

# CatSper and Two-Pore channels (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

Jean-Ju Chung<sup>1</sup>, David E. Clapham<sup>1</sup>, David L. Garbers<sup>2</sup> and Dejian Ren<sup>3</sup>

1. Harvard Medical School, USA
2. Formerly of the University of Texas, USA
3. University of Pennsylvania, USA

## Abstract

CatSper channels (CatSper1-4, **nomenclature as agreed by NC-IUPHAR [13]**) are putative 6TM, voltage-gated, alkalization-activated calcium permeant channels that are presumed to assemble as a tetramer of  $\alpha$ -like subunits and mediate the current  $I_{\text{CatSper}}$  [21]. In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels ( $\text{Ca}_v$ ) [36]. CatSper1 [36], CatSper2 [33] and CatSper3 and 4 [25, 19, 32], in common with a putative 2TM auxiliary CatSper $\beta$  protein [24] and two putative 1TM associated CatSper $\gamma$  and CatSper $\delta$  proteins [42, 11], are restricted to the testis and localised to the principle piece of sperm tail. The novel cross-species CatSper channel inhibitor, RU1968, has been proposed as a useful tool to aid characterisation of native CatSper channels [37].

Two-pore channels (TPCs) are structurally related to CatSper,  $\text{Ca}_v$ s and  $\text{Na}_v$ s. TPCs have a 2x6TM structure with twice the number of TMs of CatSper and half that of  $\text{Ca}_v$ s. There are three animal TPCs (TPC1-TPC3). Humans have TPC1 and TPC2, but not TPC3. TPC1 and TPC2 are localized in endosomes and lysosomes [4]. TPC3 is also found on the plasma membrane and forms a voltage-activated, non-inactivating  $\text{Na}^+$  channel [5]. All the three TPCs are  $\text{Na}^+$ -selective under whole-cell or whole-organelle patch clamp recording [44, 7, 6]. The channels may also conduct  $\text{Ca}^{2+}$  [29].

## Contents

This is a citation summary for CatSper and Two-Pore channels in the [Guide to Pharmacology](#) database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

[GtoPdb](#) is an expert-driven guide to pharmacological targets and the substances that act on them. GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a citation for the relevant parts of the database, and also provides a reference list for the research cited by those parts.

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current

version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

## Database links

### CatSper and Two-Pore channels

<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=70>

### Introduction to CatSper and Two-Pore channels

<http://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=70>

#### Channels and Subunits

##### CatSper1

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=388>

##### CatSper2

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=389>

##### CatSper3

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=390>

##### CatSper4

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=391>

##### TPC1

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=392>

##### TPC2

<http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=393>

## References

1. Avenarius MR, Hildebrand MS, Zhang Y, Meyer NC, Smith LL, Kahrizi K, Najmabadi H and Smith RJ. (2009) Human male infertility caused by mutations in the CATSPER1 channel protein. *Am. J. Hum. Genet.* **84**: 505-10 [PMID:19344877]
2. Avidan N, Tamary H, Dgany O, Cattan D, Pariente A, Thulliez M, Borot N, Moati L, Barthelme A and Shalmon L *et al.*. (2003) CATSPER2, a human autosomal nonsyndromic male infertility gene. *Eur. J. Hum. Genet.* **11**: 497-502 [PMID:12825070]
3. Brenker C, Goodwin N, Weyand I, Kashikar ND, Naruse M, Krähling M, Müller A, Kaupp UB and Strünker T. (2012) The CatSper channel: a polymodal chemosensor in human sperm. *EMBO J.* **31**: 1654-65 [PMID:22354039]
4. Calcraft PJ, Ruas M, Pan Z, Cheng X, Arredouani A, Hao X, Tang J, Rietdorf K, Teboul L and Chuang KT *et al.*. (2009) NAADP mobilizes calcium from acidic organelles through two-pore channels. *Nature* **459**: 596-600 [PMID:19387438]
5. Cang C, Aranda K and Ren D. (2014) A non-inactivating high-voltage-activated two-pore Na<sup>+</sup> channel that supports ultra-long action potentials and membrane bistability. *Nat Commun* **5**: 5015 [PMID:25256615]
6. Cang C, Bekele B and Ren D. (2014) The voltage-gated sodium channel TPC1 confers endolysosomal excitability. *Nat. Chem. Biol.* **10**: 463-9 [PMID:24776928]
7. Cang C, Zhou Y, Navarro B, Seo YJ, Aranda K, Shi L, Battaglia-Hsu S, Nissim I, Clapham DE and Ren D. (2013) mTOR regulates lysosomal ATP-sensitive two-pore Na<sup>(+)</sup> channels to adapt to metabolic state. *Cell* **152**: 778-90 [PMID:23394946]
8. Carlson AE, Burnett LA, del Camino D, Quill TA, Hille B, Chong JA, Moran MM and Babcock DF. (2009) Pharmacological targeting of native CatSper channels reveals a required role in maintenance of sperm hyperactivation. *PLoS ONE* **4**: e6844 [PMID:19718436]
9. Carlson AE, Quill TA, Westenbroek RE, Schuh SM, Hille B and Babcock DF. (2005) Identical phenotypes of CatSper1 and CatSper2 null sperm. *J. Biol. Chem.* **280**: 32238-44 [PMID:16036917]
10. Carlson AE, Westenbroek RE, Quill T, Ren D, Clapham DE, Hille B, Garbers DL and Babcock DF. (2003) CatSper1 required for evoked Ca<sup>2+</sup> entry and control of flagellar function in sperm. *Proc. Natl. Acad. Sci.*

- U.S.A. **100**: 14864-8 [PMID:14657352]
11. Chung JJ, Navarro B, Krapivinsky G, Krapivinsky L and Clapham DE. (2011) A novel gene required for male fertility and functional CATSPER channel formation in spermatozoa. *Nat Commun* **2**: 153 [PMID:21224844]
  12. Chung JJ, Shim SH, Everley RA, Gygi SP, Zhuang X and Clapham DE. (2014) Structurally distinct Ca(2+) signaling domains of sperm flagella orchestrate tyrosine phosphorylation and motility. *Cell* **157**: 808-22 [PMID:24813608]
  13. Clapham DE and Garbers DL. (2005) International Union of Pharmacology. L. Nomenclature and structure-function relationships of CatSper and two-pore channels. *Pharmacol. Rev.* **57**: 451-4 [PMID:16382101]
  14. Grimm C, Holdt LM, Chen CC, Hassan S, Müller C, Jörs S, Cuny H, Kissing S, Schröder B and Butz E *et al.*. (2014) High susceptibility to fatty liver disease in two-pore channel 2-deficient mice *Nat Commun* **5**: 4699 [PMID:25144390]
  15. Hildebrand MS, Avenarius MR, Fellous M, Zhang Y, Meyer NC, Auer J, Serres C, Kahrizi K, Najmabadi H and Beckmann JS *et al.*. (2010) Genetic male infertility and mutation of CATSPER ion channels. *Eur. J. Hum. Genet.* **18**: 1178-84 [PMID:20648059]
  16. Ho K, Wolff CA and Suarez SS. (2009) CatSper-null mutant spermatozoa are unable to ascend beyond the oviductal reservoir. *Reprod. Fertil. Dev.* **21**: 345-50 [PMID:19210926]
  17. Ishibashi K, Suzuki M and Imai M. (2000) Molecular cloning of a novel form (two-repeat) protein related to voltage-gated sodium and calcium channels. *Biochem. Biophys. Res. Commun.* **270**: 370-6 [PMID:10753632]
  18. Jin J, Jin N, Zheng H, Ro S, Tafolla D, Sanders KM and Yan W. (2007) Catsper3 and Catsper4 are essential for sperm hyperactivated motility and male fertility in the mouse. *Biol. Reprod.* **77**: 37-44 [PMID:17344468]
  19. Jin JL, O'Doherty AM, Wang S, Zheng H, Sanders KM and Yan W. (2005) Catsper3 and catsper4 encode two cation channel-like proteins exclusively expressed in the testis. *Biol. Reprod.* **73**: 1235-42 [PMID:16107607]
  20. Kirichok Y and Lishko PV. (2011) Rediscovering sperm ion channels with the patch-clamp technique *Mol. Hum. Reprod.* **17**: 478-99 [PMID:21642646]
  21. Kirichok Y, Navarro B and Clapham DE. (2006) Whole-cell patch-clamp measurements of spermatozoa reveal an alkaline-activated Ca<sup>2+</sup> channel. *Nature* **439**: 737-40 [PMID:16467839]
  22. Lishko PV, Botchkina IL and Kirichok Y. (2011) Progesterone activates the principal Ca<sup>2+</sup> channel of human sperm. *Nature* **471**: 387-91 [PMID:21412339]
  23. Lishko PV and Kirichok Y. (2010) The role of Hv1 and CatSper channels in sperm activation *J. Physiol. (Lond.)* **588**: 4667-72 [PMID:20679352]
  24. Liu J, Xia J, Cho KH, Clapham DE and Ren D. (2007) CatSperbeta, a novel transmembrane protein in the CatSper channel complex. *J. Biol. Chem.* **282**: 18945-52 [PMID:17478420]
  25. Lobley A, Pierron V, Reynolds L, Allen L and Michalovich D. (2003) Identification of human and mouse CatSper3 and CatSper4 genes: characterisation of a common interaction domain and evidence for expression in testis. *Reprod. Biol. Endocrinol.* **1**: 53 [PMID:12932298]
  26. Lucas JB, Salyer RD and Watson DW. (2003) Gangrenous primary cutaneous mucormycosis of the scalp in an iatrogenically immunosuppressed trauma patient. *Otolaryngol Head Neck Surg* **128**: 912-4 [PMID:12825050]
  27. Martínez-López P, Santi CM, Treviño CL, Ocampo-Gutiérrez AY, Acevedo JJ, Alisio A, Salkoff LB and Darszon A. (2009) Mouse sperm K<sup>+</sup> currents stimulated by pH and cAMP possibly coded by Slo3 channels. *Biochem. Biophys. Res. Commun.* **381**: 204-9 [PMID:19338774]
  28. Miki K and Clapham DE. (2013) Rheotaxis guides mammalian sperm. *Curr. Biol.* **23**: 443-52 [PMID:23453951]
  29. Morgan AJ and Galione A. (2014) Two-pore channels (TPCs): current controversies. *Bioessays* **36**: 173-83 [PMID:24277557]

30. Navarro B, Kirichok Y and Clapham DE. (2007) KSper, a pH-sensitive K<sup>+</sup> current that controls sperm membrane potential. *Proc. Natl. Acad. Sci. U.S.A.* **104**: 7688-92 [PMID:17460039]
31. Nikpoor P, Mowla SJ, Movahedin M, Ziaee SA and Tiraihi T. (2004) CatSper gene expression in postnatal development of mouse testis and in subfertile men with deficient sperm motility. *Hum. Reprod.* **19**: 124-8 [PMID:14688170]
32. Qi H, Moran MM, Navarro B, Chong JA, Krapivinsky G, Krapivinsky L, Kirichok Y, Ramsey IS, Quill TA and Clapham DE. (2007) All four CatSper ion channel proteins are required for male fertility and sperm cell hyperactivated motility. *Proc. Natl. Acad. Sci. U.S.A.* **104**: 1219-23 [PMID:17227845]
33. Quill TA, Ren D, Clapham DE and Garbers DL. (2001) A voltage-gated ion channel expressed specifically in spermatozoa. *Proc. Natl. Acad. Sci. U.S.A.* **98**: 12527-31 [PMID:11675491]
34. Quill TA, Sugden SA, Rossi KL, Doolittle LK, Hammer RE and Garbers DL. (2003) Hyperactivated sperm motility driven by CatSper2 is required for fertilization. *Proc. Natl. Acad. Sci. U.S.A.* **100**: 14869-74 [PMID:14657366]
35. Reardon AJ, Le Goff M, Briggs MD, McLeod D, Sheehan JK, Thornton DJ and Bishop PN. (2000) Identification in vitreous and molecular cloning of opticin, a novel member of the family of leucine-rich repeat proteins of the extracellular matrix. *J. Biol. Chem.* **275**: 2123-9 [PMID:10636917]
36. 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* **413**: 603-9 [PMID:11595941]
37. Rennhack A, Schiffer C, Brenker C, Fridman D, Nitao ET, Cheng YM, Tamburrino L, Balbach M, Stölting G and Berger TK *et al.*. (2018) A novel cross-species inhibitor to study the function of CatSper Ca<sup>2+</sup> channels in sperm. *Br. J. Pharmacol.* **175**: 3144-3161 [PMID:29723408]
38. Roychoudhury C, Jacobs BS, Baker PL, Schultz D, Mehta RH and Levine SR. (2004) Acute ischemic stroke in hospitalized medicare patients: evaluation and treatment. *Stroke* **35**: e22-3 [PMID:14657452]
39. Sakurai Y, Kolokoltsov AA, Chen CC, Tidwell MW, Bauta WE, Klugbauer N, Grimm C, Wahl-Schott C, Biel M and Davey RA. (2015) Ebola virus. Two-pore channels control Ebola virus host cell entry and are drug targets for disease treatment. *Science* **347**: 995-8 [PMID:25722412]
40. Smith JF, Syritsyna O, Fellous M, Serres C, Mannowetz N, Kirichok Y and Lishko PV. (2013) Disruption of the principal, progesterone-activated sperm Ca<sup>2+</sup> channel in a CatSper2-deficient infertile patient. *Proc. Natl. Acad. Sci. U.S.A.* **110**: 6823-8 [PMID:23530196]
41. Strünker T, Goodwin N, Brenker C, Kashikar ND, Weyand I, Seifert R and Kaupp UB. (2011) The CatSper channel mediates progesterone-induced Ca<sup>2+</sup> influx in human sperm. *Nature* **471**: 382-6 [PMID:21412338]
42. Wang H, Liu J, Cho KH and Ren D. (2009) A novel, single, transmembrane protein CATSPERG is associated with CATSPER1 channel protein. *Biol. Reprod.* **81**: 539-44 [PMID:19516020]
43. Wang X, Zhang X, Dong XP, Samie M, Li X, Cheng X, Goschka A, Shen D, Zhou Y and Harlow *et al.*. (2012) TPC proteins are phosphoinositide-activated sodium-selective ion channels in endosomes and lysosomes. *Cell* **151**: 372-83 [PMID:23063126]
44. Xia J and Ren D. (2009) Egg coat proteins activate calcium entry into mouse sperm via CATSPER channels. *Biol. Reprod.* **80**: 1092-8 [PMID:19211808]
45. Zeng XH, Yang C, Kim ST, Lingle CJ and Xia XM. (2011) Deletion of the Slo3 gene abolishes alkalization-activated K<sup>+</sup> current in mouse spermatozoa. *Proc. Natl. Acad. Sci. U.S.A.* **108**: 5879-84 [PMID:21427226]
46. Zhang Y, Malekpour M, Al-Madani N, Kahrizi K, Zanganeh M, Lohr NJ, Mohseni M, Mojahedi F, Daneshi A and Najmabadi H *et al.*. (2007) Sensorineural deafness and male infertility: a contiguous gene deletion syndrome. *J. Med. Genet.* **44**: 233-40 [PMID:17098888]