SK-Ca1 Small Conductance Calcium Activated Potassium Channel

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Introduction

The SK1 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 $[Ca^{++}]$. 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 (UCL1530, **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	SK1
Subtypes	
Classification Numbers	KCNN1
Alternate or Previous Names	SK1,SKCa1
Comments	

Target Structure

Protein Information

SK1 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	hKCNN1	
Organism Name	human	
Gene Accession #	NM_002248	U69883 Kohler et al (1996), AF1311938 Litt et al (1999), AF131939 Litt et al (1999) isoform generated by skipping of exon 9 are lacking the ability to bind calmodulin Zhang et al (2001).
SwissProt Accession #	Q92952	
# of Amino Acid Residues	561	
Protein Sequence Motifs		hKCNN1 contains 1 consensus site for N-glycosylation, 1 consensus site for cAMP- and cGMP-dependent protein kinase phosphorylation, 7 consensus sites for Protein kinase C phosphorylation, 5 consensus sites for Casein kinase II phosphorylation, 4 consensus sites for N-myristoylation, 2 leucine zipper motives and 2 prolin-rich regions.
Chromosomal Localization	19p13.1	Litt et al (1999), Ganshani et al (2000) NT_011288 genomic working draft sequence chromosome 19, AH007779 all Exons, Exon 1 AF131938, Exon 2 AF131939, Exon 3 AF131940, Exon 4 AF131941, Exon 5 AF131942, Exon 6 AF131943, Exon 7 AF131944, Exon 8 AF131945, Exon 9 AF131946, Exon 10 AF131947, Exon 11 AF131948

	Number or Name	Comments
Subunit Name	rKCNN1	
Organism Name	rat	
Gene Accession #	NM_01931	Kohler et al (1996) U69885
SwissProt Accession #	P70606	
# of Amino Acid Residues	537	
Protein Sequence Motifs		rKCNN1 contains contains 1 consensus site for N-glycosylation, 1 consensus site for cAMP- and cGMP-dependent protein kinase phosphorylation, 8 consensus sites for Protein kinase C phosphorylation, 6 consensus sites for Casein kinase II phosphorylation, 5 consensus sites for N-myristoylation and 1 leucine zipper motive.
Chromosomal Localization		

	Number or Name	Comments
Subunit Name	mKCNN1	
Organism Name	mouse	
Gene Accession #	AF116525	Transcript starts with exon 3.1 Shmukler et al (2001), NM_032397 NCBI automated annotation project. isoforms I through VIII are generated by alternative splicing of exons 8, 8a, and 9.

SwissProt Accession #	Q9EQR3	
# of Amino Acid Residues	580	
Protein Sequence Motifs		mKCNN1 contains 1 consensus site for Nglycosylation, 1 consensus site for cAMP and cGMPdeependent protein kinase phosphorylation, 8 consensus sites for protein kinaseC phosphorylation, 5 consensus sites for caseinkinase II physphorylation, 5 consensus sites for Nmyristoylation, 1 glutamate rich region and 2 leucine zipper motives.
Chromosomal Localization	8	NW_000344 Mus musculus WGS supercontig Mm8_WIFeb01_189, AF297870 exon 11 Shmukler et al (2001), AF299358 Exon A Shmukler et al (2001), AF297869 exons 3 through 10 Shmukler et al (2001), AH010601 exons 3 through 11 Shmukler et al (2001).

	Number or Name	**Comments**
Subunit Name	mKCNN1 isoform	
Organism Name	mouse	
Gene Accession #	AF303463	Shmukler et al (2001) containes exon A, AF303462 containes exons C/B1 and AF303461 containes exons C/B1/B2. All transcripts joined exon 3.2 and have the same ORF starting at Met 44.
SwissProt Accession #	Q9EQR3	
# of Amino Acid Residues	536	
Protein Sequence Motifs		mKCNN1 isoform contains 1 consensus site for Nglycosylation, 1 consensus site for cyclic AMP and cyclic GMPdeependent protein kinase phosphorylation, 7 consensus sites for protein kinaseC phosphorylation, 5 consensus sites for caseinkinase II physphorylation, 5 consensus sites for Nmyristoylation, 1 glutamate rich region and 2 leucine zipper motives.
Chromosomal Localization	8	NW_000344 Mus musculus WGS supercontig Mm8_WIFeb01_189, AF297870 exon 11 Shmukler et al (2001), AF299358 Exon A Shmukler et al (2001), AF297869 exons 3 through 10 Shmukler et al (2001), AH010601 exons 3 through 11 Shmukler et al (2001) supercontig Mm8_WIFeb01_189, AF297870 exon 11 Shmukler et al (2001), AF299358 Exon A Shmukler et al (2001), AF297869 exons 3 through 10 Shmukler et al (2001), AH010601 exons 3 through 11 Shmukler et al (2001).

Localization

Protein

Neurons Hille (2001)

mRNA

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

Ligands, Substrates, Ions

Ligands

Ca^{++}, calmodulin

Substrates

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

Ions

	Value	Units	Reference	Remarks
Potassium **Conductance**	4-20	pS	Hille (2001)	The higher conductance is measured with elevated external potassium 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 for SKchannels are thought to be **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 Devor et al (1996) but not BK channels.

Agonist / Activator / Substrate

	Value	Units	Organism	Organ Tissue	Cell Line/Type	Reference	Comments
Agent: 1-ethyl-benzimidazolinone (1-EBIO)							
Ki:	~ 650	µM	human KCNN1		Xenopus oocytes	Pedarzani et al (2001)	1-EBIO activates directly the channel and requires the presence of intracellular Ca^{++} method: electrophysiology (whole cell) Ki value estim ated from a comparison with rKCNN2.

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: UCL 1684							
IC50:	0.8	nM	human KCNN1		HEK 293	Stroebaek et al (2000)	Method used: electrophysiology (whole cell).

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: UCL 1848							
IC50:	1	nM	human KCNN1	N	HEK 293; COS-7	Shah et al (2000)	Method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: apamin							
IC50:	3; 8	nM	human KCNN1		HEK 293; COS-7	Stroebaek et al (2000)	Method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: apamin							
IC50:	>100	nM	human KCNN1		Xenopus oocytes	Kohler et al (1996)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Leiurutoxin / scyllatoxin							
IC50:	80; 325	nM	human KCNN1		HEK-293; COS-7	Stroebaek et al (2000); 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 KCNN1		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:	400	nM	human KCNN1		HEK-293; COS-7	Stroebaek et al (2000); Shah et al (2000)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: tubocurarine							
IC50:	23	μM	human KCNN1		HEK-293; COS-7	Stroebaek et al (2000); Shah et al (2000)	method used: electrophysiology (whole cell)

Journal Citations

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