Potassium

Overview: Potassium channels are fundamental regulators of excitability. They control the frequency and the shape of action potential waveform, the secretion of hormones and neurotransmitters and cell membrane potential. Their activity may be regulated by voltage, calcium and neurotransmitters (and the signalling pathways they stimulate). They consist of a primary pore-forming α subunit often associated with auxiliary regulatory subunits. Because there are over 70 different genes encoding K channels α subunits in the human genome, it is beyond the scope of this guide to treat each subunit individually. Instead, channels have been grouped into families and subfamilies based on their structural and functional properties. Due to space constraints, the Ensembl ID for only one member of each subfamily is given. Ensembl information for the other subfamily members can be found from links therein. The three main families are the 2TM (two transmembrane domain), 4TM and 6TM families. A standardized nomenclature for potassium channels has been proposed by the NC-IUPHAR subcommittees on potassium channels (see Goldstein *et al*., 2005; Gutman *et al*., 2005; Kubo *et al*., 2005; Wei *et al*., 2005).

The 2TM family of K channels

The 2TM domain family of K channels are also known as the inward-rectifier K channel family. This family includes the strong inward-rectifier K channels (K_{IR}2.x), the G protein-activated inward-rectifier K channels (K_{IR}3.x) and the ATP-sensitive K channels [K_{IR}6.x, which combine with sulphonylurea receptors (SUR)]. The pore-forming α subunits form tetramers, and heteromeric channels may be formed within subfamilies (e.g. K_{IR}3.2 with K_{IR}3.3).

Subfamily group	K_{IR}1.x	K_{IR}2.x	K_{IR}3.x	K_{IR}4.x
Subtypes	K_{IR}1.1 (ROMK1)	K_{IR}2.1–2.4 (IRK1–4)	K_{IR}3.1–3.4 (GIRK1–4)	K_{IR}4.1–4.2
Ensembl ID	ENSG00000151704 (K_{IR}1.1)	ENSG00000123700 (K_{IR}2.1)	ENSG00000162989 (K_{IR}3.1)	ENSG00000177807 (K_{IR}4.1)
Activators	–	–	PIP_2, Gβγ	–
Inhibitors	–	$[Mg^{2+}]_i$, polyamines (internal)	–	–
Functional characteristic	Inward-rectifier current	IK_1 in heart, 'strong' inward-rectifier current	G protein-activated inward-rectifier current	Inward-rectifier current

Subfamily group	K_{IR}5.x	K_{IR}6.x	K_{IR}7.x
Subtypes	K_{IR}5.1	K_{IR}6.1–6.2 (K_{ATP})	K_{IR}7.1
Ensembl ID	ENSG00000153822 (K_{IR}5.1)	ENSG00000121361 (K_{IR}6.1)	ENSG00000115474 (K_{IR}7.1)
Activators	–	Minoxidil, cromakalim, diazoxide, nicorandil	–
Inhibitors	–	Tolbutamide, glibenclamide	–
Functional characteristic	Inward-rectifier current	ATP-sensitive, inward-rectifier current	Inward-rectifier current
Associated subunits	–	SUR1, SUR2A, SUR2B	–

The 4TM family of K channels

The 4TM family of K channels are thought to underlie many leak currents in native cells. They are open at all voltages and regulated by a wide array of neurotransmitters and biochemical mediators. The primary pore-forming α subunit contains two pore domains (indeed, they are often referred to as two-pore domain K channels or K2P), and so it is envisaged that they form functional dimers rather than the usual K channel tetramers. There is some evidence that they can form heterodimers within subfamilies (e.g. K_{2P}3.1 with K_{2P}9.1). There is no current, clear, consensus on nomenclature of 4TM K channels, nor on the division into subfamilies (see Goldstein *et al*., 2005). The suggested division into subfamilies, below, is based on similarities in both structural and functional properties within subfamilies.

Subfamily group	'TWIK'	'TREK'	'TASK'	'TALK'	'THIK'	'TRESK'
Subtypes	K_{2P}1.1 (TWIK1) K_{2P}6.1 (TWIK2) K_{2P}7.1 (KNCK7)	K_{2P}2.1 (TREK1) K_{2P}10.1 (TREK2) K_{2P}4.1 (TRAAK)	K_{2P}3.1 (TASK1) K_{2P}9.1 (TASK3) K_{2P}15.1 (TASK5)	K_{2P}16.1 (TALK1) K_{2P}5.1 (TASK2) K_{2P}17.1 (TASK4)	K_{2P}13.1 (THIK1) K_{2P}12.1 (THIK2)	K_{2P}18.1 (TRESK)
Ensembl ID	ENSG00000135750 (K_{2P}1.1)	ENSG00000082482 (K_{2P}2.1)	ENSG00000171301 (K_{2P}3.1)	ENSG00000164626 (K_{2P}5.1)	ENSG00000152315 (K_{2P}13.1)	ENSG00000186795 (K_{2P}18.1)
Activators	–	Halothane (not TRAAK), riluzole, stretch, heat, arachidonic acid, acid pH_i	Halothane, alkaline pH_o (K_{2P}3.1)	Alkaline pH_O	–	–
Inhibitors	Acid pH_i	–	Anandamide (K_{2P}3.1, K_{2P}9.1) ruthenium red (K_{2P}9.1) acid pH_O	–	Halothane	Arachidonic acid
Functional characteristic	Background current	Background current	Background current	Background current	Background current	Background current

The K_{2P}7.1, K_{2P}15.1 and K_{2P}12.1 subtypes, when expressed in isolation, are non-functional. All 4TM channels are insensitive to the classical potassium channel blockers TEA and 4-AP, but are blocked to varying degrees by Ba^{2+} ions.

The 6TM family of K channels

The 6TM family of K channels comprises the voltage-gated K_V subfamilies, the KCNQ subfamily, the EAG subfamily (which includes herg channels), the Ca^{2+}-activated Slo subfamily (actually with 7TM) and the Ca^{2+}-activated SK subfamily. As for the 2TM family, the pore-forming α subunits form tetramers, and heteromeric channels may be formed within subfamilies (e.g. K_V1.1 with K_V1.2; KCNQ2 with KCNQ3).

Subfamily group	K_V1.x	K_V2.x	K_V3.x	K_V4.x
Subtypes	K_V1.1–K_V1.8 Shaker-related	K_V2.1–2.2 Shab-related	K_V3.1–3.4 Shal-related	K_V4.1–4.3 Shaw-related
Ensembl ID	ENSG00000111262 (K_V1.1)	ENSG00000158445 (K_V2.1)	ENSG00000129159 (K_V3.1)	ENSG00000102057 (K_V4.1)
Inhibitors	TEA potent (1.1), TEA moderate (1.3, 1.6), 4-AP potent (1.4), α-dendrotoxin (1.1, 1.2, 1.6), margatoxin (1.1, 1.2, 1.3), noxiustoxin (1.2, 1.3)	TEA moderate	TEA potent, 4-AP potent (3.1, 3.2), BDS-1 (3.4)	–
Functional characteristics	K_V (1.1–1.3, 1.5–1.8), K_A (1.4)	K_V (2.1)	K_V (3.1, 3.2), K_A (3.3, 3.4)	K_A
Associated subunits	K_V β_1, K_V β_2	K_V5.1, K_V6.1–6.3, K_V8.1, K_V9.1–9.3	MiRP2 (K_V3.4)	KChIP, KChAP

Subfamily group	K_V7.x ('KCNQ')	K_V10.x, K_V11.x, K_V12.x ('EAG')	K_{Ca}1.x, K_{Ca}4.x, K_{Ca}5.x ('Slo')	K_{Ca}2.x, K_{Ca}3.x ('SK')
Subtypes	K_V7.1–7.5 (KCNQ1-5)	K_V10.1–10.2 (eag1–2) K_V11.1–11.3 (erg1-3, herg 1–3) K_V12.1–12.3 (elk1-3)	K_{Ca}1.1, K_{Ca}4.1–4.2, K_{Ca}5.1 Slo (BK), Slack, Slick	K_{Ca}2.1–2.3 (SK1–SK3) K_{Ca}3.1 (SK4, IK)
Ensembl ID	ENSG00000053918 (K_V7.1)	ENSG00000143473 (K_V10.1)	ENSG00000156113 (K_{Ca}1.1)	ENSG00000105642 (K_{Ca}2.1)
Activators	Retigabine (K_V7.2,–5)	–	NS004, NS1619	–
Inhibitors	TEA (K_V7.2, 7.4), XE991 (K_V7.1, 7.2, 7.4, 7.5), linopirdine	E-4031 (K_V11.1), astemizole (K_V11.1), terfenadine (K_V11.1)	TEA, charybdotoxin, iberiotoxin	Charybdotoxin (K_{Ca}3.1), apamin (K_{Ca}2.1–2.3)
Functional characteristic	K_V7.1 – cardiac IK_S K_V7.2/7.3–M current	K_V11.1 – cardiac IK_R	Maxi K_{Ca} K_{Na} (slack & slick)	SK_{Ca} (K_{Ca}2.1–2.3) IK_{Ca} (K_{Ca}3.1)
Associated subunits	minK, MiRP2 (K_V.7.1)	minK, MiRP1 (erg1)	–	–

Abbreviations: 4-AP, 4-aminopyridine; **BDS-1**, blood depressing substance 1; **E-4031**, 1-(2-(6-methyl-2-pyridyl)ethyl)-4-(4-methylsulphonyl aminobenzoyl)piperidine; **NS004**, 1-(2-hydroxy-5-chlorophenyl)-5-trifluromethyl-2-benzimidazolone; **NS1619**, 1-(2′-hydroxy-5′-trifluromethylphenyl)-5-trifluro-methyl-2(3*H*)benzimidazolone; **PIP_2**, phosphatidylinositol 4,5, bisphosphate; **TEA**, tetraethylammonium; **XE991**, 10,10-*bis*(4-pyridinylmethyl)-9(10*H*)-anthracene

Further Reading

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