

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

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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 (IUPHAR¹) 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 ($K_{Ca2.1}$, 2.2, and 2.3) (Kohler et al., 1996) and the "intermediate-conductance" channel $K_{Ca3.1}$ (Ishii et al., 1997; Joiner et al., 1997). These channels are voltage-insensitive and are activated by low concentrations of internal Ca^{2+} ($<1.0 \mu M$), in contrast to $K_{Ca1.1}$ (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 $K_{Ca1.1}$ (Slo or Slo1), $K_{Ca4.1}$ (Slack or Slo2.2), $K_{Ca4.2}$ (Slick or Slo2.1), and $K_{Ca5.1}$ (Slo3). $K_{Ca1.1}$ 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_{Ca2} and K_{Ca3} channels, binding of calcium by $K_{Ca1.1}$ 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, $K_{Ca4.1}$, 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 $K_{Ca1.1}$, 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+} . $K_{Ca4.2}$ and $K_{Ca4.1}$ are activated by internal Na^{+} and Cl^{-} (Yuan et al., 2003),

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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	<i>KCNMA1</i>	Slo, Slo1, BK
K _{Ca} 2.1	<i>KCNN1</i>	SK _{Ca} 1
K _{Ca} 2.2	<i>KCNN2</i>	SK _{Ca} 2
K _{Ca} 2.3	<i>KCNN3</i>	SK _{Ca} 3
K _{Ca} 3.1	<i>KCNN4</i>	IK _{Ca} 1
K _{Ca} 4.1	<i>KCNT1</i>	Slack, Slo2.2
K _{Ca} 4.2	<i>KCNT2</i>	Slick, Slo2.1
K _{Ca} 5.1	<i>KCNU1</i>	Slo3

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

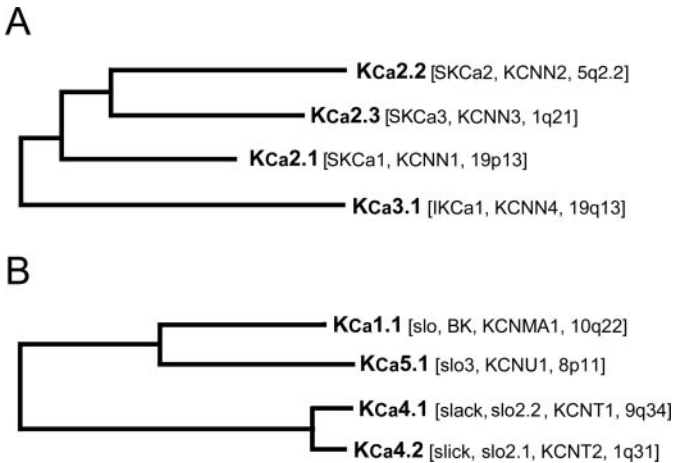


FIG. 1. Phylogenetic tree for K_{Ca} channels. A, K_{Ca}2/3 group. B, K_{Ca}1/4/5 group. Amino acid sequence alignments and phylogenetic analysis for these two groups of four human K_{Ca} channels were generated as described in the legend for Fig. 1 of “International Union of Pharmacology LIII. Nomenclature 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.

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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)-2H-indol-2-one.

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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 <i>KCNN1</i> 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), oligodendrogloma, 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-hexahydro-5,27:13,18:21,24-trietheno-11,7-methano-7*H*-dibenzo[*b,n*] [1,5,12,16] tetraazacyclotricosine-5,13-dilum ditrifluoroacetate.

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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 <i>KCNN2</i> 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, trifluoperazine, 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-1H-indole-2,3-dione-3-oxime; SK, small-conductance K⁺ channel; EBIO, 1-ethyl-2-benzimidazolinone; UCL1684, 6,12,19,20,25,26-hexahydro-5,27:13,18:21,24-trietheno-11,7-methano-7H-dibenzo [*b,n*] [1,5,12,16] tetraazacyclotricosine-5,13-dilum ditrifluoroacetate.

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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} <i>KCNN3</i> 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⁺ (<i>K_d</i> = 0.6 μM) 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-benzimidazole-5,13-dilum ditrifluoroacetate.

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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} <i>KCNN4</i> 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-4H-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} cetidil, 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-1H-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-2H-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-1H-azepin-1-yl)but-2-yne hydrogen oxalate; IBMX, 3-isobutyl-1-methylxanthine; TEA, tetraethylammonium; EDHF, endothelium-derived hyperpolarizing factor.

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TABLE 7
K_{Ca}4.1 channels

Channel name	K _{Ca} 4.1
Description	Sodium-activated potassium channel, rat (<i>Slack</i>) ortholog gated by voltage and synergistically by internal Na ⁺ and Cl ⁻
Other names	<i>Slack</i> , <i>Slo2.2</i> , 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 <i>Slack</i> and <i>Slo1</i> , ³ no β -subunits identified
Functional assays	Voltage-clamp, patch-clamp
Current	K ⁺ -selective
Conductance	25–65pS (<i>Slack</i>), ³ 60–180pS (<i>Slack/Slo1</i> heteromeric channels) ³ ; 88pS (80 mM symmetric K ⁺), 165pS (160 mM symmetric K ⁺), prominent multiple subconductance states (<i>Slack</i>) ⁶
Ion selectivity	K ⁺ -selective
Activation	Gated by voltage (weakly voltage-sensitive) and synergistically by internal Na ⁺ and Cl ⁻ (half-maximal Na ⁺ activation [Na ⁺] _{0.5} = 15 mM with 160 mM Cl ⁻ ; half-maximal Cl ⁻ 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 μ M) ³
Radioligands	None
Channel distribution	Brain, testis, kidney (mouse <i>Slo2.2</i>) ⁶ ; brain [brainstem (red nucleus, oculomotor nucleus, mesencephalic trigeminal, trapezoid nucleus, gigantocellularis, vestibular nucleus), olfactory bulb, frontal cortex, hippocampus], kidney, testis (rat <i>Slack</i>) ¹ ; neuronal immunohistochemical staining observed in cell bodies and axonal tracts
Physiological functions	Not established
Mutations and pathophysiology	Not established; <i>C. elegans slo-2</i> 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.
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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	<i>Slick</i> , <i>Slo2.1</i> , 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 <i>Slo2.1</i>) ⁵ ; brain (olfactory bulb, supraoptic nucleus, hippocampus, somatosensory and visual cortex, thalamus, deep cerebellar nucleus, oculomotor nucleus, auditory nuclei), heart ² (rat <i>Slick</i>); neuronal immunohistochemical staining observed in cell bodies and axonal tracts
Physiological functions	Not established
Mutations and pathophysiology	Not established; <i>C. elegans slo-2</i> 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.
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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.
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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 <i>KCNU1</i> 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 <i>Slo3</i>)
Conductance	106pS with 160 mM symmetric K ⁺ (mouse <i>Slo3</i>) ²
Ion Selectivity	P _{K+} /P _{Na+} = 5.0 (mouse <i>Slo3</i>) 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.
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