-80 pS, respectively.
- Members of this family may combine to form the potassium current known as the M-current.
- Slack/Slo2 is sodium-activated and calcium-insensitive, while Slo3 is pH-activated and calcium-insensitive.
- Potency and specificity of the agents listed may vary according to subtype.
- Most potassium channels are expressed in many different tissues. This list reflects tissues where various channel types are predominantly expressed and characterized.