0031-6997/05/5704-527–540$7.00
PHARMACOLOGICAL REVIEWS
Vol. 57, No. 4
50410/3070847
Pharmacol Rev 57:527–540, 2005
Printed in U.S.A

International Union of Pharmacology. LV. Nomenclature and Molecular Relationships of Two-P Potassium Channels

STEVE A. N. GOLDSTEIN, DOUGLAS A. BAYLISS, DONGHEE KIM, FLORIAN LESAGE, LEIGH DANIEL PLANT, AND SINDHU RAJAN

Department of Pediatrics and Institute for Molecular Pediatric Sciences. Pritzker School of Medicine, University of Chicago, Chicago, Illinois (S.A.N.G., L.D.P., S.R.); Department of Pharmacology, University of Virginia Health System, Charlottesville, Virginia (D.A.B.); Department of Physiology, Rosalind Franklin University of Medicine and Science, The Chicago Medical School, Chicago, Illinois (D.K.); and Institut de Pharmacologie Moléculaire et Cellulaire, Valbonne, France (F.L.)

Introduction

In less than a decade since their discovery, the study of K_{2P} channels has revealed that background leak of potassium ions via dedicated pathways is a highly regulated mechanism to control cellular excitability. Potassium leak pathways, active at rest, stabilize membrane potential below firing threshold and expedite repolarization. Although the existence of leak currents was proposed in 1952 by Hodgkin and Huxley, they remained a biophysical curiosity for more than 4 decades. Identification of the first molecular correlate of a potassium leak current was preceded by cloning of potassium channels in *Saccharomyces cerevisiae* and *Caenorhabditis elegans* with two pore-forming P loops in each subunit and four or eight transmembrane (TM[1]) domains (Ketchum et al., 1995). Thereafter, K_{2P}Ø was isolated by functional expression cloning from the neuromuscular tissue of *Drosophilia melanogaster* (Goldstein et al., 1996). Biophysical characterization revealed K_{2P}Ø to be a potassium-selective channel with the predicted attributes of a background conductance, that is, a voltage-independent portal showing Goldman-Hodgkin-Katz (open) rectification. When the concentration of potassium is symmetrical across the membrane, K_{2P}Ø currents change in a linear manner with voltage; under physiological conditions (high internal and low external potassium), K_{2P}Ø passes greater outward than inward currents (Goldstein et al., 2001).

A striking feature of K_{2P} channels is their subunit body plan: each has two P loops and four TM domains. This distinct 2P/4TM topology can be found in more than 70 predicted homologs in genome databases. Fifteen mammalian genes in the family are designated as *KCNK* genes encoding the K_{2P} channels (Fig. 1); most readily reveal ion channel function upon expression. As expected for regulators of excitability, K_{2P} channels are under tight control by a plethora of chemical and physical stimuli, including oxygen tension, pH, lipids, mechanical stretch, neurotransmitters, and G protein-coupled receptors; the channels are also the molecular targets for certain volatile and local anesthetics (Lesage and Lazdunski, 2000). Regulation of K_{2P} channels alters the attributes subject to change in any ion channel: number of pores at the site of operation, open probability, and unitary current (Plant et al., 2005). Nonetheless, some regulatory changes are striking; for example, phosphorylation of K_{2P}2 endows the open rectifier with sensitivity to voltage (Bockenhauer et al., 2001), and desumoylation of K_{2P}1 (removal of covalently-bound small ubiquitin-modifier protein) relieves chronic silencing of

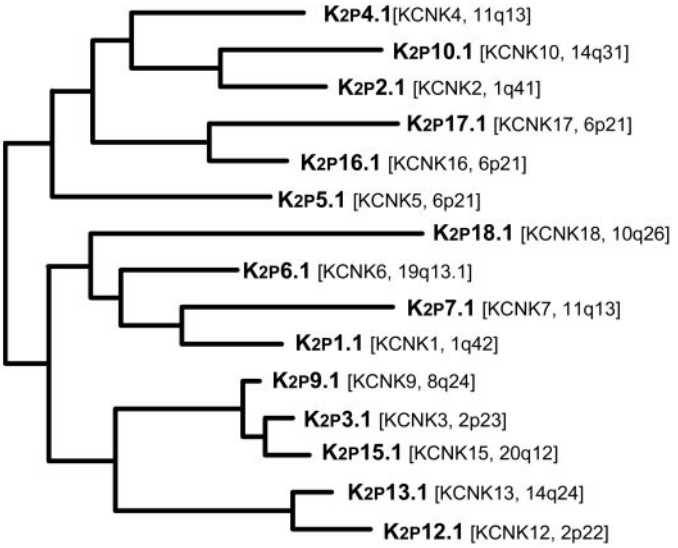

FIG. 1. Phylogenetic tree for K_{2P} channels. Amino acid sequence alignments and phylogenetic analysis for the 15 known members of the human K_{2P} family were generated as described in the legend for Fig. 1 of "LIII. Nomenclature and Molecular Relationships of Voltage-Gated Potassium Channels." K_{2P}18.1 was added to the topology shown in the previous edition of this compendium by use of maximum parsimony and neighbor-joining algorithms. International Union of Pharmacology and HUGO Gene Nomenclature Committee names of the genes are shown together with their chromosomal localization.

Address correspondence to: Dr. Steve A. N. Goldstein, Department of Pediatrics and Institute for Molecular Pediatric Sciences, Pritzker School of Medicine, University of Chicago, Chicago, IL 60637. E-mail: sangoldstein@uchicago.edu

Article, publication date, and citation information can be found at http://pharmrev.aspetjournals.org.
doi:10.1124/pr.57.4.12.

[1] Abbreviations: TM, transmembrane.

complexes that reside in the plasma membrane, thereby revealing that the protein can function as an ion channel and operates like K_{2P}Ø as an open rectifier (Plant et al., 2005; Rajan et al., 2005). Tables 1 through 15 present the properties of K_{2P}1.1 through K_{2P}18.1 channels.

REFERENCES

Bockenhauer D, Zilberberg N, and Goldstein SA (2001) KCNK2: reversible conversion of a hippocampal potassium leak into a voltage-dependent channel. *Nat Neurosci* **4:**486–491.

Goldstein SA, Bockenhauer D, O'Kelly I, and Zilberberg N (2001) Potassium leak channels and the KCNK family of two-P-domain subunits. *Nat Rev Neurosci* **2:**75–84.

Goldstein SAN, Price LA, Rosenthal DN, and Pausch MH (1996) ORK1, a potassium-selective leak channel with two pore domains cloned from *Drosophila* melanogaster by expression in *Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* **93:** 13256–13261.

Ketchum KA, Joiner WJ, Sellers AJ, Kaczmarek LK, and Goldstein SAN (1995) A new family of outwardly-rectifying potassium channel proteins with two pore domains in tandem. *Nature (Lond)* **376:**690–695.

Lesage F and Lazdunski M (2000) Molecular and functional properties of two-pore-domain potassium channels. *Am J Physiol Renal Physiol.* **279:**F793–F801.

Plant LD, Rajan S, and Goldstein SA (2005) K2P channels and their protein partners. *Curr Opin Neurobiol* **15:**326–333.

Rajan S, Plant LD, Rabin ML, Butler MH, and Goldstein SAN (2005) Sumoylation silences the plasma membrane leak K^+ channel K2P1. *Cell* **121:**37–47.

All authors serve as the Subcommittee on K_{2P} Channels of the Nomenclature Committee of the International Union of Pharmacology.

TABLE 1
K_{2P}1.1 channels

Channel name	K_{2P}1.1
Description	Two-pore domain potassium channel subunit[1]
Other names	KCNK1, TWIK-1, hOHO
Molecular information	Human: 336aa, NM_002245, chr. 1q42-43, KCNK1,[2, 3] GeneID: 3775, PMID: 8605869[1] Rat: 336aa, AF022819 Mouse: 336aa, NM_008430, chr. 8, kcnk1[4]
Associated subunits	Small ubiquitin-related modifier protein (SUMO-1) is covalently attached at lysine 274[6]; exchange factor (EFA6) for small G protein ADP-ribosylation factor 6 (ARF6) (see "Comments")[7]
Functional assays	Electrophysiological
Current	Open rectifier
Conductance	32pS
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Not established
Gating inhibitors	None
Blockers	External pH (6.7)[6]
Radioligands	None
Channel distribution	Brain, heart, lung, kidney, liver, placenta[4,5]
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Covalent attachment of SUMO to lysine 274 silences K_{2P}1; mutation of lysine 274 or desumoylation of K_{2P}1 by a SUMO-specific protease (SENP) reveals an open rectifier; like K_{2P}3 and K_{2P}9, K_{2P}1 is blocked by extracellular acidification due to titration of a histidine residue in the first pore loop; EFA6 interacts with the C-terminal part of K_{2P}1—this interaction may be important for channel internalization and recycling[7]

aa, amino acid; chr., chromosome; SUMO, small ubiquitin-related modifier protein.

1. Lesage F, Guillemare E, Fink M, Duprat F, Lazdunski M, Romey G, and Barhanin J (1996) TWIK-1, a ubiquitous human weakly inward rectifying K^+ channel with a novel structure. *EMBO J* **15:**1004–1011.

2. Orias M, Velazquez H, Tung F, Lee G, and Desir GV (1997) Cloning and localization of a double-pore K channel, KCNK1: exclusive expression in distal nephron segments. *Am J Physiol* **273:** F663–F666.

3. Lesage F, Mattei MG, Fink M, Barhanin J, and Lazdunski M (1996) Assignment of the human weak inward rectifier K+ channel TWIK-1 gene to chromosome 1q42-q43. *Genomics* **34:**153–155.

4. Lesage F, Lauritzen I, Duprat F, Reyes R, Fink M, Heurteaux C, and Lazdunski M (1997) The structure, function and distribution of the mouse TWIK-1 K^+ channel. *FEBS Lett* **402:**28–32.

5. Goldstein SAN, Wang KW, Ilan N, and Pausch M (1998) Sequence and function of the two P domain potassium channels: implications of an emerging superfamily. *J Mol Med* **76:**13–20.

6. Rajan S, Plant LD, Rabin ML, Butler MH, and Goldstein SAN (2005) Sumoylation silences the plasma membrane leak K^+ channel K2P1. *Cell* **121:**37–47.

7. Decressac S, Franco M, Bendahhou S, Warth R, Knauer S, Barhanin J, Lazdunski M, and Lesage F (2004) ARF6-dependent interaction of the TWIK1 K + channel with EFA6, GDP/GTP exchange factor for ARF6. *EMBO Rep* **5:**1171–1175.

TABLE 2
K_{2P}2.1 channels

Channel name	K_{2P}2.1
Description	Two-pore domain potassium channel subunit[1]; open rectifier or voltage-dependent
Other names	KCNK2, TREK-1, TPKC1
Molecular information	Human: 426aa, NM_014217, chr. 1q41, KCNK2,[2] GeneID: 3776, PMID: 9003761[3] Rat: 426aa, AF325671, chr. 5 Mouse: 411aa, XM_123605, chr. 1, kcnk2[3]
Associated subunits	Not established
Functional assays	Electrophysiological
Current	Open or voltage-dependent[4,5] (see "Comments")
Conductance	90pS (see "Comments")
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Arachidonic acid (10 mM) and unsaturated fatty acids,[10] lysophospholipids,[7] volatile anesthetics,[6,11] mechanical stress,[7,11] internal acidification[12]
Gating inhibitors	None
Blockers	Ba^{2+} (1 mM), quinidine (100 mM), PKA, PKC
Radioligands	None
Channel distribution	Brain,[2] heart
Physiological functions	Not established
Mutations and pathophysiology	Characterization of K_{2P}2 knockout mice suggests a loss of sensitivity to general anesthetics and increased vulnerability to ischemia and reperfusion injury[8,9]
Pharmacological significance	Not established
Comments	Phosphorylation of serine 348 regulates reversible interconversion between leak and voltage-dependent phenotypes[5]; "activation" and "deactivation" with voltage steps seem to be instantaneous; the mouse variant may have a smaller conductance

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

1. Goldstein SAN, Wang KW, Ilan N, and Pausch M (1998) Sequence and function of the two P domain potassium channels: implications of an emerging superfamily. *J Mol Med* **76:**13–20.

2. Meadows HJ, Benham CD, Cairns W, Gloger I, Jennings C, Medhurst AD, Murdock P, and Chapman CG (2000) Cloning, localisation and functional expression of the human orthologue of the TREK-1 potassium channel. *Pflueg Arch Eur J Physiol* **439:**714–722.

3. Fink M, Duprat F, Lesage F, Reyes R, Romey G, Heurteaux C, and Lazdunski M (1996) Cloning, functional expression and brain localization of a novel unconventional outward rectifier K^+ channel. *EMBO J* **15:**6854–6862.

4. Maingret F, Lauritzen I, Patel AJ, Heurteaux C, Reyes R, Lesage F, Lazdunski M, and Honoré E (2000) TREK-1 is a heat-activated background K(+) channel. *EMBO J* **19:**2483–2491.

5. Bockenhauer D, Zilberberg N, and Goldstein SAN (2001) KCNK2: reversible conversion of a hippocampal potassium leak into a voltage-dependent channel. *Nat Neurosci* **4:**486–491.

6. Terrenoire C, Lauritzen I, Lesage F, Romey G, and Lazdunski M (2001) A TREK-1-like potassium channel in atrial cells inhibited by beta-adrenergic stimulation and activated by volatile anesthetics. *Circ Res* **89:**336–342.

7. Maingret F, Patel AJ, Lesage F, Lazdunski M, and Honoré E (2000). Lysophospholipids open the two-pore domain mechano-gated K(+) channels TREK-1 and TRAAK. *J Biol Chem* **275:**10128–10133.

8. Buckler KJ and Honoré E (2004) The lipid-activated K2P channel TREK-1 is resistant to hypoxia: implication for ischemic neuroprotection. *J Physiol* **562:**213–222.

9. Heurteaux C, Guy N, Laigle C, Blondeau N, Duprat F, Mazzuca M, Lang-Lazdunski L, Widmann C, Zanzouri M, Romey G, et al. (2004) TREK-1, a K^+ channel involved in neuroprotection and general anesthesia. *EMBO J* **23:**2684–2695.

10. Patel AJ, Honoré E, Lesage F, Fink M, Romey G, and Lazdunski M (1999) Inhalational anesthetics activate two-pore-domain background K+ channels. *Nat Neurosci* **2:**422–426.

11. Maingret F, Patel AJ, Lesage F, Lazdunski M, and Honoré E (1999) Mechano- or acid stimulation, two interactive modes of activation of the TREK-1 potassium channel. *J Biol Chem* **274:**26691–26696.

TABLE 3
K_{2P}3.1 channels

Channel name	K_{2P}3.1
Description	Two-pore domain potassium channel subunit; open rectifier
Other names	KCNK3, TASK-1, TBAK-1, OAT-1
Molecular information	Human: 394aa, NM_002246, chr. 2p24.1-23.3,[1] KCNK3,[2] GeneID: 3777, PMID: 9312005[20] Rat: 411aa, NP_203694, kcnk3[3] Mouse: 409aa, AF065162, chr. 5B,[1] kcnk3
Associated subunits	14-3-3[16, 17] and p11 (annexin II subunit),[18] see "Comments"
Functional assays	Electrophysiological
Current	Open rectifier[4]
Conductance	10pS[5]
Ion selectivity	$Rb^+ > K^+ > Cs^+ > NH_4^+ \gg Na^+ > Li^+$
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Volatile anesthetics[6,7]: halothane (1 mM),[5] isofluorane (2 mM)
Gating inhibitors	None
Blockers	Ba^{2+} (500 mM), external pH (7.3),[8–10] arachidonic acid (100 mM) (see "Comments"), and anandamide (3 μM)[19]
Radioligands	None
Channel distribution	Brain,[11] heart,[12] lung, kidney,[13] small intestine, colon, pancreas, prostate, uterus, placenta
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation and deactivation with voltage steps seems to be instantaneous, but there is also a small, time-dependent change in P_o; current is half-blocked at pH 7.3 at physiological external conditions—increasing external potassium decreases proton blockade; pharmacology studies of the rat variant reveal blockade also by zinc, TEA, and quinidine[14,15]; K_{2P}3-like currents are reported in cerebellar granular neurons and motor-neurons[11,15]; interaction with 14-3-3 protein is essential for forward trafficking; K_{2P}3 can form heterodimers with K_{2P}9.1 in heterologous expression systems consistent with electrophysiological studies that suggest heterodimerzation; K_2P3 is also suggested to be a target for transmitter modulation of neuronal excitability[11,15]

aa, amino acids; chr., chromosome; TEA, tetrylethylammonium.

1. Manjunath NA, Bray-Ward P, Goldstein SAN, and Gallagher PG (1999) Assignment of the 2P domain, acid-sensitive potassium channel gene OAT1 (KCNK3) to human chromosome 2p23.3p24.1 and murine chromosome band 5B by in situ hybridization. *Cytogenet Cell Gen* **86:**242–243.

2. Kim D, Fujita A, Horio Y, and Kurachi Y (1998) Cloning and functional expression of a novel cardiac two-pore background K^+ channel (cTBAK-1). *Circ Res* **82:**513–518.

3. Leonoudakis D, Gray AT, Winegar BD, Kindler CH, Harada M, Taylor DM, Chavez RA, Forsayeth JR, and Yost CS (1998) An open rectifier potassium channel with two pore domains in tandem cloned from rat cerebellum. *J Neurosci* **18:**868–877.

4. Lopes CMB, Gallagher PG, Wong C, Buck M, and Goldstein SAN (1998) OATs: open, acid-sensitive, two P domain K^+ channels from mouse heart. *J Biophys* **74:**A44.

5. Washburn CP, Sirois JE, Talley EM, Guyenet PG, and Bayliss DA (2002) Serotonergic raphe neurons express TASK channel transcripts and a TASK-like pH- and halothane-sensitive K^+ conductance. *J Neurosci* **22:**1256–1265.

6. Buckler KJ, Williams BA, and Honoré E (2000) An oxygen-, acid- and anaesthetic-sensitive TASK-like background potassium channel in rat arterial chemo-receptor cells. *J Physiol (Lond)* **525:**135–142.

7. Sirois JE, Lei Q, Talley EM, Lynch C 3rd, and Bayliss DA (2000) The TASK-1 two-pore domain K^+ channel is a molecular substrate for neuronal effects of inhalation anesthetics. *J Neurosci* **20:**6347–6354.

8. Duprat F, Lesage F, Fink M, Reyes R, Heurteaux C, and Lazdunski M (1997) TASK, a human background K^+ channel to sense external pH variations near physiological pH. *EMBO J* **16:**5464–5471.

9. Lopes CMB, Gallagher PG, Buck ME, Butler MH, and Goldstein SAN (2000) Proton block and voltage-gating are potassium-dependent in the cardiac leak channel Kcnk3. *J Biol Chem* **275:**16969–16978.

10. Lopes CMB, Zilberberg N, and Goldstein SAN (2001) Block of Kcnk3 by protons: evidence that 2-P-domain potassium channel subunits function as homodimers. *J Biol Chem* **276:**24449–24452.

11. Millar JA, Barratt L, Southan AP, Page KM, Fyffe RE, Robertson B, and Mathie A (2000) A functional role for the two-pore domain potassium channel TASK-1 in cerebellar granule neurons. *Proc Natl Acad Sci USA* **97:**3614–3618.

12. Kim Y, Bang H, and Kim D (1999) TBAK-1 and TASK-1, two-pore K(+) channel subunits: kinetic properties and expression in rat heart. *Am J Physiol* **277:**H1669–H1678.

13. Czirjak G, Fischer T, Spat A, Lesage F, and Enyedi P (2000) TASK (TWIK-related acid-sensitive K^+ channel) is expressed in glomerulosa cells of rat adrenal cortex and inhibited by angiotensin II. *Mol Endocrinol* **14:**863–874.

14. Kindler CH, Yost CS, and Gray AT (1999) Local anesthetic inhibition of baseline potassium channels with two pore domains in tandem. *Anesthesiology* **90:**1092–1102.

15. Talley EM, Lei QB, Sirois JE, and Bayliss DA (2000) TASK-1, a two-pore domain K^+ channel, is modulated by multiple neurotransmitters in motoneurons. *Neuron* **25:**399–410.

16. Rajan S, Preisig-Muller R, Wischmeyer E, Nehring R, Hanley PJ, Renigunta V, Musset B, Schlichthorl G, Derst C, Karschin A, et al. (2002) Interaction with 14-3-3proteins promotes functional expression of the potassium channels TASK-1 and TASK-3. *J Physiol* **545:**13–26.

17. O'Kelly I, Butler MH, Zilberberg N, and Goldstein SA (2002) Forward transport. 14-3-3 binding overcomes retention in endoplasmic reticulum by dibasic signals. *Cell* **111:**577–588.

18. Girard C, Tinel N, Terrenoire C, Romey G, Lazdunski M, and Borsotto M (2002) p11, an annexin II subunit, an auxiliary protein associated with the background K^+ channel, TASK-1. *EMBO J* **21:**4439–4448.

19. Maingret F, Patel AJ, Lazdunski M, and Honoré E (2001) The endocannabinoid anandamide is a direct and selective blocker of the background K(+) channel TASK-1. *EMBO J* **15:**47–54.

20. Duprat F, Lesage F, Fink M, Reyes R, Heurteaux C, and Lazdunski M (1997) TASK, a human background K^+ channel to sense external pH variations near physiological pH. *EMBO J* **16:**5464–5471.

TABLE 4
K_{2P}4.1 channels

Channel name	K_{2P}4.1
Description	Two-pore domain potassium channel subunit; open rectifier
Other names	KCNK4, TRAAK
Molecular information	Human: 393aa, NM_016611, chr. 11q13, KCNK4,[1] GeneID: 50801, PMID: 10767409[1] Rat: 397aa, NM_053804, kcnk4 Mouse: 398aa, NM_008431, chr. 19, kcnk4
Associated subunits	Not established
Functional assays	Electrophysiological[2]
Current	Open rectifier
Conductance	46pS
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Arachidonic acid (10 mM),[3] mechanical stress,[4] heat[6] (see "Comments"), unsaturated fatty acids,[3] lysopholipids,[7] riluzole[8]
Gating inhibitors	None
Blockers	Gd^+
Radioligands	None
Channel distribution	Brain,[5] kidney, small intestine, placenta, prostate
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation and deactivation with voltage steps seem to be instantaneous; knockout mice have no obvious phenotype[9]; the open probability of K_{2P}4 increases with temperature with an activation threshold of 31°C in COS-7 cells

aa, amino acids; chr., chromosome.

1. Lesage F, Maingret F, and Lazdunski M (2000) Cloning and expression of human TRAAK, a poly-unsaturated fatty acids-activated and mechano-sensitive K(+) channel. *FEBS Lett* **471:**137–140.

2. Kim Y, Bang H, Gnatenco C, and Kim D (2001) Synergistic interaction and the role of C-terminus in the activation of TRAAK K^+ channels by pressure, free fatty acids and alkali. *Pflueg Arch Eur J Physiol* **442:**64–72.

3. Fink M, Lesage F, Duprat F, Heurteaux C, Reyes R, Fosset M, and Lazdunski M (1998) A neuronal two P domain K^+ channel stimulated by arachidonic acid and polyunsaturated fatty acids. *EMBO J* **17:**3297–3308.

4. Maingret F, Fosset M, Lesage F, Lazdunski M, and Honoré E (1999) TRAAK is a mammalian neuronal mechanogated K+ channel. *J Biol Chem* **274:**1381–1387.

5. Reyes R, Lauritzen I, Lesage F, Ettaiche M, Fosset M, and Lazdunski M (2000) Immunolocalization of the arachidonic acid and mechanosensitive baseline traak potassium channel in the nervous system. *Neuroscience* **95:**893–901.

6. Kang DW, Choe CY, and Kim D (2005) Thermosensitivity of the two-pore domain K^+ channels TREK-2 and TRAAK. *J Physiol* **564.1:**103–116.

7. Maingret F, Patel AJ, Lesage F, Lazdunski M, and Honoré E (2000) Lysophospholipids open the two-pore domain mechano-gated K(+) channels TREK-1 and TRAAK. *J Biol Chem* **275:**10128–10133.

8. Duprat F, Lesage F, Patel AJ, Fink M, Romey G, and Lazdunski M (2000) The neuroprotective agent riluzole activates the two P domain K + channels TREK-1 and TRAAK. *Mol Pharmacol* **57:**906–912.

9. Heurteaux C, Guy N, Laigle C, Blondeau N, Duprat F, Mazzuca M, Lang-Lazdunski L, Widmann C, Zanzouri M, Romey G, et al. (2004) TREK-1, a K^+ channel involved in neuroprotection and general anesthesia. *EMBO J* **23:**2684–2695.

TABLE 5
K_{2P}5.1 channels

Channel name	K_{2P}5.1
Description	Two-pore domain potassium channel subunit; open rectifier
Other names	KCNK5, TASK-2
Molecular information	Human: 499aa, NM_003740, chr. 6p21, KCNK5,[1] GeneID: 8645, PMID: 9812978[1] Rat: not cloned Mouse: 502aa, NM_021542, kcnk5
Associated subunits	Not established
Functional assays	Electrophysiological
Current	Open rectifier
Conductance	See "Comments"
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Volatile anaesthetics[2]: halothane (~570 mM)
Gating inhibitors	None
Blockers	Quinidine (22 mM), external pH (6.5),[6] local anesthetics: lidocaine (1 mM), bupivacaine (1 mM), clofilium (25 μM)[7]
Radioligands	None
Channel distribution	Brain,[3] kidney, liver, small intestine, pancreas, placenta
Physiological functions	A role in cell volume regulation[7,8] (see "Comments") and sensing external basolateral pH changes associated with HCO_3^- transport in primary-cultured proximal tubular cells[4]
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation and deactivation with voltage steps seem instantaneous; the conductance of K_{2P}5 depends on the ionic conditions; the slope conductance was reported as 15pS with 5 mM external potassium and as high as 60pS when external potassium is high (155 mM)[1]—this may reflect an Na^+-dependent inward rectification that becomes progressively less pronounced with time[5]; like K_{2P}16 and 17, current through K_{2P}5 channels is diminished at physiological pH; channel open probability increases with external pH; formation of an intersubunit disulfide bridge in K_{2P}5 does not affect channel activity[9]; exposure to hypotonicity (change from 300–200 mOsm in external solution) enhanced mK_{2P}5 currents when this channel was heterologously expressed in HEK293 cells, and osmotic cell shrinkage led to inhibition (change from 300–400 mOsm in external solution)

aa, amino acids; chr., chromosome.

1. Reyes R, Duprat F, Lesage F, Fink M, Salinas M, Farman N, and Lazdunski M (1998) Cloning and expression of a novel pH-sensitive two pore domain K^+ channel from human kidney. *J Biol Chem* **273:**30863–30869.

2. Gray AT, Zhao BB, Kindler CH, Winegar BD, Mazurek MJ, Xu J, Chavez RA, Forsayeth JR, and Yost CS (2000) Volatile anesthetics activate the human tandem pore domain baseline K^+ channel KCNK5. *Anesthesiology* **92:**1722–1730.

3. Gabriel A, Abdallah M, Yost CS, Winegar BD, and Kindler CH (2002) Localization of the tandem pore domain K^+ channel KCNK5 (TASK-2) in the rat central nervous system. *Brain Res Mol Brain Res* **98:**153–163.

4. Warth R, Barriere H, Meneton P, Bloch M, Thomas J, Tauc M, Heitzmann D, Romeo E, Verrey F, Mengual R, et al. (2004) Proximal renal tubular acidosis in TASK2 K^+ channel-deficient mice reveals a mechanism for stabilizing bicarbonate transport. *Proc Natl Acad Sci USA* **101:**8215–8220.

5. Morton MJ, Chipperfield S, Abohamed A, Sivaprasadarao A, and Hunter M (2004) Na^+-induced in ward rectification in the two-pore domain K^+ channel, TASK-2. *Am J Physiol Renal Physiol* **288:**F162–F169.

6. Kang DW and Kim D (2004) Single channel properties and pH sensitivity of two-pore domain K+ channels of the TALK family. *Biochem Biophys Res Comm* **315:**836–844.

7. Niemeyer MI, Cid LP, Barros LF, and Sepulveda FV (2001) Modulation of the two-pore domain acid-sensitive K+ channel TASK-2 (KCNK5) by changes in cell volume. *J Biol Chem* **276:**43166–43174.

8. Barriere H, Belfodil R, Rubera I, Tauc M, Lesage F, Poujeol C, Guy N, Barhanin J, and Poujeol P (2003) Role of TASK2 potassium channels regarding volume regulation in primary cultures of mouse proximal tubules. *J Gen Physiol* **122:**177–190.

9. Niemeyer MI, Cid LP, Valenzuela X, Paeile V, and Sepulveda FV (2003) Extracellular conserved cysteine forms anointer subunit disulphide bridge in the KCNK5 (TASK-2) K+ channel without having an essential effect upon activity. *Mol Membr Biol* **20:**185–191.

TABLE 6
K_{2P}6.1 channels

Channel name	K_{2P}6.1
Description	Two-pore domain potassium channel subunit; open rectifier
Other names	KCNK6, TWIK-2, TOSS
Molecular information	Human: 313aa,[1] NM_004823, chr0.19q13-1,[2] KCNK6, GeneID: 9424, PMID: 10359073[1] Rat: 313aa, NM_053806, kcnk6 Mouse: not cloned
Associated subunits	Not established
Functional assays	Electrophysiological
Current	Open rectifier[3,4]
Conductance	<5pS
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Arachidonic acid
Gating inhibitors	None
Blockers	Ba^{2+} (100 μM), quinidine (100 mM), volatile anesthetics
Radioligands	None
Channel distribution	Pancreas, placenta, heart (see "Comments")
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation and deactivation with voltage steps seem to be instantaneous; displays time-dependent inactivation at depolarized potentials[4]; the rat variant has been reported to be widely expressed (including brain, lung, kidney, liver, spleen, heart, esophagus, stomach, colon, and skeletal muscle)

aa, amino acids; chr., chromosome; TOSS, TWIK-originated similarity sequence.

1. Pountney DJ, Gulkarov I, Vega-Saenz de Miera E, Holmes D, Saganich M, Rudy B, Artman M, and Coetzee WA (1999) Identification and cloning of TWIK-originated similarity sequence (TOSS): a novel human 2-pore K^+ channel principal subunit. *FEBS Lett* **450:**191–196.

2. Gray AT, Kindler CH, Sampson ER, and Yost CS (1999) Assignment of KCNK6 encoding the human weak inward rectifier potassium channel TWIK-2 to chromosome band 19q13.1 by radiation hybrid mapping. *Cytogenet Cell Genet* **84:**190–191.

3. Chavez RA, Gray AT, Zhao BB, Kindler CH, Mazurek MJ, Mehta Y, Forsayeth JR, and Yost CS (1999) TWIK-2, a new weak inward rectifying member of the tandem pore domain potassium channel family. *J Biol Chem* **274:**7887–7892.

4. Patel AJ, Maingret F, Magnone V, Fosset M, Lazdunski M, and Honoré E (2000) TWIK-2, an inactivating 2P domain K^+ channel. *J Biol Chem* **275:**28722–28730.

TABLE 7
K_{2P}7.1 channels

Channel name	K_{2P}7.1
Description	Two-pore domain potassium channel subunit
Other names	KCNK7, kcnk8 (see "Comments")
Molecular information	Human: 307aa (see "Comments"), NM_033347, chr0.11q13, KCNK7, GeneID:10089, PMID: 10206991[1] Rat: not cloned Mouse: 335aa, NM_010609, chr. 19,2B, kcnk8 (see "Comments")[1,2]
Associated subunits	Not established
Functional assays	Electrophysiological
Current	Not established (see "Comments")
Conductance	Not established
Ion selectivity	Not established
Activation	Not established
Inactivation	Not established
Activators	None
Gating inhibitors	None
Blockers	None
Radioligands	None
Channel distribution	Brain (human), retina (mouse)
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	The product of this gene has not yet been shown to form a functional channel; five splice variants have been identified in human; the mouse isolate was cited as kcnk6 and then kcnk8 but is now called K_{2P}7 due to its homology and syntenic location to human KCNK7[2]

aa, amino acids; chr., chromosome.

1. Salinas M, Reyes R, Lesage F, Fosset M, Heurteaux C, Romey G, and Lazdunski M (1999) Cloning of a new mouse two-P domain channel subunit and a human homologue with a unique pore structure. *J Biol Chem* **274:**11751–11760.

2. Bockenhauer D, Nimmakayalu MA, Ward DC, Goldstein SAN, and Gallagher PG (2000) Genomic organization and chromosomal localization of the murine 2 P domain potassium channel gene Kcnk8: conservation of gene structure in 2P domain potassium channels. *Gene* **261:**365–372.

TABLE 8
K_{2P}9.1 channels

Channel name	K_{2P}9.1
Description	Two-pore domain potassium channel subunit; open rectifier
Other names	KCNK9, TASK-3
Molecular information	Human: 374aa, NM_016601, chr0.8q24-3, KCNK9,[1–3] GeneID: 51305, PMID:10734076 Rat: 395aa, NM_053405, kcnk9 Mouse: not cloned
Associated subunits	14-3-3 (see "Comments")[7,8]
Functional assays	Electrophysiological[1–3,5–11]
Current	Not established (see "Comments")
Conductance	27pS (see "Comments")
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	None
Gating inhibitors	None
Blockers	External pH (6.5),[3] ruthenium red (700 nM)[8]
Radioligands	None
Channel distribution	Brain (see "Comments")[1]
Physiological functions	See "Comments"[4–6]
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation and deactivation with voltage steps seem to be instantaneous; the guinea pig variant is reported to have the same conductance and distribution as human and a conductance of 60pS; Northern blot analysis suggests that rat K_{2P}9.1 expression outside the CNS is extremely low, as is noted for the human and guinea pig gene; K_{2P}9 gene is amplified in several human carcinomas, and overexpression of K_{2P}9 protein in cell lines promotes tumor formation[4,5]; like K_{2P}3, surface expression of K_{2P}9 depends on its association with 14-3-3 to release it from the endoplasmic reticulum[7,8]; potential heterodimerization of K_{2P}9 is discussed under K_{2P}3[9]

aa, amino acids; chr., chromosome; CNS, central nervous system.

1. Chapman CG, Meadows HJ, Godden RJ, Campbell DA, Duckworth M, Kelsell RE, Murdock PR, Randall AD, Rennie GI, and Gloger IS (2000) Cloning, localisation and functional expression of a novel human, cerebellum specific, two pore domain potassium channel. *Mol Brain Res* **82:**74–83.
2. Kim Y, Bang H, and Kim D (2000) TASK-3, a new member of the tandem pore K(+) channel family. *J Biol Chem* **275:**9340–9347.
3. Rajan S, Wischmeyer E, Xin Liu G, Preisig-Muller R, Daut J, Karschin A, and Derst C (2000) TASK-3, a novel tandem pore domain acid-sensitive K^+ channel—an extracellular histidine as pH sensor. *J Biol Chem* **275:**16650–16657.
4. Mu D, Chen L, Zhang X, See LH, Koch CM, Yen C, Tong JJ, Spiegel L, Nguyen KC, Servoss A, et al. (2003) Genomic amplification and oncogenic properties of the KCNK9 potassium channel gene. *Cancer Cell* **3:**297–302.
5. Pei L, Wiser O, Slavin A, Mu D, Powers S, Jan LY, and Hoey T (2003) Oncogenic potential of TASK3 (Kcnk9) depends on K+ channel function. *Proc Natl Acad Sci USA* **100:**7803–7807.
6. Lauritzen I, Zanzouri M, Honoré E, Duprat F, Ehrengruber MU, Lazdunski M, and Patel AJ (2003) K^+-dependent cerebellar granule neuron apoptosis: role of TASK leak K+ channels. *J Biol Chem* **278:**32068–32076.
7. Rajan S, Preisig-Muller R, Wischmeyer E, Nehring R, Hanley PJ, Renigunta V, Musset B, Schlichthorl G, Derst C, Karschin A, et al. (2002) Interaction with 14-3-3 proteins promotes functional expression of the potassium channels TASK-1 and TASK-3. *J Physiol* **545:**13–26.
8. O'Kelly I, Butler MH, Zilberberg N, and Goldstein SA (2002) Forward transport. 14-3-3binding overcomes retention in endoplasmic reticulum by dibasic signals. *Cell* **111:**577–588.
9. Kang DW, Han JH, Talley EM, Bayliss DA, and Kim D (2004) Functional expression of TASK-1/TASK-3 heteromer in cerebellar granule neurons. *J Physiol* **554:**64–77.
10. Czirjak G and Enyedi P (2003) Ruthenium red inhibits TASK-3 potassium channel by interconnecting glutamate 70 of the two subunits. *Mol Pharmacol* **63:**646–652.
11. Vega-Saenz de Miera E, Lau DH, Zhadina M, Pountney D, Coetzee WA, and Rudy B (2001) KT3.2 and KT3.3, two novel human two-pore K(+) channels closely related to TASK-1. *J Neurophysiol* **86:**130–142.

TABLE 9
K_{2P}10.1 channels

Channel name	K_{2P}10.1
Description	Two-pore domain potassium channel subunit; open rectifier[1]
Other names	KCNK10, TREK-2
Molecular information	Human: 538aa (see 'Comments'), NM_138317, chr0.14q31, KCNK10, GeneID: 54207, PMID: 10747911[1] Rat: 538aa, NM_023096, kcnk10 Mouse: not cloned
Associated subunits	Not established
Functional assays	Electrophysiological
Current	Open rectifier[2]
Conductance	100pS (see "Comments")
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Arachidonic acid, docosahexaenoic acid, linoleic acid, lysophosphatidylcholine,[3] intracellular acidification, volatile anesthetics: halothane (~1 mM), isoflurane (~1 mM); riluzole (~1 mM), heat,[6] mechanical stress[3]
Gating inhibitors	None
Blockers	Quinidine (100 mM), PKA, PKC
Radioligands	None
Channel distribution	Kidney, pancreas, prostate, thymus, liver, heart (see "Comments")[2]
Physiological functions	See "Comments"[4, 5]
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation and deactivation with voltage steps seem to be instantaneous; splice variants have been identified in human and rat; the rat variant is reported to have a conductance of 68pS and to be expressed in brain; K_{2P}10-like currents are observed in cerebellar granular neurons, magnocellular neurosecretory cells of rat supraoptic nucleus,[4,5] rat cortical astrocytes,[7] and insulin-secreting MIN6 cells[8]

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

1. Bang H, Kim Y, and Kim D (2000) TREK-2, a new member of the mechano-sensitive tandem-pore K^+ channel family. *J Biol Chem* **275:**17412–17419.
2. Gu W, Schlichthorl G, Hirsch JR, Engels H, Karschin C, Karschin A, Derst C, Steinlein OK, and Daut J (2002) Expression pattern and functional characteristics of two novel splice variants of the two-pore-domain potassium channel TREK-2. *J Physiol* **539:**657–668.
3. Lesage F, Terrenoire C, Romey G, and Lazdunski M (2000) Human TREK2, a 2P domain mechano-sensitive K^+ channel with multiple regulations by polyunsaturated fatty acids, lysophospholipids, and Gs, Gi, and Gq protein-coupled receptors. *J Biol Chem* **275:**28398–28405.
4. Han J, Truell J, Gnatenco C, and Kim D (2002) Characterization of four types of background potassium channels in rat cerebellar granule neurons. *J Physiol* **542:**431–444.
5. Han J, Gnatenco C, Sladek CD, and Kim D (2003) Background and tandem-pore potassium channels in magnocellular neurosecretory cells of the rat supraoptic nucleus. *J Physiol* **546:**625–639.
6. Kang DW, Choe CY, and Kim D (2005) Thermosensitivity of the two-pore domain K^+ channels TREK-2 and TRAAK. *J Physiol* **564:**103–116.
7. Gnatenco C, Han JH, Snyder AK, and Kim D (2002) Functional expression of TREK-2 K+ channel in cultured astrocytes. *Brain Res* **931:**56–67.
8. Kang DW, Choe C, and Kim D (2004) Functional expression ofTREK-2 in insulin-secreting MIN6 cells. *Biochem Biophys Res Commun* **323:**323–331.

TABLE 10
K_{2P}12.1 channels

Channel name	K_{2P}12.1
Description	Two-pore domain potassium channel subunit[1]
Other names	KCNK12, THIK-2
Molecular information	Human: 430aa, NM_022055, chr0.2p22-p21, KCNK12, GeneID: 56660, PMID: 11060316[1] Rat: 430aa, NM_022292, kcnk12 Mouse: not cloned
Associated subunits	Not established
Functional assays	Electrophysiological
Current	Not established (see "Comments")[1,2]
Conductance	No function demonstrated
Ion selectivity	Not established
Activation	Not established
Inactivation	Not established
Activators	None
Gating inhibitors	None
Blockers	None
Radioligands	None
Channel distribution	Brain, heart, lung, kidney, liver, small intestine, colon, pancreas, prostate, placenta, spleen, thymus, ovary
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	The product of this gene has not yet been shown to be a functional channel

aa, amino acids; chr., chromosome.

1. Rajan S, Wischmeyer E, Karschin C, Preisig-Muller R, Grzeschik KH, Daut J, Karschin A, and Derst C (2001) THIK-1 and THIK-2, a novel subfamily of tandem pore domain K^+ channels. *J Biol Chem* **276:**7302–7311.

2. Girard C, Duprat F, Terrenoire C, Tinel N, Fosset M, Romey G, Lazdunski M, and Lesage F (2001) Genomic and functional characteristics of novel human pancreatic 2P domain K^+ channels. *Biochem Biophys Res Commun* **282:**249–256.

TABLE 11
K_{2P}13.1 channels

Channel name	K_{2P}13.1
Description	Two-pore domain potassium channel subunit; open rectifier[1]
Other names	KCNK13, THIK-1
Molecular information	Human: 408aa, NM_022054, chr0.14q24.1-24.3, KCNK13, GeneID: 56659, PMID: 11060316[1] Rat: 405aa, NM_022293, kcnk13 Mouse: not cloned
Associated subunits	Not established
Functional assays	Electrophysiological
Current	Open rectifier
Conductance	Not established
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Arachidonic acid (0.98 mM)
Gating inhibitors	None
Blockers	Ba^{2+}, halothane (2.83 mM)
Radioligands	None
Channel distribution	Brain, heart, lung, kidney, liver, spleen
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation and deactivation with voltage steps seem to be instantaneous; K_{2P}13-like channels are found in the central nervous system of *Aplysia californica*[2]

aa, amino acids; chr., chromosome.

1. Rajan S, Wischmeyer E, Karschin C, Preisig-Muller R, Grzeschik KH, Daut J, Karschin A, and Derst C (2001) THIK-1 and THIK-2, a novel subfamily of tandem pore domain K^+ channels. *J Biol Chem* **276:**7302–7311.

2. Jezzini SH and Moroz LL (2004) Identification and distribution of a two-pore domain potassium channel in the CNS of *Aplysia californica*. *Brain Res Mol Brain Res* **27:**7–38.

TABLE 12
K_{2P}15.1 channels

Channel name	K_{2P}15.1
Description	Two-pore domain potassium channel subunit
Other names	KCNK15, TASK-5,[1,2] KT3.3[3]
Molecular information	Human: 330aa, NM_022358, chr0.20q12, KCNK15, GeneID: 60598, PMID: 11409881[1] Rat: 318aa, AF467250 Mouse: 324aa, XM_141526
Associated subunits	Not established
Functional assays	Electrophysiological
Current	Not established (see "Comments")
Conductance	Not established
Ion selectivity	Not established
Activation	Not established
Inactivation	Not established
Activators	None
Gating inhibitors	None
Blockers	None
Radioligands	None
Channel distribution	Brain, heart, lung, kidney, liver, pancreas, adrenal gland, thyroid, salivary gland, placenta
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	The product of this gene has not yet been shown to be a functional channel

aa, amino acids; chr., chromosome.

1. Kim D and Gnatenco C (2001) TASK-5, a new member of the tandem-pore K(+) channel family. *Biochem Biophys Res Commun* **284:**923–930.
2. Ashmole I, Goodwin PA, and Stanfield PR (2001) TASK-5, a novel member of the tandem pore K^+ channel family. *Pflueg Arch Eur J Physiol* **442:**828–833.
3. Vega-Saenz de Miera E, Lau DH, Zhadina M, Pountney D, Coetzee WA, and Rudy B (2001) KT3.2 and KT3.3, two novel human two-pore K(+) channels closely related toTASK-1. *J Neurophysiol* **86:**130–142.

TABLE 13
K_{2P}16.1 channels

Channel name	K_{2P}16.1
Description	Two-pore domain potassium channel subunit; open rectifier
Other names	KCNK16, TALK-1
Molecular information	Human: 309aa, NM_032115, chr0.6p21.1-2, KCNK16, GeneID: 83795, PMID: 11263999[1] Rat: not cloned Mouse: 337aa, XM_138942
Associated subunits	Not established
Functional assays	Electrophysiological[1]
Current	Open rectifier
Conductance	21pS at −60 mV and 10 pS at +60 mV[2]
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Isoflurane (~800 mM), nitric oxide and reactive oxygen species[3]
Gating inhibitors	None
Blockers	Ba^{2+} (1 mM), quinidine (100 mM), chloroform (~800 mM), external pH (see "Comments")
Radioligands	None
Channel distribution	Heart, lung, liver, pancreas,[1] and placenta
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation and deactivation with voltage steps seem to be instantaneous; the open probability of both K_{2P}16 and 17 increases with external pH—at present, it is unclear whether this represents proton block at physiological levels or activation of the channel by supraphysiological alkaline pHo; there are four splice variants of K_{2P}16, two of which are functional[4]

aa, amino acids; chr., chromosome.

1. Girard C, Duprat F, Terrenoire C, Tinel N, Fosset M, Romey G, Lazdunski M, and Lesage F (2001) Genomic and functional characteristics of novel human pancreatic 2P domain K(+) channels. *Biochem Biophys Res Commun* **282:**249–256.
2. Kang D and Kim D (2004) Single-channel properties and pH sensitivity of two-pore domain K^+ channels of the TALK family. *Biochem Biophys Res Commun* **315:**836–844.
3. Duprat F, Girard C, Jarretou G, and Lazdunski M (2004) Pancreatic two P domain K^+ channels TALK-1 and TALK-2 are activated by nitric oxide and reactive oxygen species. *J Physiol* **562:**235–244.
4. Han JH, Kang D, and Kim D (2003) Functional properties of four splice variants of a human pancreatic tandem-pore K^+ channel, TALK-1. *Am J Physiol* **285**:C529–C538.

TABLE 14
K_{2P}17.1 channels

Channel name	K_{2P}17.1
Description	Two-pore domain potassium channel subunit; open rectifier
Other names	KCNK17, TASK-4, TALK-2
Molecular information	Human: 332aa, NM_031460, chr0.6p21.1-2, KCNK17,[1] GeneID: 89822, PMID: 11263999[1] Rat: not cloned Mouse: not cloned
Associated subunits	Not established
Functional assays	Electrophysiological[1]
Current	Open rectifier
Conductance	Not established
Ion selectivity	Not established
Activation	See "Comments"
Inactivation	See "Comments"
Activators	Nitric oxide and reactive oxygen species[3]
Gating inhibitors	None
Blockers	Ba^{2+}, external pH,[2,3] chloroform (~800 mM)
Radioligands	None
Channel distribution	Heart, lung, liver, pancreas,[1] placenta
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation and deactivation with voltage steps seem to be instantaneous; the open probability of K_{2P}17 increases as pHo is raised above physiological levels (see K_{2P}16)

aa, amino acids; chr., chromosome.

1. Girard C, Duprat F, Terrenoire C, Tinel N, Fosset M, Romey G, Lazdunski M, and Lesage F (2001) Genomic and functional characteristics of novel human pancreatic 2P domain K(+) channels. *Biochem Biophys Res Commun* **282:**249–256.

2. Decher N, Maier M, Dittrich W, Gassenhuber J, Bruggemann A, Busch AE, and Steinmeyer K (2001) Characterization of TASK-4, a novel member of the pH-sensitive, two-pore domain potassium channel family. *FEBS Lett* **492:**84–89.

3. Duprat F, Girard C, Jarretou G, and Lazdunski M (2004) Pancreatic two P domain K^+ channels TALK-1 and TALK-2 are activated by nitric oxide and reactive oxygen species. *J Physiol* **562:**235–244.

TABLE 15
K_{2P}18.1 channels

Channel name	K_{2P}18.1
Description	Two-pore domain potassium channel subunit; open rectifier
Other names	KCNK18, TRESK-1/TRESK-2 (see "Comments")
Molecular information	Human: 384aa, NM_181840, chr. 10q26.11, GeneID: 338567, PMID: 12754259[1] Rat: 405aa, NM_001003820 Mouse: 394aa, NM_207261
Associated subunits	Not established
Functional assays	Electrophysiological[1]
Current	Open rectifier
Conductance	13pS at +60 mV and 16pS at −60 mV for mouse K_{2P}18[3]
Ion selectivity	Not established
Activation	Rapid
Inactivation	Slow
Activators	Cytoplasmic Ca^{2+} via calcineurin, volatile anesthetics[2,4]
Gating inhibitors	None
Blockers	Ba^{2+} (3 mM), quinine (100 mM) quinidine (100 mM), free fatty acids, external acidic pH
Radioligands	None
Channel distribution	Cerebrum, cerebellum, brain stem, spinal cord, and testis
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Activation is instantaneous; single channel currents are noninactivating and time-dependent; TRESK2 was cloned from mouse testis and shares 65% homology with human K_{2P}18; as study continues, it will become clear whether this is the true correlate of the human channel or a distinct gene (K_{2P}19); personal communication indicates that distinct cDNAs for both TRESK-1 and TRESK-2 are present in human tissues (D. Kim, personal communication)

aa, amino acids; chr., chromosome.

1. Sano Y, Inamura K, Miyake A, Mochizuki S, Kitada C, Yokoi H, Nozawa K, Okada H, Matsushime H, and Furuichi K (2003) A novel two-pore domain K^+ channel, TRESK, is localized in the spinal cord. *J Biol Chem* **278:**27406–27412.

2. Czirjak G, Toth ZE, and Enyedi P (2004) The two-pore-domain K^+ channel, TRESK, is activated by the cytoplasmic calcium signal through calcineurin. *J Biol Chem* **279:**18550–18558.

3. Kang D, Mariash E, and Kim D (2004) Functional expression of TRESK-2, a new member of the tandem-pore K + channel family. *J Biol Chem* **279:**28063–28070.

4. Liu C, Au JD, Zou HL, Cotton JF, and Yost CS (2004) Potent activation of the human tandem pore domain K channel TRESK with clinical concentrations of volatile anesthetics. *Anesth Analg* **99:**1715–1722.