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International Union of Pharmacology. L. Nomenclature and Structure-Function Relationships of CatSper and Two-Pore Channels

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Introduction

CatSper channels (CatSper1–4) are named after the first putative cation channel of sperm (Quill et al., 2001; Ren et al., 2001). CatSpers are putative six-transmembrane (6TM[1]) voltage-gated Ca^{2+}-permeant channels and seem to be specific to sperm cells. CatSper1 and 2 are each essential for the hyperactivation of sperm cell motility, which is required for fertility. Sequence identities among these CatSper family members range between 22 and 27% across the ion transport domain (Lobley et al., 2003).

Structural Features

All CatSpers are most closely related to the 6TM voltage-gated sodium channel (Na_VBP) in bacteria, with the next closest relatives being the large mammalian Ca_V and Na_V channel classes (Fig. 1). CatSpers have an S4 transmembrane segment with positively charged amino acids interspersed between every three amino acids. CatSper1 also contains a remarkable abundance of histidine residues in its amino terminus.

Functional Features

CatSper1 is localized to the plasma membrane of the sperm tail (Ren et al., 2001). Targeted disruption of the CatSper1 gene led to a male sterile phenotype in an otherwise normal mouse. Whereas the mating behavior, sperm count, and sperm cell morphology of the mutant mice were indistinguishable from those of the wild type, mutant sperm cells were sluggish, displayed reduced basal velocity, and lacked vigorous beating and bending in the tail region. Mutant sperm cells could not fertilize eggs with an intact zona pellucida but could fertilize eggs whose outer layers had been enzymatically removed (Ren et al., 2001). Further studies showed that CatSper1-null sperm cells could not be hyperactivated (Carlson et al., 2003). Interestingly, depolarization evoked an increase in intracellular Ca^{2+} in wild-type sperm cells but not in CatSper1-null sperm cells (Carlson et al., 2003). CatSper2-null mice and sperm cells have an indistinguishable phenotype from CatSper1-null mice. Male mice lacking CatSper2 were also sterile due to the absence of the hyperactivated motility needed for penetration of the extracellular matrix of the egg (Quill et al., 2003). In one study in humans, subfertile men with deficient sperm cell motility had significantly reduced expression of CatSper1 (Nikpoor et al., 2004). CatSper2 has been implicated by linkage analysis in human asthenoteratozoospermia (Avidan et al., 2003).

Recently, spermatazoa were patch-clamped, and the CatSper1-dependent current was shown to be an alkaline-potentiated, voltage-activated, calcium-selective channel (Kirichok et al., 2006). CatSpers have not yet been functional in numerous heterologous expression systems or spermatocytes, apparently because they are not targeted to the plasma membrane of nonsperm cells (Ren et al., 2001). Little is known about CatSpers3 and 4.

Two-Pore Channels

The two-pore channels TPC1 and TPC2 are putative cation-selective ion channels related to CatSper and transient receptor potential channels and, more distantly, to Na_v and Ca_v channels. The TPCN1 (Hs.524763; Mm.114054) and N2 (Hs.503051; Mm.102235) genes encode proteins with two repeats of a 6TM domain. Each domain has a positively charged voltage sensor segment. TPC1 mRNA is detected at relatively high levels in kidney, liver, and lung, and immunohistochemistry of kidney shows that TPC1 was expressed in the inner medullary collecting ducts (Ishibashi et al., 2000). Neither TPC has been functionally expressed in heterologous cells to date, and no genetic data are available.

Tables 1 through 4 list the attributes of CatSper1 through CatSper4, respectively.

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[1] Abbreviations: TM, transmembrane; TPC, two-pore channel.

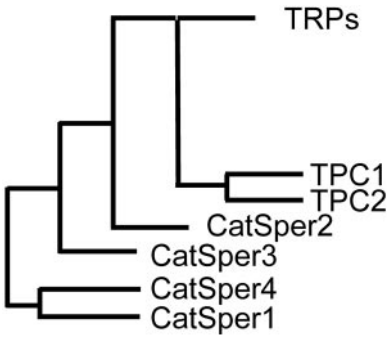

FIG. 1. CatSper and TPC family tree. See "International Union of Pharmacology. XLIX. Nomenclature and Structure-Function Relationships of Transient Receptor Potential Channels" for more details.

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TABLE 1
CatSper1 channel

Channel name	CatSper1
Description	Putative voltage-gated cation-selective ion channel subunit
Other names	CatSper[1]
Molecular information	Human unigene: Hs0.189105: AF407333; chr. 11q12.1 Mouse unigene: Mm0.87321: AF407332; mouse chr. 19 A
Associated subunits	None reported
Functional assays	Calcium imaging, patch-clamp of sperm cells[2]
Current	Ca^{2+}-selective, voltage-dependent; potentiated at pH 8[2]
Conductance	Not established
Ion selectivity	Ca^{2+}-selective[2]
Activation	Voltage-gated, increasing pH shifts activation voltage to more hyperpolarized potentials[2]
Inactivation	Not established
Activators	Increased pH[2]
Gating inhibitors	Not established
Blockers	Not established
Radioligands	None
Channel distribution	Mature sperm cells
Physiological functions	CatSper1 is essential for the hyperactivation of sperm motility, which is required for sperm cell fertility
Mutations and pathophysiology	Not established
Pharmacological significance	Not established

chr., chromosome.

1. Ren D, Navarro B, Perez G, Jackson AC, Hsu S, Shi Q, Tilly JL, and Clapham DE (2001) A sperm ion channel required for sperm motility and male fertility. *Nature (Lond)* **413:**603–609.
2. Kirichok Y, Navarro B, and Clapham DE (2006) Whole-cell patch clamp measurements of spermatazoa reveal an alkaline-activated Ca^{2+} channel. *Nature (Lond.)*, in press.

TABLE 2
CatSper2 channel

Channel name	CatSper2[1]
Description	Putative voltage-gated calcium-selective ion channel subunit
Other names	None
Molecular information	Human unigene: Hs0.389181: AF411817; chr. 15q14; four splice variants Mouse unigene: Mm0.271895: NM_153075; chr. 2E5
Associated subunits	Not established
Functional assays	Calcium imaging
Current	Not established
Conductance	Not established
Ion selectivity	Putative Ca^{2+}-permeant
Activation	Putative voltage-gated
Inactivation	Not established
Activators	Not established
Gating inhibitors	Not established
Blockers	Not established
Radioligands	None
Channel distribution	Mature sperm cells
Physiological functions	CatSper2 is essential for the hyperactivation of sperm motility, which is required for male fertility; CatSper2 has been implicated by linkage analysis in human asthenoteratozoospermia[2]
Mutations and pathophysiology	Not established
Pharmacological significance	Not established

chr., chromosome.

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TABLE 3
CatSper3 channel

Channel name	CatSper3[1,2]
Description	Putative voltage-gated cation-selective ion channel subunit
Other names	CatSper4 (AY263400)
Molecular information	Human unigene: Hs0.444355: AF432876; chr. 5q31.1 Mouse unigene: Mm0.159795; chr. 13 B2
Associated subunits	Not established
Functional assays	Not established
Current	Not established
Conductance	Not established
Ion selectivity	Putative Ca^{2+}-permeant
Activation	Putative voltage-gated
Inactivation	Not established
Activators	Not established
Gating inhibitors	Not established
Blockers	Not established
Radioligands	None
Channel distribution	Testis
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established

chr., chromosome.
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TABLE 4
CatSper4 channel

Channel name	CatSper4
Description	Putative voltage-gated cation-selective ion channel subunit
Other names	
Molecular information	Human unigene: Hs0.123532: BN000273; chr. 1p35.3 Mouse unigene: Mm0.79072: NM_177866; chr. 4 D3
Associated subunits	Not established
Functional assays	Not established
Current	Not established
Conductance	Not established
Ion selectivity	Putative Ca^{2+}-permeant
Activation	Putative voltage-gated
Inactivation	Not established
Activators	Not established
Gating inhibitors	Not established
Blockers	Not established
Radioligands	None
Channel distribution	Testis
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established

chr., chromosome.
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