IK-Ca Intermediate Conductance Calcium Activated Potassium Channel

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Introduction

The IK calcium-activated potassium channel belongs to the family of **potassium channels** that consist of one pore region (1P) with six 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 intermediate size compared to calcium-activated potassium channels with large and **small** single-channel conductances Hille (2001). This channel type was first extensively investigated and observed in erythrocytes by Gardos Gardos (1958) and is still referred to as the "Gardos channel." In addition to the different single-channel conductance, it has also a specific pharmacology, i.e., is blocked by **charybdotoxin** (ChTX), a peptide toxin isolated from scorpion venom. In addition, the channel is also blocked by **clotrimazole** and can be activated by 1-EBIO (1-ethyl-benzimidazolinone).

Nomenclature

Superfamily	1P6T potassium channels
Family	Voltage independent **Ca^{++}-activated potassium channels**
Type	IK1
Subtypes	
Classification Numbers	KCNN4
Alternate or Previous Names	IK1, IKCa1, KCa4, SK4, Gardoschannel (native channel),
Comments	

Target Structure

Protein Information

IK1 is a pore-forming subunit. The functional channel consists of four identical subunits (homotetramer), each with one pore region (1P) and six 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	HIK1	
Organism Name	Human	
Gene Accession #	AF022150	Ishii et al (1997), Joiner et al (1997), Logsdon et al (1997)

SwissProt Accession #	O15554	
# of Amino Acid Residues	427	
Protein Sequence Motifs		hIK1 contains three consensus sites for N-glycosilation, one consensus site for phosphorylation by PKA, four consensus sites for phosphorylation by PKC, two consensus sites for phosphorylation by Casein kinase II, nine consensus sites for N-myristoylation, and three leucine zipper patterns
Chromosomal Localization	19q13.13-19q13.2	

	Number or Name	**Comments**
Subunit Name	mIK1	
Organism Name	Mouse	
Gene Accession #	AF042487	Vandorpe et al. Vandorpe et al (1998)
SwissProt Accession #	O89109	
# of Amino Acid Residues	425	
Protein Sequence Motifs		mIK1 contains two consensus sites for N-glycosilation, one consensus site for phosphorylation by PKA, five consensus sites for phosphorylation by PKC, two consensus sites for phosphorylation by Casein kinase II, one consensus sites for phosphorylation by tyrosine kinase, seven consensus sites for N-myristoylation, and two leucine zipper patterns
Chromosomal Localization		

	Number or Name	**Comments**
Subunit Name	rIK1	
Organism Name	Rat	
Gene Accession #	AJ133438	Warth et al. Warth et al (1999)
SwissProt Accession #	Q9QYW1	
# of Amino Acid Residues	425	
Protein Sequence Motifs		rIK1 contains two consensus sites for N-glycosilation, one consensus site for phosphorylation by PKA, four consensus sites for phosphorylation by PKC, two consensus sites for phosphorylation by Casein kinase II, one consensus site for phosphorylation by tyrosine kinase, six consensus sites for N-myristoylation, and two leucine zipper patterns
Chromosomal Localization		

Localization

Protein

Erythrocytes Gardos (1958), activated T lymphocytes Grissmer et al (1993), Logsdon et al (1997), some endothelial and epithelial cells Jensen et al (1998)

mRNA

Colon (+), **prostate** (+), stomach (++), fetal **liver** (+), salivary gland (++++), **mammary gland** (+), **kidney** (++), liver (+), small intestine (+), spleen (+), thymus (++), lymph node (+), bone marrow (++), **lung** (+++), trachea (+++), placenta (+++); not found in **brain**; all data from Jensen et al. Jensen et al (1998)

Ligands, Substrates, Ions

Ligands

Ca^{++}, calmodulin

Substrates

Name	Km value	Km units	Reference	Remarks
Ca++ Calmodulin	~300	nM	Grissmer et al (1993) Fanger et al (1999)	

Ions

	Value	Units	Reference	Remarks
Potassium				
Conductance	20-80	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 **membrane potential** of cells.

Endogenous Regulation

Developmental Expression

Low level of functional expression in resting T lymphocytes and upregulation of functional channels in response to antigens and mitogens Grissmer et al (1993)

Protein Partners

Calmodulin

Pharmacological Regulation

Selective peptide blocker is Maurotoxin Castle et al (2001), and nonspecific peptide blocker is **charybdotoxin** Hille (2001). Highly selective nonpeptide blockers are **clotrimazole** Alvarez et al (1992) and TRAM-34 Wulff et al (2000), a clotrimazole derivative. Nonselective, more unspecific blockers are nitrendipine, **nifedipine**, **verapamil**, **diltiazem**, **cetiedil**, micanozole, ecanozole, and tetraethylammonium. Openers are 1-ethyl-benzimidazolinone (1-EBIO) Devor et al (1996) and 5,6 dichloro-1-ethyl-benzimidazolinone (DC-EBIO); EBIO activates also **SK channels** but not BK channels. Other less potent openers are chlorzoxazone and zoxazoloamine Singh et al (2000)

Agonist / Activator / Substrate

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: 1-EBIO							
Ki:	74	μM	Human KCNN4		HEK-293	Jensen et al (1998)	1-EBIO activates directly the channel and requires the presence of intracellular Ca^{++} method: electrophysiology (whole cell)

Agonist / Activator / Substrate

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: 1-EBIO							
Ki:	210	μM	Human	Colon carninoma; endogeneously expressed	T84	Singh et al (2001)	method used: short-circuit current

Agonist / Activator / Substrate

	Value	Units	Organism	Organ Tissue	Cell Line/Type	Reference	Comments
Agent: 1-EBIO							
Ki:	210	μM	Human KCNN4		HEK-293	Singh et al (2001)	methods used: Rb uptake and single-channel recording

Agonist / Activator / Substrate

	Value	Units	Organism	Organ Tissue	Cell Line/Type	Reference	Comments
Agent: DC-EBIO							
Ki:	19	μM	Human	Colon carninoma; endogeneously expressed	T84	Singh et al (2001)	method used: short-circuit current

Agonist / Activator / Substrate

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: DC-EBIO							
Ki:	19	μM	Human KCNN4		HEK-293	Singh et al (2001)	methods used: Rb uptake and single-channel recording

Agonist / Activator / Substrate

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Chlorzoxazone							
Ki:			Human	Colon carninoma; endogeneously expressed	T84	Singh et al (2000)	method used: short-circuit current, Rb uptake, single-channel recording

Agonist / Activator / Substrate

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Zoxazoloamine							
Ki:			Human	Colon carninoma; endogeneously expressed	T84	Singh et al (2000)	method used: short-circuit current, Rb uptake, single-channel recording

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Charybdotoxin							
IC50:	10	nM	Human KCNN4		HEK-293	Jensen et al (2001)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Maurotoxin							
IC50:	1	nM	Human KCNN4		CHO	Castle et al (2001)	method used: electrophysiology and Rb efflux

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Stichodactyla toxin							
IC50:	291	nM	Human KCNN4		HEK-293	Jensen et al (1998)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Margatoxin							
IC50:	459	nM	Human KCNN4		HEK-293	Jensen et al (1998)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Clotrimazole							
IC50:	70	nM	Human KCNN4		COS-7	Wulff et al (2000)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Miconazole							
IC50:	790	nM	Human KCNN4		HEK-293	Jensen et al (1998)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: TRAM 34							
IC50:	20	nM	Human KCNN4		COS-7	Wulff et al (2000)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Nitrendipine							
IC50:	27	nM	human KCNN4		HEK-293	Jensen et al (1998)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Nimodipine							
IC50:	1	μM	Human KCNN4		COS-7	Wulff et al (2000)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Nifedipine							
Kd:							it is likely that the blocking effect is direct and not through the block of voltage-gated Ca channels
IC50:	1.5	μM	Human KCNN4	n/a since exogeneously expressed	HEK-293	Jensen et al (1998)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Cetiedil							
IC50:	79	nM	Human KCNN4		HEK-293	Jensen et al (1998)	method used: electrophysiology (whole cell)

Antagonist / Inhibitor

	Value	Units	Organism	Organ Tissue	Cell Line/ Type	Reference	Comments
Agent: Tetraethylammonium							
IC50:	40	mM	Human	T cells		Grissmer et al (1993)	method used: electrophysiology (whole cell)

Journal Citations

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