CatSper channels

Overview: CatSper channels (CatSpers1–4; nomenclature as agreed by NC-IUPHAR, Clapham and Garbers, 2005) are putative 6TM, voltage-gated, calcium-permeant channels that are presumed to assemble as a tetramer of α-like subunits and mediate the current $I_{CatSper}$. In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels (Ca_v) (Ren *et al.*, 2001). CatSper1 (Ren *et al.*, 2001), CatSper2 (Quill *et al.*, 2001) and CatSpers3 and 4 (Lobley *et al.*, 2003; Lin *et al.*, 2005; Qi *et al.*, 2007), in common with a recently identified putative 2TM-auxiliary CatSperβ protein (Liu *et al.*, 2007) and a putative 1TM-associated CatSperγ protein (Wang *et al.*, 2009), are restricted to the testis and localized to the principle piece of sperm tail.

Nomenclature	CatSper1	CatSper2	CatSper3	CatSper4
Ensembl ID	ENSG00000175294	ENSG00000166762	ENSG00000152705	ENSG00000188782
Activators	Constitutively active, weakly facilitated by membrane depolarization, strongly augmented by intracellular alkalinization	–	–	–
Blockers	Cd^{2+} (200 μM), Ni^{2+} (300 μM), ruthenium red (10 μM)	–	–	–
Functional characteristics	Calcium-selective ion channel ($Ba^{2+} > Ca^{2+} >> Mg^{2+} >> Na^{+}$); quasilinear monovalent cation current in the absence of extracellular divalent cations; alkalinization shifts the voltage dependence of activation towards negative potentials ($V_{½}$ at pH 6.0 = +87 mV; $V_{½}$ at pH 7.5 = +11 mV)	Required for $I_{CatSper}$	Required for $I_{CatSper}$	Required for $I_{CatSper}$

CatSper channel subunits expressed singly, or in combination, fail to functionally express in heterologous expression systems (Quill *et al.*, 2001; Ren *et al.*, 2001). The properties of CatSper1 tabulated above are derived from whole cell voltage-clamp recordings comparing currents endogenous with spermatozoa isolated from the *corpus epididymis* of wild-type and *Catsper1*$^{(-/-)}$ mice (Kirichok *et al.*, 2006). $I_{CatSper}$ is also undetectable in the spermatozoa of *Catsper2*$^{(-/-)}$, *Catsper3*$^{(-/-)}$ or *Catsper4*$^{(-/-)}$ mice, and CatSper 1 associates with CatSpers2, 3 or 4 in heterologous expression systems (Qi *et al.*, 2007). Moreover, targeted disruption of *Catspers1*, *2*, *3* or *4* genes results in an identical phenotype in which spermatozoa fail to exhibit the hyperactive movement (whip-like flagellar beats) necessary for penetration of the egg *cumulus* and *zona pellucida* and subsequent fertilization. Such disruptions are associated with a deficit in alkalinization- and depolarization-evoked Ca^{2+} entry into spermatozoa (Carlson *et al.*, 2003; 2005; Qi *et al.*, 2007). Thus, it is likely that the CatSper pore is formed by a heterotetramer of CatSpers1–4 (Qi *et al.*, 2007). CatSper channels are required for the increase in intracellular Ca^{2+} concentration in sperm evoked by egg *zona pellucida* glycoproteins (Xia and Ren, 2009). The driving force for Ca^{2+} entry is principally determined by a mildly outwardly rectifying K^{+} channel (KSper) that, like CatSpers, is activated by intracellular alkalinization (Navarro *et al.*, 2007). KSper is not yet identified, but its properties are most consistent with mSlo3, a protein detected only in testis (Navarro *et al.*, 2007).

Further Reading

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