0031-6997/05/5704-463–472$7.00
PHARMACOLOGICAL REVIEWS
Vol. 57, No. 4
50407/3069986
Pharmacol Rev 57:463–472, 2005
Printed in U.S.A

International Union of Pharmacology. LII. Nomenclature and Molecular Relationships of Calcium-Activated Potassium Channels

AGUAN D. WEI, GEORGE A. GUTMAN, RICHARD ALDRICH, K. GEORGE CHANDY, STEPHAN GRISSMER, AND HEIKE WULFF

Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, Missouri (A.D.W.); Departments of Microbiology and Molecular Genetics (G.A.G.) and Physiology and Biophysics (K.G.C.), University of California, Irvine, Irvine, California; Molecular and Cellular Physiology Department, Stanford University, Stanford, California (R.A.); Department of Medical Pharmacology and Toxicology, University of California, Davis, Davis, California (H.W.); and Department of Applied Physiology, University Ulm, Ulm, Germany (S.G.)

Introduction

The second major group of six/seven transmembrane potassium-selective channels consists of the K_{Ca} channels (for reviews, see Lingle, 2002; Magleby, 2003; Moczydlowski, 2004; Stocker, 2004; Cox, 2005), and Table 1 shows the International Union of Pharmacology (IUPHAR[1]) names of the members of this group together with their HUGO Gene Nomenclature Committee (HGNC) designations and other commonly used names. The phylogenetic trees in Fig. 1 illustrate the fact that these channels form two well defined but only distantly related groups.

One of these groups (Fig. 1A) includes the three "small-conductance" K_{Ca} channels (K_{Ca}2.1, 2.2, and 2.3) (Kohler et al., 1996) and the "intermediate-conductance" channel K_{Ca}3.1 (Ishii et al., 1997; Joiner et al., 1997). These channels are voltage-insensitive and are activated by low concentrations of internal Ca^{2+} ($<$1.0 μM), in contrast to K_{Ca}1.1 (KCNMA1, Slo1), which is activated by both voltage and internal Ca^{2+}. The three small-conductance K_{Ca} channels are sensitive to block by apamin (100 pM–10 nM), which distinguishes them from all other K_{Ca} channels. Both small- and intermediate-conductance K_{Ca} channels play important roles in many processes involving Ca^{2+}-dependent signaling in both electrically excitable and nonexcitable cells. They do not bind Ca^{2+} directly but rather detect Ca^{2+} by virtue of calmodulin, which is constitutively bound to the C-terminal region (Xia et al., 1998; Fanger et al., 1999). Binding of calcium to this calmodulin results in conformational changes that are in turn responsible for channel gating (Schumacher et al., 2001).

The tree shown in Fig. 1B illustrates the sequence relationships within the second group of K_{Ca} channels, which includes K_{Ca}1.1 (Slo or Slo1), K_{Ca}4.1 (Slack or Slo2.2), K_{Ca}4.2 (Slick or Slo2.1), and K_{Ca}5.1 (Slo3). K_{Ca}1.1 has been extensively studied in the brain, cochlea, and muscle, and alternate splicing of its mRNA is known to produce considerable functional diversity (Weiger et al., 2002; Faber and Sah, 2003). Unlike the K_{Ca}2 and K_{Ca}3 channels, binding of calcium by K_{Ca}1.1 is not dependent on its association with calmodulin but is thought to be mediated by at least three divalent cation binding sites in the cytoplasmic carboxyl domain of each channel subunit. Two independent high-affinity Ca^{2+} binding sites are formed by a negatively charged segment in the distal carboxyl terminal portion, termed the "calcium bowl" (Schreiber and Salkoff, 1997) and within the first RCK domain encoded by the proximal C-terminal portion (Bao et al., 2002; Xia et al., 2002). A third low-affinity divalent cation binding site is also found in the first RCK domain (Shi et al., 2002), which contributes to activation by Mg^{2+} and Ca^{2+} at high concentrations ($>$1 mM).

The three other members of this group, K_{Ca}4.1, 4.2, and 5.2 (Joiner et al., 1997; Schreiber et al., 1998; Yuan et al., 2003), were all included in the K_{Ca} nomenclature since they all are clearly members of this structurally related group of genes. However, much more is now known about the functional properties of the members of this gene family than was known when these names were assigned several years ago, and this presents a possible conundrum for a nomenclature based on functional rather than structural similarity. Unlike the founding member K_{Ca}1.1, which is in fact activated by internal Ca^{2+}, none of the other members of this group seems to be similarly Ca^{2+}-activated. In fact, for the most part, these three are insensitive to internal Ca^{2+}. K_{Ca}4.2 and K_{Ca}4.1 are activated by internal Na^+ and Cl^- (Yuan et al., 2003),

Address correspondence to: Dr. Aguan D. Wei, Department of Anatomy and Neurobiology, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110. E-mail: a.wei@wustl.edu

A.D.W. and H.W. serve as the Subcommittee on K_{Ca} Channels of the Nomenclature Committee of the International Union of Pharmacology.

Article, publication date, and citation information can be found at http://pharmrev.aspetjournals.org.
doi:10.1124/pr.57.4.9.

[1] Abbreviations: IUPHAR, International Union of Pharmacology; HGNC, HUGO Gene Nomenclature Committee; RCK, regulator of K^+ conductance.

TABLE 1
K_{Ca} channels

IUPHAR names of the members of the K_{Ca} group of potassium channels are shown, together with their HGNC designations and other commonly used names.

IUPHAR	HGNC	Other
$K_{Ca}1.1$	*KCNMA1*	Slo, Slo1, BK
$K_{Ca}2.1$	*KCNN1*	$SK_{Ca}1$
$K_{Ca}2.2$	*KCNN2*	$SK_{Ca}2$
$K_{Ca}2.3$	*KCNN3*	$SK_{Ca}3$
$K_{Ca}3.1$	*KCNN4*	$IK_{Ca}1$
$K_{Ca}4.1$	*KCNT1*	Slack, Slo2.2
$K_{Ca}4.2$	*KCNT2*	Slick, Slo2.1
$K_{Ca}5.1$	*KCNU1*	Slo3

BK, big-conductance K^+ channel; SK, small-conductance K^+ channel; IK, intermediate-conductance K^+ channel.

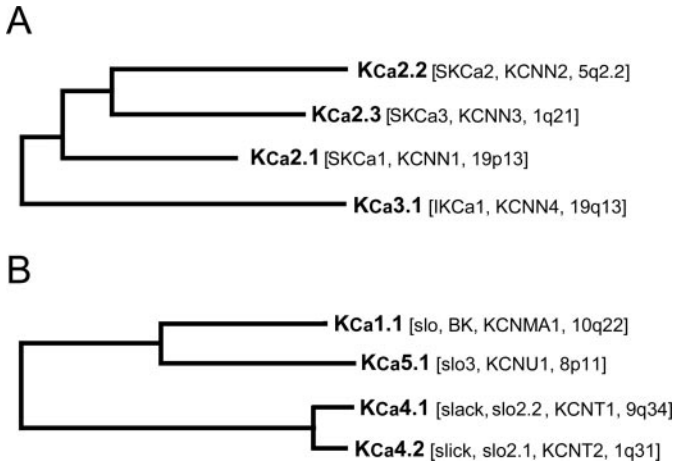

FIG. 1. Phylogenetic tree for K_{Ca} channels. A, $K_{Ca}2/3$ group. B, $K_{Ca}1/4/5$ group. Amino acid sequence alignments and phylogenetic analysis for these two groups of four human K_{Ca} channels were generated as described in the legend for Fig. 1 of "International of Union of Pharmacology LIII. Nomenclature and Molecular Relationships of Voltage-Gated Potassium Channels." No new channels have been added to these topologies since they appeared in the earlier edition of this compendium. IUPHAR and HGNC names of the genes are shown together with other commonly used names and their chromosomal localization.

and $K_{Ca}5.1$ is activated by internal alkalization (OH^-) (Schreiber et al., 1998). Therefore, although they are structurally related to $K_{Ca}1.1$, these three channels cannot correctly be described as "calcium-activated" channels based on functional criteria. This may be a subject for discussion among researchers in this field and those bodies responsible for standardizing gene nomenclature.

Tables 2 through 9 present the $K_{Ca}1.1$ through $K_{Ca}5.1$ channels.

REFERENCES

Bao L, Rapin AM, Holmstrand EC, and Cox DH (2002) Elimination of the BK_{Ca} channel's high-affinity Ca^{2+} sensitivity. *J Gen Physiol* **120:**173–189.

Cox DH (2005) The BK_{Ca} channel's Ca^{2+}-binding sites, multiple sites, multiple ions. *J Gen Physiol* **125:**253–255.

Faber ESL and Sah P (2003) Calcium-activated potassium channels: multiple contributions to neuronal function. *Neuroscientist* **9:**181–194.

Fanger CM, Ghanshani S, Logsdon NJ, Rauer H, Kalman K, Zhou J, Beckingham K, Chandy KG, Cahalan MD, and Aiyar J (1999) Calmodulin mediates calcium-dependent activation of the intermediate conductance K_{Ca} channel, $IK_{Ca}1$. *J Biol Chem* **274:**5746–5754.

Ishii TM, Silvia C, Hirschberg B, Bond CT, Adelman JP, and Maylie J (1997) A human intermediate conductance calcium-activated potassium channel. *Proc Natl Acad Sci USA* **94:**11651–11656.

Joiner WJ, Tang MD, Wang LY, Dworetzky SI, Boissard CG, Gan L, Gribkoff VK, and Kaczmarek LK (1998) Formation of intermediate-conductance calcium-activated potassium channels by interaction of Slack and Slo subunits. *Nat Neurosci* **1:**462–469.

Joiner WJ, Wang LY, Tang MD, and Kaczmarek LK (1997) hSK4, a member of a novel subfamily of calcium-activated potassium channels. *Proc Natl Acad Sci USA* **94:**11013–11018.

Kohler M, Hirschberg B, Bond CT, Kinzie JM, Marrion NV, Maylie J, and Adelman JP (1996) Small-conductance, calcium-activated potassium channels from mammalian brain. *Science* **273:**1709–1714.

Lingle CJ (2002) Setting the stage for molecular dissection of the regulatory components of BK channels. *J Gen Physiol* **120:**261–265.

Magleby KL (2003) Gating mechanism of BK (Slo1) channels: so near, yet so far. *J Gen Physiol* **121:**81–96.

Moczydlowski EG (2004) BK channel news: full coverage on the calcium bowl. *J Gen Physiol* **123:**471–473.

Schreiber M and Salkoff L (1997) A novel calcium-sensing domain in the BK channel. *Biophys J* **73:**1355–1363.

Schreiber M, Wei A, Yuan A, Gaut J, Saito M, and Salkoff L (1998) Slo3, a novel pH-sensitive K^+ channel from mammalian spermatocytes. *J Biol Chem* **273:**3509–3516.

Schumacher MA, Rivard AF, Bachinger HP, and Adelman JP (2001) Structure of the gating domain of a Ca^{2+}-activated K^+ channel complexed with Ca^{2+}/calmodulin. *Nature (Lond)* **410:**1120–1124.

Shi J, Krishnamoorthy G, Yang Y, Hu L, Chaturvedi N, Harilal D, Qin J, and Cui J (2002) Mechanism of magnesium activation of calcium-activated potassium channels. *Nature (Lond)* **418:**876–880.

Stocker M (2004) Ca^{2+}-activated K+ channels: molecular determinants and function of the SK family. *Nat Rev Neurosci* **5:**758–770.

Weiger TM, Hermann A, and Levitan IB (2002) Modulation of calcium-activated potassium channels. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* **188:**79–87.

Xia XM, Fakler B, Rivard A, Wayman G, Johnson-Pais T, Keen JE, Ishii T, Hirschberg B, Bond CT, Lutsenko S, et al. (1998) Mechanism of calcium gating in small-conductance calcium-activated potassium channels. *Nature (Lond)* **395:**503–507.

Xia XM, Zeng X, and Lingle CJ (2002) Multiple regulatory sites in large-conductance calcium-activated potassium channels. *Nature (Lond)* **418:**880–884.

Yuan A, Santi CM, Wei A, Wang ZW, Pollak K, Nonet M, Kaczmarek L, Crowder CM, and Salkoff L (2003) The sodium-activated potassium channel is encoded by a member of the Slo gene family. *Neuron* **37:**765–773.

TABLE 2
K_{Ca}1.1 channels

Channel name	K_{Ca}1.1
Description	Large conductance, calcium- and voltage-activated potassium channel
Other names	Slo[1–8], Slo1, BK channel, maxi K^+ channel
Molecular information	Human: 1182aa, NM_001014797 (transcript variant 1), chr. 10q22.3,[6] KCNMA1 Mouse: 1171aa, NM_010610, chr. 14; Rat: 1243aa, NM_031828, chr. 15p16
Associated subunits	KCNMB1–4,[29] BK-β,[9,10] heteromeric association with Slack (rat),[11] β2-adrenergic receptor[23]
Functional assays	Voltage clamp, membrane potential, radioligand binding
Current	Maxi K^+ calcium-activated current in cochlea, smooth muscle, neurones in brain
Conductance	260pS[2–8]
Ion selectivity	$P_K/P_{Na} > 50$
Activation	Calcium and voltage
Inactivation	Inactivating K_{Ca}1.1 channels have been studied extensively in chromaffin cells and have been reported in other cell types[30,31]; inactivation is conferred by the β2- and β3-subunits
Activators	Intracellular calcium, NS1608 and NS1619,[12] BMS204352,[13] DHS-1,[14] estradiol,[16] Mg^{2+} (1–10 nM)[27]
Gating inhibitors	None
Blockers	TEA (0.14 mM), charybdotoxin (2.9 nM), and iberiotoxin (1.7 nM)[17]; paxilline (1.9 nM)[15]; slotoxin (1.5 nM)[18]; BmP09 Chinese scorpion toxin (27 nM)[28]
Radioligands	[^{125}I]charybdotoxin (K_d = 34 pM),[19] [^{125}I]iberiotoxin-D17Y/Y36F mutant (K_d = 5 pM),[20] [^{19}F]racemic BMS204352[13]
Channel distribution	Ubiquitous, brain (cerebellum, habenula, striatum, olfactory bulb, neocortex, granule and pyramidal cells of the hippocampus), skeletal muscle, smooth muscle (vascular, uterine, gastric, bladder), adrenal cortex, cochlear hair cells, odontoblasts, pancreatic islet cells, colonic and kidney epithelium
Physiological functions	Pleiotropic, selectivity coupled with N-type, voltage-activated calcium channels to mediate fast afterhyperpolarization in neurones, electrical tuning of nonspiking properties of cochlear hair cells, presynaptic regulation of neurotransmitter release, effector of calcium sparks in smooth muscles
Mutations and pathophysiology	Mouse knockouts of α- and β-subunits viable, ataxia,[26] defects in audition,[25] incontinence,[24,32] erectile dysfunction[33]
Pharmacological significance	Channel openers may have applications in stroke, epilepsy, bladder over-reactivity, asthma, hypertension, gastric hypermotility and psychoses[13,17,21]
Comments	Multiple alternative splice forms exist; stress hormones control alternative splicing[22]

aa, amino acids; chr., chromosome; TEA, tetraethylammonium; NS1608, *N*-(3-(trifluoromethyl)phenyl)-*N*′-(2-hydroxy-5-chlorophenyl)urea; NS1619, 1-(2-hydroxy-5-trifluoromethyl-phenyl)-5-trifluoromethyl-1,3-dihydro-benzimidazol-2-one; BMS204352, (+/−)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6(trifluoromethyl)-2*H*-indol-2-one.

1. Atkinson NS, Robertson GA, and Ganetzky B (1991) A component of calcium-activated potassium channels encoded by the Drosophila slo locus. *Science* **253:**551–555.
2. Butler A, Tsunoda S, McCobb DP, Wei A, and Salkoff L (1993) mSlo, a complex mouse gene encoding ′maxi′ calcium-activated potassium channels. *Science* **261:**221–224.
3. Knaus HG, Garcia-Calvo M, Kaczorowski GJ, and Garcia, ML (1994) Subunit composition of the high conductance calcium-activated potassium channel from smooth muscle, a representative of the mSlo and slowpoke family of potassium channels. *J Biol Chem* **269:**3921–3924.
4. Pallanck L and Ganetzky B (1994) Cloning and characterization of human and mouse homologs of the Drosophila calcium-activated potassium channel gene, slowpoke. *Hum Mol Genet* **3:** 1239–1243.
5. Lagrutta A, Shen KZ, North RA, and Adelman JP (1994) Functional differences among alternatively spliced variants of Slowpoke, a Drosophila calcium-activated potassium channel. *J Biol Chem* **269:**20347–20351.
6. Tseng-Crank J, Foster CD, Krause JD, Mertz R, Godinot N, DiChiara TJ, and Reinhart PH (1994) Cloning, expression, and distribution of functionally distinct Ca (2+)-activated K+ channel isoforms from human brain. *Neuron* **13:**1315–1330.
7. Wei A, Solaro C, Lingle C, and Salkoff L (1994) Calcium sensitivity of BK-type KCa channels determined by a separable domain. *Neuron* **13:**671–681.
8. Meera P, Wallner M, Song M, and Toro L (1997) Large conductance voltage- and calcium-dependent K^+ channel, a distinct member of voltage-dependent ion channels with seven N-terminal transmembrane segments (S0-S6), an extracellular N terminus, and an intracellular (S9-S10) C terminus. *Proc Natl Acad Sci USA* **94:**14066–14071.
9. Jiang Z, Wallner M, Meera P, and Toro L (1999) Human and rodent MaxiK channel beta-subunit genes: cloning and characterization. *Genomics* **55:**57–67.
10. Weiger TM, Holmqvist MH, Levitan IB, Clark FT, Sprague S, Huang WJ, Ge P, Wang C, Lawson D, Jurman ME, et al. (2000) A novel nervous system beta subunit that downregulates human large conductance calcium-dependent potassium channels. *J Neurosci* **20:**3563–3570.
11. Joiner WJ, Tang MD, Wang LY, Dworetzky SI, Boissard CG, Gan L, Gribkoff VK, and Kaczmarek LK (1998) Formation of intermediate-conductance calcium-activated potassium channels by interaction of Slack and Slo subunits *Nat Neurosci* **1:**462–469.
12. Strobaek D, Christophersen P, Holm NR, Moldt P, Ahring PK, Johansen TE, and Olesen SP (1996) Modulation of the Ca^{2+}-dependent K^+ channel, hslo, by the substituted diphenylurea NS 1608, paxilline and internal Ca^{2+}. *Neuropharmacology* **35:**903–914.
13. Gribkoff VK, Starrett JE, Dworetzky SI, Hewawasam P, Boissard CG, Cook DA, Frantz SW, Heman K, Hibbard JR, Huston K, et al. (2001) Targeting acute ischemic stroke with a calcium-sensitive opener of maxi-Kpotassium channels. *Nat Med* **7:**471–477.
14. McManus OB, Harris GH, Giangiacomo KM, Feigenbaum P, Reuben JP, Addy ME, Burka JF, Kaczorowski GJ, and Garcia, ML (1993) An activator of calcium-dependent potassium channels isolated from a medicinal herb. *Biochemistry* **32:**6128–6133.
15. Sanchez M and McManus OB (1996) Paxilline inhibition of the alpha-subunit of the high conductance calcium-activated potassium channel. *Neuropharmacology* **35:**963–968.
16. Valverde MA, Rojas P, Amigo J, Cosmelli D, Orio P, Bahamonde MI, Mann GE, Vergara C and Latorre R (1999) Acute activation of Maxi-K channels (hSlo) by estradiol binding to the beta subunit. *Science* **285:**1929–1931.
17. Kaczorowski GJ, Knaus HG, Leonard RJ, McManus OB, and Garcia ML (1996) High-conductance calcium-activated potassium channels; structure, pharmacology, and function. *J Bioenerg Biomembr* **28:**255–267.
18. Garcia-Valdes J, Zamudio FZ, Toro L, and Possani LD (2001) Slotoxin, alphaKTx1.11, a new scorpion peptide blocker of MaxiK channels that differentiates between alpha and alpha + beta (beta1 or beta4) complexes. *FEBS Lett* **505:**369–373.
19. Garcia-Calvo M, Knaus HG, McManus OB, Giangiacomo KM, Kaczorowski GJ, and Garcia ML (1994) Purification and reconstitution of the high-conductance, calcium-activated potassium channel from tracheal smooth muscle. *J Biol Chem* **269:**676–682.
20. Koschak A, Koch RO, Liu J, Kaczorowski GJ, Reinhart PH, Garcia ML, and Knaus HG (1997) [^{125}I]Iberiotoxin-D19Y/Y36F, the first selective, high specific activity radioligand for high-conductance calcium-activated potassium channels. *Biochemistry* **36:**1943–1952.
21. Coghlan MJ, Carrol WA, and Gopalakrishnan M (2001) Recent developments in the biology and medicinal chemistry of potassium channel modulators: update from a decade of progress. *J Med Chem* **44:**1–27.
22. Xie J and McCobb DP (1998) Control of alternative splicing of potassium channels by stress hormones. *Science* **280:**443–446.
23. Liu G, Shi J, Yang L, Cao L, Park SM, Cui J, and Marx SO (2004) Assembly of a Ca2+-dependent BK channel signaling complex by binding to beta2 adrenergic receptor. *EMBO J* **23:**2196–2205.

24. Meredith AL, Thorneloe KS, Werner ME, Nelson MT, and Aldrich RW (2004) Overactive bladder and incontinence in the absence of the BK large conductance Ca2+-activated K + channel. *J Biol Chem* **279:**36746–36752.
25. Ruttiger L, Sausbier M, Zimmermann U, Winter H, Braig C, Engel J, Knirsch M, Arntz C, Langer P, et al. (2004) Deletion of the Ca2+-activated potassium (BK) alpha-subunit but not the BK beta1-subunit leads to progressive hearing loss. *Proc Natl Acad Sci USA* **101:**12922–12927.
26. Sausbier M, Hu H, Arntz C, Feil S, Kamm S, Adelsberger H, Sausbier U, Sailer CA, Feil R, Hofmann F, et al. (2004) Cerebellar ataxia and Purkinje cell dysfunction caused by Ca2+-activated K+ channel deficiency. *Proc Natl Acad Sci USA* **101:**9474–9478.
27. Shi J, Krishnamoorthy G, Yang Y, Hu L, Chaturvedi N, Harilal D, Qin J, and Cui J (2002) Mechanism of magnesium activation of calcium-activated potassium channels. *Nature (Lond)* **418:**876–880.
28. Yao J, Chen X, Li H, Zhou Y, Yao L, Wu G, Zhang N, Zhou Z, Xu T, Wu H, et al. (2005) BmP09, a long-chain scorpion peptide blocker of BK channels. *J Biol Chem* **280:**14819–14828.
29. Brenner R, Jegla TJ, Wickenden A, Liu Y, and Aldrich RW (2000) Cloning and functional characterization of novel BK potassium channel beta subunits, hKCNMB3 and hKCNMB4. *J Biol Chem* **275:**6453–6461.
30. Xia XM, Ding JP, and Lingle CJ (1999) Molecular basis for the inactivation of Ca^{2+}- and voltage-dependent BK channels in adrenal chromaffin cells and rat insulinoma tumor cells. *J Neurosci* **19:**5255–5264.
31. Lingle CJ, Solaro CR, Prakriya M, and Ding JP (1996) Calcium-activated potassium channels in adrenal chromaffin cells. *Ion Channels* **4:**261–301.
32. Petkov GV, Bonev AD, Heppner TJ, Brenner R, Aldrich RW, and Nelson MT (2001) Related beta1-subunit of the Ca2+-activated K+ channel regulates contractile activity of mouse urinary bladder smooth muscle. *J Physiol* **537:**443–452.
33. Werner ME, Zvara P, Meredith AL, Aldrich RW, and Nelson MT (2005) Erectile dysfunction in mice lacking the large conductance calcium-activated potassium (BK) channel. *J Physiol* **567 (Pt 2):**545–556.

TABLE 3
K_{Ca}2.1 channels

Channel name	$K_{Ca}2.1$
Description	Small-conductance, calcium-activated potassium channel; activated via a calmodulin-dependent mechanism
Other names	SK1[1,2], SKCa1
Molecular information	Human: 543aa, NM_002248, chr. 19p13.1,[3] *KCNN1* Mouse: 580aa, NM_032397, chr. 8 Rat: 536aa, NM_019313, chr. 16p14
Associated subunits	Calmodulin tightly complexed to C terminus[4]
Functional assays	Electrophysiology
Current	Small-conductance, calcium-activated K^+ current in neurones[1]
Conductance	9.2pS (symmetric K^+), 2–3pS (normal Ringer)
Ion selectivity	K^+-selective
Activation	Activated by intracellular Ca^{2+} (K_d = 0.7 μM, n_H = 4)[4]
Inactivation	None
Activators	Ca^{2+}, EBIO (630 μM),[5] NS309 (30 nM),[6] riluzole (2 μM)
Gating inhibitors	None
Blockers	UCL1684 (1 nM),[7] apamin (8 nM),[8] tamapin (42 nM),[9] leiurotoxin/scyllatoxin (325 nM),[10] dequalinium (400 nM), leiurotoxin-Dab7 (6 μM),[10] fluoxetine (7 μM), tubocurarine (23 μm), bicuculline (1.1 μM)[14]
Radioligands	[^{125}I]apamin[11]
Channel distribution	Brain (amygdala > hippocampus, caudate nucleus, foetal brain > cerebellum > thalamus, substantia nigra, spinal cord, pituitary gland), oligodendroglioma, glioblastoma, gastric tumour, aorta[4,12]
Physiological functions	Involved in the afterhyperpolarization in vertebrate neurones
Mutations and pathophysiology	Not established
Pharmacological significance	Modulators of SK channel subtypes may have potential use in the treatment of myotonic muscular dystrophy, gastrointestinal dysmotility, memory disorders, epilepsy narcolepsy, and alcohol intoxication[13]
Comments	Channel is voltage-independent and weakly rectifying; intron-exon structure of $K_{Ca}2.1$–$K_{Ca}2.3$ (SK) and $K_{Ca}3.1$ (IK) genes are conserved

aa, amino acids; chr., chromosome; NS309, 6,7-dichloro-1*H*-indole-2,3-dione-3-oxime; SK, small-conductance K^+ channel; IK, intermediate-conductance K^+ channel; EBIO, 1-ethyl-2-benzimidazolinone; UCL1684, 6,12,19,20,25,26-hexahycro-5,27:13,18:21,24-trietheno-11,7-methano-7*H*-dibenzo[*b*,*n*] [1,5,12,16] tetraazacyclotricosine-5,13-dilum ditrifluoroacetate.

1. Kohler M, Hirschberg B, Bond CT, Kinzie JM, Marrion NV, Maylie J, and Adelman JP (1996) Small-conductance, calcium-activated potassium channels from mammalian brain. *Science* **273:**1709–1714.
2. Litt M, LaMorticella D, Bond CT, and Adelman JP (1999) Gene structure and chromosome mapping of the human small-conductance calcium-activated potassium channel SK1gene (KCNN1). *Cytogenet Cell Genet* **86:**70–73.
3. Ghanshani S, Wulff H, Miller MJ, Rohm H, Neben A, Gutman GA, Cahalan MD, and Chandy KG (2000) Up-regulation of the IKCa1 potassium channel during T-cell activation. Molecular mechanism and functional consequences. *J Biol Chem* **275:**37137–37149.
4. Xia XM, Fakler B, Rivard A, Wayman G, Johnson-Pais T, Keen JE, Ishii T, Hirschberg B, Bond CT, Lutsenko S, et al. (1998) Mechanism of calcium gating in small-conductance calcium-activated potassium channels. *Nature (Lond)* **395:**503–507.
5. Dale TJ, Cryan JE, Chen MX, Trezise DJ (2002) Partial apamin sensitivity of human small conductance Ca^{2+}-activated K^+ channels stable expressed in Chinese hamster ovary cells. *Naunyn Schmiedeberg's Arch Pharmacol* **366:**470–477.
6. Strobaek D, Teuber L, Jorgensen TD, Ahring PK, Kaer K, Hansen RS, Olesen SP, Christophersen P, and Skaaning-Jensen B (2004) Activation of human IK and SK Ca^{2+} -activated K^+ channels by NS309 (6,7-dichloro-1H-indole-2,3-dione3-oxime). *Biochim Biophys Acta* **1665:**1–5.
7. Strobaek D, Jorgensen TD, Christophersen P, Ahring PK, and Olesen S-P (2000) Pharmacological characterization of small-conductance Ca^{2+}-activated K^+ channels stably expressed in HEK 293 cells. *Br J Pharmacol* **129:**991–999.
8. Shah M and Haylett DG (2000) The Pharmacology of hSK1 Ca^{2+}-activated K^+ channels expressed in mammalian cell lines. *Br J Pharmacol* **129:**627–630.
9. Pedarzani P, D'hoedt D, Doorty KB, Wadsworth JD, Joseph JS, Jeyaseelan K, Kini RM, Gadre SV, Sapatnekar SM, Stocker M, et al. (2002) Tamapin, a venompeptide from the Indian red scorpion (*Mesobuthus tamulus*) that targets small conductance Ca^{2+}-activated K^+ channels and after hyperpolarization currents in central neurons. *J Biol Chem* **277:**46101–46109.
10. Shakkottai VG, Regaya I, Wulff H, Fajloun Z, Tomita H, Fathallah M, Cahalan MD, Gargus JJ, Sabatier JM, and Chandy KG (2001) Design and characterization of a highly selective peptide inhibitor of the small conductance calcium-activated K^+ channel, SKCa2. *J Biol Chem* **276:**43145–43151.
11. Romey G, Hugues M, Schmid-Antomarchi H, and Lazdunski M (1984) Apamin: a specific toxin to study a class of Ca^{2+}-dependent K^+ channels. *J Physiol (Paris)* **79:**259–264.
12. Stocker M and Pedarzani P (2000) Differential distribution of three Ca^{2+}-activated K^+ channel subunits, SK1, SK2, and SK3, in the adult rat central nervous system. *Mol Cell Neurosci* **15:**476–493.
13. Coghlan MJ, Carrol WA, and Gopalakrishnan M (2001) Recent developments in the biology and medicinal chemistry of potassium channel modulators: update from a decade of progress. *J Med Chem* **44:**1–27.
14. Khawaled R, Bruening-Wright A, Adelman JP, and Maylie J (1999) Bicuculline block of small-conductance calcium-activated potassium channels. *Pflugers Arch Eur J Physiol* **438:**314–321.

TABLE 4
K_{Ca}2.2 channels

Channel name	K_{Ca}2.2
Description	Small-conductance, calcium-activated potassium channel; activated via a calmodulin-dependent mechanism
Other names	SK2,[1] SKCa2
Molecular information	Human: 579aa, NM_021614 (transcript variant 1), chr. 5q22.3,[2] *KCNN2* Mouse: 574aa, NM_080465, chr. 18 Rat: 580aa, NM_019314, chr. 18q11
Associated subunits	Calmodulin tightly complexed to C terminus,[3,4] protein kinase CK2 and protein phosphatase 2A[23]
Functional assays	Electrophysiology
Current	Small-conductance, calcium-activated K^+ current in neurones possibly underlies the medium I_{AHP} current in hippocampal neurones
Conductance	9.9pS (symmetric K^+), 2–3pS (normal Ringer)[5]
Ion selectivity	K^+-selective[5]
Activation	Activated by intracellular Ca^{2+} (K_d = 0.6 μM, n_H = 4)[5]
Inactivation	None
Activators	EBIO,[6] chlorzoxazone, zoxazolamine,[7] NS309 (30 nM),[8] riluzole (2 μM)
Gating inhibitors	None
Blockers	Tamapin (24 pM),[9] apamin (60–200 pM),[1,10] leiurotoxin/scyllatoxin (200 pM), leiuritoxin-Dab7 (3.8 nM), PO5 (22 nM), Tskappa (80 nM), Pi1-OH (>1 μM), Pi1-NH2 (100 nM), and maurotoxin (1 μM),[11] UCL1684 (250pM),[12] tubocurarine (5 μM)[10]; with micromolar affinity: amitriptyline, carbamazepine, chlorpromazine, cyproheptadine, fluoxetine, imipramine, tacrine, trifluperazine,[13] bicuculline (1.1 μM)[22]
Radioligands	[^{125}I]apamin[14]
Channel distribution	Brain (spinal cord > hippocampus, cerebellum > amygdala > foetal brain > corpus callosum, thalamus, caudate nucleus, substantia nigra),[15] pituitary gland, melanocyte, melanoma, germ cell tumor, prostate, oligodendroglioma, lung, Jurkat T cells,[16] liver, heart,[17] skeletal muscle, myometrium
Physiological functions	Underlies the medium afterhyperpolarization in vertebrate neurones[18,19]
Mutations and pathophysiology	Dominant-negative suppression of K_{Ca}2.2 channels in deep cerebellar nuclei in a transgenic mouse causes cerebellar ataxia[20]
Pharmacological significance	Modulators of SK channel subtypes may have potential use in the treatment of myotonic muscular dystrophy, gastrointestinal dysmotility, memory disorders, epilepsy, narcolepsy, and alcohol intoxication[21]; K_{Ca}2.2 openers have been proposed for the treatment of cerebellar ataxia[20]
Comments	The channel is voltage-independent and weakly rectifying; shared intron-exon structure with members of the K_{Ca}2 and K_{Ca}3 subfamilies[2]

aa, amino acids; chr., chromosome; NS309, 6,7-dichloro-1*H*-indole-2,3-dione-3-oxime; SK, small-conductance K^+ channel; EBIO, 1-ethyl-2-benzimidazolinone; UCL1684, 6,12,19,20,25,26-hexahycro-5,27:13,18:21,24-trietheno-11,7-methano-7*H*-dibenzo [*b*,*n*] [1,5,12,16] tetraazacyclotricosine-5,13-dilum ditrifluoroacetate.

1. Kohler M, Hirschberg B, Bond CT, Kinzie JM, Marrion NV, Maylie J, and Adelman JP (1996) Small-conductance, calcium-activated potassium channels from mammalian brain. *Science* **273:**1709–1714.

2. Ghanshani S, Wulff H, Miller MJ, Rohm H, Neben A, Gutman GA, Cahalan MD, and Chandy KG (2000) Up-regulation of the IKCa1 potassium channel during T-cell activation. Molecular mechanism and functional consequences. *J Biol Chem* **275:**37137–37149.

3. Xia XM, Fakler B, Rivard A, Wayman G, Johnson-Pais T, Keen JE, Ishii T, Hirschberg B, Bond CT, Lutsenko S, et al. (1998) Mechanism of calcium gating in small-conductance calcium-activated potassium channels. *Nature (Lond)* **395:**503–507.

4. Schumacher MA, Rivard AF, Bachinger HP, and Adelman JP (2001) Structure of the gating domain of a Ca^{2+}-activated K^+ channel complexed with Ca^{2+}/calmodulin. *Nature (Lond)* **410:**1120–1124.

5. Hirschberg B, Maylie J, Adelman JP, and Marrion NV (1998) Gating of recombinant small-conductance Ca-activated K^+ channels by calcium. *J Gen Physiol* **111:**565–581.

6. Pedarzani P, Mosbacher J, Rivard A, Cingolani LA, Oliver D, Stocker M, Adelman JP, and Fakler B (2001) Control of electrical activity in central neurons by modulating the gating of small-conductance Ca^{2+}-activated K^+ channels. *J Biol Chem* **276:**9762–9769.

7. Cao Y, Dreixler JC, Roizen JD, Roberts MT, and Houamed KM (2001) Modulation of recombinant small-conductance Ca^{2+}-activated K^+ channels by the muscle relaxant chlorzoxazone and structurally related compounds. *J Pharmacol Exp Ther* **296:**683–689.

8. Strobaek D, Teuber L, Jorgensen TD, Ahring PK, Kaer K, Hansen RS, Olesen SP, Christophersen P, and Skaaning-Jensen B (2004) Activation of human IK and SK Ca^{2+} -activated K^+ channels by NS309 (6,7-dichloro-1H-indole-2,3-dione3-oxime). *Biochim Biophys Acta* **1665:**1–5.

9. Pedarzani P, D'hoedt D, Doorty KB, Wadsworth JD, Joseph JS, Jeyaseelan K, Kini RM, Gadre SV, Sapatnekar SM, Stocker M, et al. (2002) Tamapin, a venompeptide from the Indian red scorpion (*Mesobuthus tamulus*) that targets small conductance Ca^{2+}-activated K^+ channels and after hyperpolarization currents in central neurons. *J Biol Chem* **277:**46101–46109.

10. Ishii TM, Maylie J, and Adelman JP (1997) Determinants of apamin and d-tubocurarine block in SK potassium channels. *J Biol Chem* **272:**23195–23200.

11. Shakkottai VG, Regaya I, Wulff H, Fajloun Z, Tomita H, Fathallah M, Cahalan MD, Gargus JJ, Sabatier JM, and Chandy KG (2001) Design and characterization of a highly selective peptide inhibitor of the small conductance calcium-activated K^+ channel, SKCa2. *J Biol Chem* **276:**43145–43151.

12. Fanger CM, Rauer H, Neben AL, Miller MJ, Rauer H, Wulff H, Rosa JC, Ganellin CR, Chandy KG, and Cahalan MD (2000) Calcium-activated potassium channels sustain calcium signaling in T lymphocytes. Selective blockers and manipulated channel expression levels. *J Biol Chem* **276:** 12249–12256.

13. Dreixler JC, Bian J, Cao Y, Roberts MT, Roizen JD, and Houamed KM (2000) Block of rat brain recombinant SK channels by tricyclic antidepressants and related compounds. *Eur J Pharmacol* **401:**1–7.

14. Romey G, Hugues M, Schmid-Antomarchi H, and Lazdunski M (1984) Apamin: a specific toxin to study a class of Ca^{2+}-dependent K^+ channels. *J Physiol (Paris)* **79:**259–264.

15. Stocker M and Pedarzani P (2000) Differential distribution of three Ca^{2+}-activated K^+ channel subunits, SK1, SK2, and SK3, in the adult rat central nervous system. *Mol Cell Neurosci* **15:**476–493.

16. Jager H, Adelman JP, and Grissmer S (2000) SK2 encodes the apamin-sensitive Ca (2+)-activated K(+) channels in the human leukemic T cell line, Jurkat. *FEBS Lett* **469:**196–202.

17. Xu Y, Tuteja D, Zhang Z, Xu D, Zhang Y, Rodriguez J, Nie L, Tuxson HR, Young JN, Glatter KA, et al. (2003) Molecular identification and functional roles of a Ca^{2+}-activated K^+ channel in human and mouse hearts. *J Biol Chem* **278:**49085–49094.

18. Villalobos C, Shakkottai VG, Chandy KG, Michelhaugh SK, and Andrade R (2004) SKCa channels mediate the medium but not the slow calcium-activated afterhyperpolarization in cortical neurons. *J Neurosci* **24:**3537–3542.

19. Bond CT, Herson PS, Strassmaier T, Hammond R, Stackman R, Maylie J, and Adelman JP (2004) Small conductance Ca^{2+}-activated K^+ channel knock-out mice reveal the identity of calcium-dependent afterhyperpolarization currents. *J Neurosci* **24:**5301–5306.

20. Shakkottai VG, Chou CH, Oddo S, Sailer CA, Knaus HG, Gutman GA, Barish ME, LaFerla FM, and Chandy KG (2004) Enhanced neuronal excitability in the absence of neurodegeneration induces cerebellar ataxia. *J Clin Investig* **113:**582–590.

21. Coghlan MJ, Carrol WA, and Gopalakrishnan M (2001) Recent developments in the biology and medicinal chemistry of potassium channel modulators: update from a decade of progress. *J Med Chem* **44:**1–27.

22. Khawaled R, Bruening-Wright A, Adelman JP, and Maylie J (1999) Bicuculline block of small-conductance calcium-activated potassium channels. *Pflugers Arch Eur J Physiol* **438:**314–321.

23. Bildl W, Strassmaier T, Thurm H, Andersen J, Eble S, Oliver D, Knipper M, Mann M, Schulte U, Adelman JP, et al. (2004) Protein Kinase CK2 is coassembled with small conductance Ca2+-activated K+ channels and regulates channel gating. *Neuron* **43:**847–858.

TABLE 5
K_{Ca}2.3 channels

Channel name	K_{Ca}2.3
Description	Small-conductance, calcium-activated potassium channel activated via a calmodulin-dependent mechanism
Other names	SK3,[1] hKCa3, SKCa3[2]
Molecular information	Human: 736aa, NM_002249 (transcript variant 1), chr. 1q21.3,[3,4] *KCNN3* Mouse: 731aa, NM_080466, chr. 3 Rat: 732aa, NM_019315, chr. 2q34
Associated subunits	Calmodulin tightly complexed to C terminus[5,6]
Functional assays	Patch-clamp
Current	Small-conductance, calcium-activated K^+ current in neurones[7]
Conductance	Not determined
Ion selectivity	K^+-selective
Activation	Activated by intracellular Ca^{2+} (K_d = 0.6 uM)[8]
Inactivation	None
Activators	EBIO, riluzole (3 μM),[9] NS309 (30 nM)[10]
Gating inhibitors	None
Blockers	Leiurotoxin/scyllatoxin (1.1 nM), apamin (10 nM), PO5 (25 nM), Tskappa (197 nM), Pi1-OH (330 nM), and Pi1-NH2 (250 nM),[11] UCL1684 (9.5 nM)[12]; with micromolar affinity: bicuculline,[9] amitriptyline, fluoxetine, desipramine, imipramine, nortriptyline, fluphenazine, promethazine, chlorpromazine
Radioligands	[^{125}I]apamine[13]
Channel distribution	Brain (substantia nigra > amygdala, caudate nucleus, thalamus, hippocampus, ventral tegmental area, cerebellum, spinal cord > corpus callosum, foetal brain), lymphocytes (germinal center B cells, tonsillar B cells, Burkitt's lymphoma, microglia), skeletal muscle (increased denervated muscle, myotonic dystrophy), myometrium, prostate, kidney, heart, pituitary gland, liver, pancreas, colon, germinal cells, head, neck, ovary, vascular endothelium[1,3,14–19]
Physiological functions	Involved in the afterhyperpolarization in vertebrate neurones[7,17] (any newer comments on this?)
Mutations and pathophysiology	Longer polyglutamine repeats are over-represented in schizophrenic (especially negative-symptom form)[2,18] individuals and in patients with anorexia nervosa[20] and spinocerebellar ataxia[21]; a four-base deletion has been found in a patient with schizophrenia[22] that truncates the protein just before the S1 segment and causes dominant-negative suppression of endogenous SK channels[23]; protein and mRNA levels are increased in skeletal muscle following denervation[24] and in patients with myotonic muscular dystrophy [25]; involved in the endothelium-mediated vasodilation (EDHF response)[19]; conditional knockout of K_{Ca}2.3 leads to hypertension[26] and bladder instability[27]
Pharmacological significance	Modulators of SK channel subtypes may have potential use in the treatment of myotonic muscular dystrophy, gastrointestinal dysmotility, memory disorders, epilepsy, narcolepsy, hypertension,[26] and urinary incontinence[27]
Comments	Channel is voltage-independent

aa, amino acids; chr., chromosome; NS309, 6,7-dichloro-1*H*-indole-2,3-dione-3-oxime; EDHF, endothelium-derived hyperpolarizing factor; EBIO, 1-ethyl-2-benzimidazolinone; SK, small-conductance K^+ channel; UCL1684, 6,12,19,20,25,26-hexahycro-5,27:13,18:21,24-trietheno-11,7-methano-7*H*-dibenzo [*b*,*n*] [1,5,12,16] tetraazacyclotricosine-5,13-dilum ditrifluoroacetate.

1. Kohler M, Hirschberg B, Bond CT, Kinzie JM, Marrion NV, Maylie J, and Adelman JP (1996) Small-conductance, calcium-activated potassium channels from mammalian brain. *Science* **273:**1709–1714.

2. Chandy KG, Fantino E, Wittekindt O, Kalman K, Tong LL, Ho TH, Gutman GA, Crocq MA, Ganguli R, Nimgaonkar V, et al. (1998) Isolation of a novel potassium channel gene hSKCa3 containing a polymorphic CAG repeat: a candidate for schizophrenia and bipolar disorder? *Mol Psychiatry* **3:**32–37.

3. Dror V, Shamir E, Ghanshani S, Kimhi R, Swartz M, Barak Y, Weizman R, Avivi L, Litmanovitch T, Fantino E, et al. (1999) hKCa3/KCNN3 potassium channel gene: association of longer CAG repeats with schizophrenia in Israeli Ashkenazi Jews, expression inhuman tissues and localization to chromosome 1q21. *Mol Psychiatry* **4:**254–260.

4. Sun G, Tomita H, Shakkottai VG, and Gargus JJ (2001) Genomic organization and promoter analysis of human KCNN3 gene. *J Hum Genet* **46:**463–470.

5. Xia XM, Fakler B, Rivard A, Wayman G, Johnson-Pais T, Keen JE, Ishii T, Hirschberg B, Bond CT, Lutsenko S, et al. (1998) Mechanism of calcium gating in small-conductance calcium-activated potassium channels. *Nature (Lond)* **395:**503–507.

6. Fanger CM, Ghanshani S, Logsdon NJ, Rauer H, Kalman K, Zhou J, Beckingham K, Chandy KG, Cahalan MD, and Aiyar J (1999) Calmodulin mediates calcium-dependent activation of the intermediate conductance KCa channel, IKCa1. *J Biol Chem* **274:**5746–5754.

7. Wolfart J, Neuhoff H, Franz O, and Roeper J (2001) Differential expression of the small-conductance, calcium-activated potassium channel SK3 is critical for pacemaker control in dopaminergic midbrain neurons. *J Neurosci* **21:**3443–3456.

8. Barfod ET, Moore AL, and Lidofsky SD (2001) Cloning and functional expression of a liver isoform of the small conductance Ca^{2+}-activated K^+ channel SK3. *Am J Physiol Cell Physiol* **280:**C836–C842.

9. Grunnet M, Jespersen T, Angelo K, Frokjaer-Jensen C, Klaerke DA, Olesen SP, and Jensen BS (2001) Pharmacological modulation of SK3 channels. *Neuropharmacology* **40:**879–887.

10. Strobaek D, Teuber L, Jorgensen TD, Ahring PK, Kaer K, Hansen RS, Olesen SP, Christophersen P, and Skaaning-Jensen B (2004) Activation of human IK and SK Ca^{2+} -activated K^+ channels by NS309 (6,7-dichloro-1H-indole-2,3-dione3-oxime). *Biochim Biophys Acta* **1665:**1–5.

11. Shakkottai VG, Regaya I, Wulff H, Fajloun Z, Tomita H, Fathallah M, Cahalan MD, Gargus JJ, Sabatier JM, and Chandy KG (2001) Design and characterization of a highly selective peptide inhibitor of the small conductance calcium-activated K^+ channel, SKCa2. *J Biol Chem* **276:**43145–43151.

12. Fanger CM, Rauer H, Neben AL, Miller MJ, Rauer H, Wulff H, Rosa JC, Ganellin CR, Chandy KG, and Cahalan MD (2000) Calcium-activated potassium channels sustain calcium signaling in T lymphocytes. Selective blockers and manipulated channel expression levels. *J Biol Chem* **276:** 12249–12256.

13. Romey G, Hugues M, Schmid-Antomarchi H, and Lazdunski M (1984) Apamin: a specific toxin to study a class of Ca^{2+}-dependent K^+ channels. *J Physiol (Paris)* **79:**259–264.

14. Stocker M and Pedarzani P (2000) Differential distribution of three Ca^{2+}-activated K^+ channel subunits, SK1, SK2, and SK3, in the adult rat central nervous system. *Mol Cell Neurosci* **15:**476–493.

15. Pribnow D, Johnson-Pais T, Bond CT, Keen J, Johnson RA, Janowsky A, Silvia C, Thayer M, Maylie J, and Adelman JP (1999) Skeletal muscle and small-conductance calcium-activated potassium channels. *Muscle and Nerve* **22:**742–750.

16. UniGene Cluster Hs0.89230; Online Mendelian Inheritance in Man (OMIM) no. 602983.

17. Hosseini R, Benton DC, Dunn PM, Jenkinson DH, and Moss GW (2001) SK3 is an important component of K (+) channels mediating the after-hyperpolarization in cultured rat SCG Neurones. *J Physiol* **535:**323–334.

18. Cardno AG, Bowen T, Guy CA, Jones LA, McCarthy G, Williams NM, Murphy KC, Spurlock G, Gray M, Sanders RD, et al. (1999) CAG repeat length in the hKCa3 gene and symptom dimensions in schizophrenia. *Biol Psychiatry* **45:**1592–1596.

19. Burnham MP, Bychkov R, Feletou M, Richards GR, Vanhoutte PM, Weston AH, and Edwards G (2002) Characterization of an apamin-sensitive small-conductance Ca^{2+}-activated K^+ channel in porcine coronary artery endothelium: relevance to EDHF. *Br J Pharmacol* **135:**1133–1143.

20. Koronyo-Hamaoui M, Danziger Y, Frisch A, Stein D, Leor S, Laufer N, Carel C, Fennig S, Minoumi M, Apter A, et al. (2002) Association between anorexia nervosa and the hsKCa3 gene: a family-based and case control study. *Mol Psychiatry* **7:**82–85.
21. Figueroa KP, Chan P, Schols L, Tanner C, Riess O, Perlman SL, Geschwind DH, and Pulst SM (2001) Association of moderate polyglutamine tract expansions in the slow calcium-activated potassium channel type 3 with ataxia. *Arch Neurol* **58:**1649–1653.
22. Bowen T, Williams N, Norton N, Spurlock G, Wittekindt OH, Morris-Rosendahl DJ, Williams H, Brzustowicz L, Hoogendoorn B, Zammit S, Jones G, et al. (2001) Mutation screening of the KCNN3 gene reveals a rare frame shift mutation. *Mol Psychiatry* **6:**259–260.
23. Miller MJ, Rauer H, Tomita H, Rauer H, Gargus JJ, Gutman GA, Cahalan MD, and Chandy KG (2001) Nuclear localization and dominant-negative suppression by a mutant SKCa3 N-terminal channel fragment identified in a patient with schizophrenia. *J Biol Chem* **276:**27753–27756.
24. Neelands TR, Herson PS, Jacobson D, Adelman JP, and Maylie J (2001) Small-conductance calcium-activated potassium currents in mouse hyperexcitable denervated skeletal muscle. *J Physiol* **536:**397–407.
25. Kimura T, Takahashi MP, Okuda Y, Kaido M, Fujimura H, Yanagihara T, and Sakoda S (2000) The expression of ion channel mRNAs in skeletal muscles from patients with myotonic muscular dystrophy. *Neurosci Lett* **295:**93–96.
26. Taylor MS, Bonev AD, Gross TP, Eckman DM, Brayden JE, Bond CT, Adelman JP, and Nelson MT (2003) Altered expression of small-conductance Ca^{2+}-activated K^+ (SK3) channels modulates arterial tone and blood pressure. *Circ Res* **93:**124–131.
27. Herrera GM, Pozo MJ, Zvara P, Petkov GV, Bond CT, Adelman JP, and Nelson MT (2003) Urinary bladder instability induced by selective suppression of the murine small conductance calcium-activated potassium (SK3) channel. *J Physiol* **551:**893–903.

TABLE 6
K_{Ca}3.1 channels

Channel name	$K_{Ca}3.1$
Description	Intermediate-conductance, calcium-activated potassium channel; activated via a calmodulin-dependent mechanism
Other names	SK41,[1] IK1,[2] Gardos channel, $K_{Ca}4$,[3] $IK_{Ca}1$[4]
Molecular information	Human: 427aa, NM_002250, chr. 19q13.2,[4,5] *KCNN4* Mouse: 425aa, NM_008433, chr. 7 Rat: 424aa, NM_023021, 1q21
Associated subunits	Calmodulin tightly complexed to C terminus[6]
Functional assays	Electrophysiology
Current	Gardos channel in erythrocytes,[7] IK current in lymphocytes,[8] fibroblasts[9]
Conductance	11pS[1–3,8]
Ion selectivity	K^+ (1) > Rb^+ (0.96) > NH_4^+ (0.17) > Cs^+ (0.07)[8]
Activation	Activated by intracellular Ca^{2+} (K_d = 0.1–0.3 μM; n_H = 1.7–4)[1–4,8]
Inactivation	None
Activators	EBIO, NS309 (10 nM),[10] DCEBIO (1 μM),[11] riluzole (1 μM), methylxanthine (theophylline, caffeine, IBMX)[12]
Gating inhibitors	None
Blockers	ChTX (5 nM),[1–4,14,15] maurotoxin (1 nM),[15] 4-phenyl-4*H*-pyran 11 (8 nM),[16] ICA17043 (11 nM),[17] TRAM-34 (20 nM),[14,15] ChTX-Glu[13,32] (33 nM),[14,15] ShK (30 nM),[14] clotrimazole (70 nM),[14,15] BgK (172 nM),[14] TRAM-3 (520 nM),[15] nitredipine (900 nM), nimodipine (1 μM), and nifedipine (4 μM),[14] UCL1608 (4 μM),[18] ketoconazole (30 μM) and econazole (12 μM),[14,15] cetiedil,[18] TEA (24 mM)[14]
Radioligands	None
Channel distribution	Placenta, prostate, erythrocytes,[19] lymphocytes,[3,4] microglia, liver, foetal liver, pancreas, hematopoietic stem cells, fibroblasts,[9] HL60, colon, Paneth cells,[20] melanomas,[21] proliferating smooth muscle cells,[22] vascular endothelium,[23] lung and colonic endothelium
Physiological functions	$K_{Ca}3.1$ is involved in volume regulation in erythrocytes[19,24]; its expression is up-regulated during activation of lymphocytes, and specific blockers suppress lymphocyte[4,8,25,26] and vascular smooth muscle cell proliferation[22]; $K_{Ca}3.1$ is involved in EDHF-mediated vasodilatation[23] and in angiogenesis[27,28]
Mutations and pathophysiology	T lymphocytes and erythrocytes from $K_{Ca}3.1$ knockout mouse show sever defect in volume regulation[29]
Pharmacological significance	$K_{Ca}3.1$ blocker ICA17043 is in clinical trials for sickle cell anemia[24]; $K_{Ca}3.1$ blockers are of potential use for the treatment of diarrhea[30] and as immunosuppressants[14,31]; TRAM-34 has been shown to treat EAE in mice[32] and prevent restenosis in rats[22] and angiogenesis in mice[28]; $K_{Ca}3.1$ blockers reduce experimental brain oedema and attenuate traumatic brain injury[33]; $K_{Ca}3.1$ openers are considered as potential therapeutics for cystic fibrosis and chronic obstructive pulmonary disease[11]
Comments	Voltage-independent calmodulin is also involved in trafficking[34]; intron-exon structure shared with $K_{Ca}2.1$–$K_{Ca}2.3$ (SK channels)

aa, amino acids; chr., chromosome; NS309, 6,7-dichloro-1*H*-indole-2,3-dione-3-oxime; IK, intermediate-conductance K^+ channel; EBIO, 1-ethyl-2-benzimidazolinone; DCEBIO, 5,6-dichloro-1-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one; ChTX, charybdotoxin; ShK, ShK toxin, a potassium channel blocker from the sea anemone *Stichodactyla helianthus*; BgK, BgK toxin, a potassium channel blocker from the sea anemone *Bunodosoma granulifera*; EAE, experimental autoimmune encephalomyelitis; SK, small-conductance K^+ channel; ICA17043, bis(4-fluorophenyl)phenyl acetamide; UCL1608, 1-[(9-benzyl)fluoren-9-yl]-4-(hexahydro-1*H*-azepin-1-yl)but-2-yne hydrogen oxalate; IBMX, 3-isobutyl-1-methylxanthine; TEA, tetraethylammonium; EDHF, endothelium-derived hyperpolarizing factor.

1. Joiner WJ, Wang LY, Tang MD, and Kaczmarek LK (1997) hSK4, a member of a novel subfamily of calcium-activated potassium channels. *Proc Natl Acad Sci USA* **94:**11013–11018.
2. Ishii TM, Silvia C, Hirschberg B, Bond CT, Adelman JP, and Maylie J (1997) A human intermediate conductance calcium-activated potassium channel. *Proc Natl Acad Sci USA* **94:**11651–11656.
3. Logsdon NJ, Kang J, Togo JA, Christian EP, and Aiyar J (1997) A novel gene, hKCa4, encodes the calcium-activated potassium channel in human T lymphocytes. *J Biol Chem* **272:**32723–32726.
4. Ghanshani S, Wulff H, Miller MJ, Rohm H, Neben A, Gutman GA, Cahalan MD, and Chandy KG (2000) Up-regulation of the IKCa1 potassium channel during T-cell activation. Molecular mechanism and functional consequences. *J Biol Chem* **275:**37137–37149.
5. Ghanshani S, Coleman M, Gustavsson P, Wu AC, Gargus JJ, Gutman GA, Dahl N, Mohrenweiser H, and Chandy KG (1998) Human calcium-activated potassium channel gene KCNN4 maps to chromosome 19q13.2 in the region deleted in diamond-black fan anemia. *Genomics* **51:**160–161.
6. Fanger CM, Ghanshani S, Logsdon NJ, Rauer H, Kalman K, Zhou J, Beckingham K, Chandy KG, Cahalan MD, and Aiyar J (1999) Calmodulin mediates calcium-dependent activation of the intermediate conductance KCa channel, IKCa1. *J Biol Chem* **274:**5746–5754.
7. Gardos G (1958) The function of calcium in the potassium permeability of human erythrocytes. *Biochim Biophys Acta* **30:**653–654.

8. Grissmer S, Nguyen AN, and Cahalan MD (1993) Calcium-activated potassium channels in resting and activated human T lymphocytes. Expression levels, calcium dependence, ion selectivity, and pharmacology. *J Gen Physiol* **102:**601–630.

9. Pena TL, Chen SH, Konieczny SF, and Rane SG (2000) Ras/MEK/ERK up-regulation of the fibroblast K_{Ca} channel FIK is a common mechanism for basic fibroblast growth factor and transforming growth factor-beta suppression of myogenesis. *J Biol Chem* **275:**13677–13682.

10. Strobaek D, Teuber L, Jorgensen TD, Ahring PK, Kaer K, Hansen RS, Olesen SP, Christophersen P, and Skaaning-Jensen B (2004) Activation of human IK and SK Ca^{2+} -activated K^+ channels by NS309 (6,7-dichloro-1H-indole-2,3-dione3-oxime). *Biochim Biophys Acta* **1665:**1–5.

11. Singh S, Syme CA, Singh AK, Devor DC, and Bridges RJ (2001) Benzimidazolone activators of chloride secretion: potential therapeutics for cystic fibrosis and chronic obstructive pulmonary disease. *J Pharmacol Exp Ther* **296:**600–611.

12. Schroder RL, Jensen BS, Strobaek D, Olesen SP, and Christophersen P (2000) Activation of the human, intermediate-conductance, Ca^{2+}-activated K^+ channel by methylxanthines. *Pflugers Arch Eur J Physiol* **440:**809–818.

13. Rauer H, Lanigan MD, Pennington MW, Aiyar J, Ghanshani S, Cahalan MD, Norton RS, and Chandy KG (2000) Structure-guided transformation of charybdotoxin yields an analog that selectively targets Ca^{2+}-activated over voltage-gated K^+ channels. *J Biol Chem* **275:**1201–1208.

14. Chandy KG, Wulff H, Beeton C, Pennington M, Gutman GA, and Cahalan MD (2004) K^+ channels as targets for specific immunomodulation. *Trends Pharmacol Sci* **25:**280–289.

15. Wulff H, Miller MJ, Haensel W, Grissmer S, Cahalan MD, and Chandy KG (2000) Design of a potent and selective inhibitor of the intermediate-conductance Ca^{2+}-activated K^+ channel, IKCa1: a potential immunosuppressant. *Proc Natl Acad Sci USA* **97:**8151–8156.

16. Urbahns K, Horvath E, Stasch JP, and Mauler F (2003) 4-Phenyl-4H-pyrans as IK (Ca) channel blockers. *Bioorg Med Chem Lett* **13:**2637–2639.

17. Stocker JW, De Franceschi L, McNaughton-Smith GA, Corrocher R, Beuzard Y, and Brugnara C (2003) ICA-17043, a novel Gardos channel blocker, prevents sickled red blood cell dehydration in vitro and in vivo in SAD mice. *Blood* **101:**2412–2418.

18. Roxburgh CJ, Ganellin CR, Athmani S, Bisi A, Quaglia W, Benton DC, Shiner MA, Malik-Hall M, Haylett DG, and Jenkinson DH (2001) Synthesis and structure-activity relationships of cetiedil analogues as blockers of the Ca^{2+}-activated K^+ permeability of erythrocytes. *J Med Chem* **44:**3244–3253.

19. Vandorpe DH, Shmukler BE, Jiang L, Lim B, Maylie J, Adelman JP, de Franceschi L, Cappellini MD, Brugnara C, and Alper SL (1998) cDNA cloning and functional characterization of the mouse Ca^{2+}-gated K^+ channel, mIK1Roles in regulatory volume decrease and erythroid differentiation. *J Biol Chem* **273**:21542–21553.

20. Ayabe T, Wulff H, Darmoul D, Cahalan MD, Chandy KG, and Ouellette AJ (2002) Modulation of mouse Paneth cell alpha-defensin secretion by mIKCa1, a Ca^{2+}-activated, intermediate conductance potassium channel. *J Biol Chem* **277:**3793–3800.

21. Meyer R, Schonherr R, Gavrilova-Ruch O, Wohlrab W, and Heinemann SH (1999) Identification of *ether a go-go* and calcium-activated potassium channels in human melanoma cells. *J Membr Biol* **171:**107–115.

22. Kohler R, Wulff H, Eichler I, Kneifel M, Neumann D, Knorr A, Grgic I, Kampfe D, Si H, Wibawa J, et al. (2003) Blockade of the intermediate-conductance calcium-activated potassium channel as a new therapeutic strategy for restenosis *Circulation* **108:**1119–1125.

23. Eichler I, Wibawa J, Grgic I, Knorr A, Brakemeier S, Pries AR, Hoyer J, and Kohler R (2003) Selective blockade of endothelial Ca^{2+}-activated small- and intermediate-conductance K^+-channels suppresses EDHF-mediated vasodilation. *Br J Pharmacol* **138:**594–601.

24. Brugnara C, Gee B, Armsby CC, Kurth S, Sakamoto M, Rifai N, Alper SL, and Platt OS (1996) Therapy with oral clotrimazole induces inhibition of the Gardos channel and reduction of erythrocyte dehydration in patients with sickle cell disease. *J Clin Investig* **97:**1227–1234.

25. Jensen BS, Odum N, Jorgensen NK, Christophersen P, and Olesen SP (1999) Inhibition of T cell proliferation by selective block of Ca (2+)-activated K (+) channels. *Proc Natl Acad Sci USA* **96:**10917–10921.

26. Khanna R, Chang MC, Joiner WJ, Kaczmarek LK, and Schlichter LC (1999) hSK4/hIK1, a calmodulin-binding K_{Ca} channel in human T lymphocytes. Roles in proliferation and volume regulation. *J Biol Chem* **274:**14838–14849.

27. Kohler R, Degenhardt C, Kuhn M, Runkel N, Paul M, and Hoyer J (2000) Expression and function of endothelial Ca^{2+}-activated K^+ channels inhuman mesenteric artery: a single-cell reverse transcriptase-polymerase chain reaction and electrophysiological study in situ. *Circ Res* **87:**496–503.

28. Grgic I, Eichler I, Heinau P, Si H, Brakemeier S, Hoyer J, and Kohler R (2005) Selective blockade of the intermediate-conductance Ca^{2+}-activated K^+ channel suppresses proliferation of microvascular and macrovascular endothelial cells and angiogenesis in vivo. *Arterioscler Thromb Vasc Biol* **25:**704–709.

29. Begenisich T, Nakamoto T, Ovitt CE, Nehrke K, Brugnara C, Alper SL, and Melvin JE (2004) Physiological roles of the intermediate conductance, Ca^{2+}-activatedpotassium channel Kcnn4. *J Biol Chem* **279:**47681–47687.

30. Rufo PA, Merlin D, Riegler M, Ferguson-Maltzman MH, Dickinson BL, Brugnara C, Alper SL, and Lencer WI (1997) The antifungal antibiotic, clotrimazole, inhibits chloride secretion by human intestinal T84 cells via blockade of distinct basolateral K^+ conductances. Demonstration of efficacy in intact rabbit colon and in an in vivo mouse model of cholera. *J Clin Investig* **100:**3111–3120.

31. Coghlan MJ, Carrol WA, and Gopalakrishnan M (2001) Recent developments in the biology and medicinal chemistry of potassium channel modulators: update from a decade of progress. *J Med Chem* **44:**1–27.

32. Reich EP, Cui L, Yang L, Pugliese-Sivo C, Golovko A, Petro M, Vassileva G, Chu I, Nomeir AA, Zhang LK, et al. (2005) Blocking ion channel KCNN4 alleviates the symptoms of experimental autoimmune encephalomyelitis in mice. *Eur J Immunol* **35:**1027–1036.

33. Mauler F, Hinz V, Horvath E, Schuhmacher J, Hofmann HA, Wirtz S, Hahn MG, and Urbahns K (2004) Selective intermediate/small-conductance calcium-activated potassium channel (KCNN4) blockers are potent and effective therapeutics in experimental brain oedema and traumatic brain injury caused by acute subdural haematoma. *Eur J Neurosci* **20:**1761–1768.

34. Joiner WJ, Khanna R, Schlichter LC, and Kaczmarek LK (2001) Calmodulin regulates assembly and trafficking of SK4/IK1 Ca^{2+}-activated K^+ channels. *J Biol Chem* **276:**37980–37985.

TABLE 7
K_{Ca}4.1 channels

Channel name	K_{Ca}4.1
Description	Sodium-activated potassium channel, rat (*Slack*) ortholog gated by voltage and synergistically by internal Na^+ and CI^-
Other names	*Slack*, *Slo2.2*, KCNT1
Molecular information	Human: 1256aa NM_020822, chr. 9q34.3, KCNT1 Mouse: XM_622105 (predicted), chr. 2 Rat: 1237aa, NM_021853, chr. 3p13
Associated subunits	Heteromeric association between rat *Slack* and *Slo1,*[3] no β-subunits identified
Functional assays	Voltage-clamp, patch-clamp
Current	K^+-selective
Conductance	25–65pS (*Slack*),[3] 60–180pS (*Slack*/*Slo1* heteromeric channels)[3]; 88pS (80 mM symmetric K^+), 165pS (160 mM symmetric K^+), prominent multiple subconductance states (*Slack*)[6]
Ion selectivity	K^+-selective
Activation	Gated by voltage (weakly voltage-sensitive) and synergistically by internal Na^+ and CI^- (half-maximal Na^+ activation $[Na^+]_{0.5}$ = 15 mM with 160 mM CI^-; half-maximal CI^- activation $[Cl^-]_{0.5}$ = 8.1 mM with 80 mM Na^+)[6]
Inactivation	None
Activators	None
Blockers	TEA, >60% block by 20 mM[2]; quindine, >90% block by 1.0 mM[2]
Gating inhibitors	Intracellular Ca^{+2} (5-fold reduction of NP_0 increasing Ca^{2+} from 0–3 μM)[3]
Radioligands	None
Channel distribution	Brain, testis, kidney (mouse *Slo2.2*)[6]; brain [brainstem (red nucleus, oculomotor nucleus, mesencephalic trigeminal, trapezoid nucleus, gigantocellularius, vestibular nucleus), olfactory bulb, frontal cortex, hippocampus], kidney, testis (rat *Slack*)[1]; neuronal immunohistochemical staining observed in cell bodies and axonal tracts
Physiological functions	Not established
Mutations and pathophysiology	Not established; *C. elegans slo-2* loss-of-function mutants hypersensitive to hypoxic death[5,6]
Pharmacological significance	Not established; native K_{Na} channels proposed to protect against hypoxic insult in cardiac muscles[4]
Comments	No published functional expression data for the human ortholog

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

1. Bhattacharjee A, Gan L, and Kaczmarek LK (2002) Localization of the Slack potassium channel in the rat central nervous system. *J Comp Neurol* **454:**241–254.
2. Bhattacharjee A, Joiner WJ, Wu M, Ynag Y, Sigworth FJ, and Kaczmarek LK (2003) Slick (Slo2.1), a rapidly-gated sodium-activated potassium channel inhibited by ATP. *J Neurosci* **23:**11681–11691.
3. Joiner WJ, Tang MD, Wang LY, Dworetzky SI, Boissard CG, Gan L, Gribkoff VK, and Kaczmarek LK (1998) Formation of intermediate-conductance-activated potassium channels by interaction of Slack and Slo subunits. *Nat Neurosci* **1:**462–469.
4. Kameyama M, Kakei M, Sato R, Shibasaki T, Matsuda H, and Irisawa H (1984) Intracellular Na^+ activates a K^+ channel in mammalian cardiac cells. *Nature (Lond)* **309:**354–356.
5. Yuan A, Dourado M, Butler A, Walton N, Wei A, and Salkoff L (2000) SLO-2, A K^+ channel with an unusual CI^- dependence. *Nat Neurosci* **3:**771–779.
6. Yuan A, Santi CM, Wei A, Wang Z-W, Pollak K, Nonet M, Kaczmarek L, Crowder CM, and Salkoff L (2003) The sodium-activated potassium channel is encoded by a member of the *Slo* gene family. *Neuron* **37:**765–773.

TABLE 8
K_{Ca}4.2 channels

Channel	K_{Ca}4.2
Description	Sodium-activated potassium channel gated by voltage, internal Na^+ and Cl^-, and inhibited by ATP
Other names	*Slick*, *Slo2.1*, KCNT2
Molecular information	Human: 1138aa, NM_198503; chr. 1q31.3, KCNT2 Mouse: 1131aa, XM_136252, chr. 1 Rat: 1142aa, NM_198762, chr. 13q13
Associated subunits	No β-subunits identified; binding to PSD-95 scaffolding protein via first PDZ domain[4]
Functional Assays	Voltage-clamp, patch-clamp
Current	K^+-selective
Conductance	141pS (130 mM symmetric K^+), multiple subconductance states[1]
Ion Selectivity	K^+-selective
Activation	Gated by voltage (weakly voltage-sensitive) and synergistically by internal Na^+ and Cl^- (5-fold increase in NP_o when Na^+ raised from 1–100 mM, with 30 mM Cl^-; 5-fold increase in NP_o when Cl^- raised from 3–130 mM, with 5 mM Na^+)[1]
Inactivation	None
Activators	None
Blockers	TEA, >60% block by 20 mM; quindine, >90% block by 1.0 mM[1]
Gating inhibitors	Intracellular ATP, >80% block by 5.0 mM
Radioligands	None
Channel distribution	Ubiquitous (mouse *Slo2.1*)[5]; brain (olfactory bulb, supraoptic nucleus, hippocampus, somatosensory and visual cortex, thalamus, deep cerebellar nucleus, oculomotor nucleus, auditory nuclei), heart[2] (rat *Slick*); neuronal immunohistochemical staining observed in cell bodies and axonal tracts
Physiological functions	Not established
Mutations and pathophysiology	Not established; *C. elegans slo-2* loss-of-function mutants are hypersensitive to hypoxic death[4,5]
Pharmacological significance	Not established; native K_{Na} channels proposed to protect against hypoxic insult in cardiac muscles[3]

aa, amino acids; chr., chromosome; PDZ, postsynaptic density 95/disc-large/zona occludens; TEA, tetraethylammonium.

1. Bhattacharjee A, Gan L, and Kaczmarek LK (2002) Localization of the Slack potassium channel in the rat central nervous system. *J Comp Neurol* **454:**241–254.
2. Bhattacharjee A, Joiner WJ, Wu M, Yang Y, Sigworth FJ, and Kaczmarek LK (2003) Slick (Slo2.1), a rapidly-gated sodium-activated potassium channel inhibited by ATPJ. *Neurosci* **23:**11681–11691.
3. Kameyama M, Kakei M, Sato R, Shibasaki T, Matsuda H, and Irisawa H (1984) Intracellular Na+ activates a K+ channel in mammalian cardiac cells. *Nature (Lond)* **309**:354–356.
4. Yuan A, Dourado M, Butler A, Walton N, Wei A, and Salkoff L (2000) SLO-2, a K^+ channel with an unusual Cl^- dependence *Nat Neurosci* **3:**771–779.
5. Yuan A, Santi CM, Wei A, Wang Z-W, Pollak K, Nonet M, Kaczmarek L, Crowder CM, and Salkoff L (2003) The sodium-activated potassium channel is encoded by a member of the Slo gene family. *Neuron* **37:**765–773.

TABLE 9
K_{Ca}5.1 channels

Channel	K_{Ca} 5.1
Description	pH-sensitive large-conductance potassium channel
Other names	Slo3, KCNMC1, Kcnma3
Molecular information	Human: BC028701 (coding sequence not defined), chr. 8p11.2,[7] *KCNU1* Mouse: 1112aa, NM_008432, chr. 8 Rat: 1243aa, NM_031828, chr. 15p16
Associated subunits	No β-subunits identified
Functional Assays	Voltage- and patch-clamp
Current	K^+-selective (mouse *Slo3*)
Conductance	106pS with 160 mM symmetric K^+ (mouse *Slo3*)[2]
Ion Selectivity	P_{K+}/P_{Na+} = 5.0 (mouse *Slo3*)[2]
Activation	Gated by voltage and internal alkalization (half-maximal activation at pH 7.5)[1–6]
Inactivation	None
Activators	None
Blockers	TEA, 50% block by 49 mM[2]
Gating inhibitors	None
Radioligands	None
Channel distribution	Testis, spermatocytes[2]
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	No published functional expression data for the human ortholog

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

1. Moss BL and Magleby KL (2001) Gating and conductance properties of BK channels are modulated by the S9-S10 tail domain of the alpha subunitA study of *mSlo1* and *mSlo3* wild-type and chimeric channels *J Gen Physiol* **118:**711–734.
2. Schreiber M, Wei A, Yuan A, Gaut J, Saito M, and Salkoff L (1998) *Slo3*, a novel pH-sensitive K+ channel from mammalian spermatocytes. *J Biol Chem* **273:**3509–3516.
3. Schreiber M, Yuan A, and Salkoff L (1999) Transplantable sites confer calcium sensitivity to BK channels. *Nat Neurosci* **2:**416–421.
4. Shi J and Cui J (2001) Intracellular Mg^{2+} enhances the function of BK-type Ca^{2+}-activated K^+ channels. *J Gen Physiol* **118:**589–606.
5. Shi J, Krishnamoorthy G, Yang Y, Hu L, Chaturvedi N, Harilal D, Qin J, and Cui J (2002) Mechanism of magnesium activation of calcium-activated potassium channels. *Nature (Lond)* **418:**876–880.
6. Xia XM, Zhang X, and Lingle CJ (2004) Ligand-dependent activation of Slo family channels is defined by interchangeable cytosolic domains. *J Neurosci* **24:**5585–5591.
7. GenBank accession no. AP000074.