SK-Ca3 Small Conductance Calcium Activated Potassium Channel

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Introduction

The SK3 small conductance calcium-activated potassium channel belongs to the family of potassium channels that consist of one pore region (1P) with 6 putative transmembrane segments (6T) per alpha subunit (1P6T). It is a potassium selective ion channel that is opened by an increase in $[Ca^{++}]_i$. The opening of the channel is independent from the applied voltage, and the single channel conductance is of small size compared to calcium-activated potassium channels with intermediate and large single channel conductances Hille (2001). This channel type is usually thought to underlie the slow after hyperpolarization seen in neuronal cells. In addition to the different single channel conductance, these channels do also have a specific pharmacology, i.e., they are blocked by apamin, a peptide toxin isolated from bee venom, as well as blocked by Scyllatoxin (Leiurustoxin I), a peptide toxin isolated from scorpion venom. In addition, the channels are also blocked selectively by several bis-quinolinium cyclophanes (UCL 1530, UCL 1684, UCL 1848, UCL 2079). The channels can be activated by 1-EBIO (1-ethyl-benzimidazolinone), similar to the calcium-activated potassium channels with intermediate conductance.

Nomenclature

Superfamily	1P6T potassium channels
Family	Voltage independent Ca^{++}-activated potassium channels
Type	SK3
Subtypes	
Classification Numbers	KCNN3
Alternate or Previous Names	SK3, hKCa3, SKCa3
Comments	

Target Structure

Protein Information

SK3 is a pore forming subunit. The functional channel consists of four identical subunits (homotetramer), each with one pore region (1P) and 6 putative transmembrane segments (6T). The Ca^{++} sensor seems to be calmodulin bound to each subunit at a region between the S6 segment and the C-terminal end of the channel.

Protein Sequence Information

	Number or Name	Comments
Subunit Name	hKCNN3	
Organism Name	human	
Gene Accession #	NM_002249	Chandy et al (1998) XM_010636, AY049734
SwissProt Accession #	Q9UGI6	
# of Amino Acid Residues	736	hKCNN3 contains two polymorphic polyglutamine (poly-Q) tracks in its N-term cytosolic region. The most common length of these poly-Q tracks are 12 and 19 Qs Chandy et al (1998).
Protein Sequence Motifs		hKCNN3 contains 2 consensus sites for N-glycosylation, 3 consensus sites for cAMP- and cGMP-dependent protein kinase phosphorylation, 10 consensus sites for Protein kinase C phosphorylation, 8 consensus sites for Casein kinase II phosphorylation, 9 consensus sites for N-myristoylation, 2 leucine zipper motives, 1 glutamine-rich, 1 histidin-rich and 1 proline-rich region.
Chromosomal Localization	5q23.1-23.2	Wittekindt et al (1998) NT_004858 Homo sapiens chromosome 1 reference genomic contig, Dror et al (1999), Sun et al (2001) AF336797.

	Number or Name	Comments
Subunit Name	hKCNN3	
Organism Name	human	
Gene Accession #	AF438203	Tomita et al (2001)
SwissProt Accession #		
# of Amino Acid Residues	426	
Protein Sequence Motifs		hKCNN3 isoform contains contains 1 consensus site for cAMP- and cGMP-dependent protein kinase phosphorylation, 6 consensus sites for Protein kinase C phosphorylation, 4 consensus sites for Casein kinase II phosphorylation, 6 consensus sites for N-myristoylation, and 2 leucine zipper motives.
Chromosomal Localization	1q21.3	Wittekindt et al (1998) NT_004858 Homo sapiens chromosome 1 reference genomic contig, AF336797 Sun et al (2001).

	Number or Name	Comments
Subunit Name	rKCNN3	
Organism Name	rat	
Gene Accession #	U69884	Kohler et al (1996) NM:019315, AF 292389 Hosseini et al (2001).
SwissProt Accession #	P70605	

# of Amino Acid Residues	733	
Protein Sequence Motifs		rKCNN3 contains 2 consensus sites for N-glycosylation, 3 consensus sites for cAMP- and cGMP-dependent protein kinase phosphorylation, 9 consensus sites for Protein kinase C phosphorylation, 8 consensus sites for Casein kinase II phosphorylation, 9 consensus sites for N-myristoylation, two leucine zipper motives, 1 glutamine-rich, 1 histidine-rich, and 1 proline-rich region.
Chromosomal Localization		

	Number or Name	Comments
Subunit Name	rKCNN3 liver isoform	
Organism Name	rat	
Gene Accession #	AF284345	Barfod et al (2001)
SwissProt Accession #	P70605	
# of Amino Acid Residues	730	
Protein Sequence Motifs		rKCNN3 liver isoform contains 2 consensus sites for N-glycosylation, 3 consensus sites for cAMP- and cGMP-dependent protein kinase phosphorylation, 9 consensus sites for Protein kinase C phosphorylation, 8 consensus sites for Casein kinase II phosphorylation, 9 consensus sites for N-myristoylation, two leucine zipper motives, 1 glutamine-rich, 1 histidine-rich, and 1 proline-rich region.
Chromosomal Localization		

	Number or Name	Comments
Subunit Name	mKCNN3	
Organism Name	mouse	
Gene Accession #	AF357241	NM_080466, NM_080466, NW_000191
SwissProt Accession #	P58391	
# of Amino Acid Residues	731	
Protein Sequence Motifs		mKCNN3 contains 2 consensus sites for N-glycosylation, 3 consensus sites for cAMP- and cGMP-dependent protein kinase phosphorylation, 9 consensus sites for Protein kinase C phosphorylation, 8 consensus sites for Casein kinase II phosphorylation, 9 consensus sites for N-myristoylation, 2 leucine zipper motives, 1 glutamine-rich, 1 histidine-rich, and 1 proline-rich region.
Chromosomal Localization		

	Number or Name	Comments
Subunit Name	pKCNN3	
Organism Name	Sus scrofa (pig)	
Gene Accession #	AY03049	

SwissProt Accession #	P58392
# of Amino Acid Residues	725
Protein Sequence Motifs	pKCNN3 contains 2 consensus sites for N-glycosylation site, 3 consensus sites for cyclic AMP- and cyclic GMP-dependent protein kinase phosphorylation, 10 consensus sites for Protein kinase C phosphorylation, 8 consensus sites for Casein kinase II phosphorylation, 9 consensus sites for N-myristoylation, 2 leucine zipper motives, 1 glutamine-rich, 1 proline-rich, and 1 histidine-rich region.
Chromosomal Localization	

Localization

Protein

Neurons Hille (2001)

mRNA

Hippocampus (CA3), dentate gyrus, subiculum, anterior olfactory nucleus, olfactory tubercle, cerebellum, and cortex Stocker et al (2000).

Ligands, Substrates, Ions

Ligands

Ca++, calmodulin

Substrates

Name	Km value	Km units	Reference	Remarks
Ca++	300	nM	Kohler et al (1996)	
Calmodulin			Xia et al (1998)	

Ions

	Value	Units	Reference	Remarks
K^+				
Conductance	4-20	pS	Hille (2001)	The higher conductance is measured with elevated external K^+ concentrations.
Voltage Dependence	none			

Effectors, Products

Establishing a link between Ca^{++}-based second messenger systems and the electrical activity of cells.

Endogenous Regulation

Protein Partners

calmodulin

Pharmacological Regulation

Selective peptide blockers are apamin and scyllatoxin Hille (2001). Highly selective non-peptide blockers are different bis-quinolinium cyclophanes Stroebaek et al (2000), Shah et al (2000). Non-selective, more unspecific blockers are d-tubocurarine, verapamil, diltiazem, and tetraethylammonium. Openers are 1-ethyl-benzimidazolinone (1-EBIO, Pedarzani et al., 2001); EBIO activates also IK channels but not BK channels. Another more specific opener seems to be riluzole Grunnet et al (2001a), Jensen et al (2001).

Agonist / Activator / Substrate

Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: 1-ethyl-benzimidazolinone (1-EBIO)						
Ki: 100	μM	Rat KCNN2	Hetero-logous expression	HEK-293	Grunnet et al (2001a)	1-EBIO activates directly the channel and requires the presence of $[Ca^{++}]_i$. Method: electrophysiology (whole cell); Ki only estimated because no saturation of the EBIO effect could be obtained due to unstable currents at [EBIO] > 500 μM.

Agonist / Activator / Substrate

Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: riluzole						
Ki: 3	μM	Rat KCNN2	Hetero-logous expression	HEK-293	Grunnet et al (2001a)	Riluzole seems to directly activate the channel and requires the presence of $[Ca^{++}]_i$. Method: electrophysiology (whole cell); Ki only estimated because no saturation of the riluzole effect could be obtained due to unstable currents at [riluzole] > 10 μM.

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: UCL1684							
IC50:	9.5	nM	Human KCNN3	Hetero-logous expression	COS-7	Fanger et al (2001)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Apamin							
IC50:	1-4	nM	Rat KCNN3	Hetero-logous expression	HEK-293;	Grunnet et al (2001a)	Method used: electrophysiology (whole cell)
IC50:	10-13	nM	Human KCNN3	Hetero-logous expression	COS-7; CHO-K1	Grunnet et al (2001a)	membrane potential (fluorescence) apamin binding

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Leiurutoxin/scyllatoxin							
IC50:	1	nM	Human KCNN3	Hetero-logous expression	COS-7	Shakkotai et al (2001)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Lei-Dab7							
IC50:	6	μM	Human KCNN3	Hetero-logous expression	COS-7	Shakkotai et al (2001)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: PO5							
IC50:	25	nM	Human KCNN3	Hetero-logous expression	COS-7	Shakkotai et al (2001)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Tsκ							
IC50:	197	nM	Human KCNN3	Hetero-logous expression	COS-7	Shakkotai et al (2001)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Pi1-NH2							
IC50:	250	nM	Human KCNN3	Hetero-logous expression	COS-7	Shakkotai et al (2001)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Dequalinium							
IC50:	30	μM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Tubocurarine							
IC50:	210	μM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Antagonist / Inhibitor

Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Bicuculline IC50: 6	μM	Rat KCNN3	Hetero-logous expression	HEK-293	Grunnet et al (2001a)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Amitriptyline IC50: 39	μM	Rat KCNN3	Hetero-logous expression	HEK-293	Grunnet et al (2001a)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Fluphenazine IC50: 13	μM	Rat KCNN3	Hetero-logous expression	HEK-293	Grunnet et al (2001a)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Promethazine IC50: 31	μM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Chlorpromazine							
Ki:	0.57	μM	Rat KCNN3	Hetero-logous expression	HEK-293	Grunnet et al (2001a)	Method used: electrophysiology (whole cell).
IC50:	33	μM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Trifluoperazine							
IC50:	48	μM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Nortriptyline							
IC50:20		μM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Desipramine							
IC50:	29	μM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Antagonist / Inhibitor

Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Imipramine IC50: 44	μM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Antagonist / Inhibitor

Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Calyculin IC50:240	nM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Antagonist / Inhibitor

Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Ocadaic acid IC50: 506	nM	Human KCNN3	Hetero-logous expression	CHO-K1	Terstappen et al (2001)	Method used: membrane potential (fluorescence).

Disorders

Longer polyglutamine repeats are over-represented in schizophrenic individuals Chandy et al (1998), Cardno et al (1999) and in patients with anorexia nervosa Koronyo-Hamaoui et al (2002) and spinocerebellar ataxia Figueroa et al (2001). A four base deletion has been found in a patient with schizophrenia Bowen et al (2001) that truncates the protein just before the S1 segment and causes dominant-negative suppression of endogeneous SK channels Miller et al (2001). Protein and mRNA levels are increased in skeletal muscle after denervation Pribnow et al (1999), Neelands et al (2001) and in patients with myotonic muscular dystrophy Renaud et al (1986), Behrens et al (1994), Kimura et al (2000).

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