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Transient Receptor Potential Canonical 7 (TRPC7): A Diacylglycerol-Activated Non-Selective Cation Channel

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Abstract

Transient receptor potential canonical 7 (TRPC7) channel is the seventh member of the mammalian TRPC channel family. TRPC7 mRNA, protein and channel activity have been detected in many tissues and organs from mouse, rat and human. TRPC7 has high sequence homology with TRPC3 and TRPC6 and all three channels are activated by membrane receptors that couple to isoforms of phospholipase C (PLC) and mediate non-selective cation currents. TRPC7, along with TRPC3 and TRPC6 can be activated by direct exogenous application of diacylglycerol (DAG) analogs and by pharmacological maneuvers that increase endogenous DAG in cells. TRPC7 shows distinct properties of activation, such as constitutive activity, susceptibility to negative regulation by extracellular Ca^{2+} and by protein kinase C. TRPC7 can form heteromultimers with TRPC3 and TRPC6. Although TRPC7 remains one of the least studied TRPC channel, its role in various cell types and physiological and pathophysiological conditions is beginning to emerge.

Keywords

TRPC7; Non-selective cation channel; Diacylglycerol; Ca^{2+} signaling; Phospholipase C

Gene, splicing etc

TRPC7 gene was first cloned by Okada et al. (1999) from mouse brain. The murine TRPC7 gene has 12 exons and is mapped to the chromosomal region 13 B2 (Numaga, Wakamori et al. 2007). Eight transcripts from mouse TRPC7 gene have been reported so far. Subsequently, Riccio et al. (2002) cloned human TRPC7 from brain. The human TRPC7 gene mapped to the chromosomal region 5q31.1 and has also 12 exons. Thus far, 10 transcripts of human TRPC7 have been identified. Both human and mouse TRPC7 genes consist of an open reading frame of 2,589 bp yielding a protein of 862 amino acids (Okada, Inoue et al. 1999, Riccio, Mattei et al. 2002). Human TRPC7 shares the common structural features of the larger TRP channel superfamily with a predicted six transmembrane segments and a pore region. Human TRPC7 has 98% overall identity with mouse TRPC7 and 81% and 75% overall identity with human TRPC3 and TRPC6, respectively (Numaga,

Wakamori et al. 2007). Rat TRPC7 gene consists of 12 exons and is mapped to the chromosomal region 17p14. In rabbit, TRPC7 gene is mapped to the third chromosome. No splice variants were reported for either rat or rabbit; detailed information on various TRPC7 splice variants in different species is shown in Table 1.

Expression

TRPC7 mRNA and protein have been detected in many tissues and organs from human, mouse, rabbit, and rat.

In human, Riccio et al. (2002) reported that human TRPC7 mRNA was broadly expressed in central nervous system (CNS) as well as some peripheral tissues (pituitary gland, kidney, intestine, prostate and cartilage). Myometrium from pregnant women and human myometrial cell lines expressed TRPC7 mRNA (Dalrymple, Slater et al. 2002, Yang, Gupta et al. 2002). TRPC7 mRNA was also detected in human coronary artery endothelial cells (Yip, Chan et al. 2004), in human undifferentiated gingival keratinocytes (Cai, Fatherazi et al. 2005), in differentiated IMR-32 neuroblastoma cells (Nasman, Bart et al. 2006), in HaCaT cells (Beck, Zholos et al. 2006) and in lung tissue (Finney-Hayward, Popa et al. 2010). Human TRPC7 protein was detected in HEK293 cells by Zagranichnaya, Wu et al. in (2005). Studies failed to detect TRPC7 mRNA in human MG-63, SaOS and U2 OS osteoblasts (Abed, Labelle et al. 2009), and in human non-small cell lung cancer (Zhang, He et al. 2010).

In mouse, Abundant TRPC7 mRNA expression was detected in mouse heart, lung, and eye and moderate expression in the brain, spleen, and testis (Okada, Inoue et al. 1999). TRPC3/6/7 mRNA were detected in retinas from mice (Warren, Allen et al. 2006, Hartwick, Bramley et al. 2007, Sekaran, Lall et al. 2007). Boisseau et al reported that TRPC7 mRNA was less abundant in embryonic brain and cortex of E13 C57BL6/J mice (Boisseau, Kunert-Keil et al. 2009). TRPC7 mRNA was also detected in murine MC3T3 osteoblasts (Abed, Labelle et al. 2009), while skeletal muscle (Jang, Lee et al. 2012) and inner ear organs from embryonic (E) and early postnatal (P) Swiss Webster mice (Asai, Holt et al. 2010) showed no TRPC7 mRNA expression. Western Blots revealed TRPC7 protein expression in rhythmically active ventral respiratory medullary brain slice preparation (Ben-Mabrouk and Tryba 2010).

In rat, TRPC7 mRNA were present in neurons throughout ganglia (Buniel, Schilling et al. 2003). Rat A7r5 vascular smooth muscle cells expressed transcripts encoding TRPC7 (Maruyama, Nakanishi et al. 2006). In rat hippocampal H19-7 cells, the levels of mRNA and protein for TRPC7 are high in proliferating cells and decline dramatically upon differentiation (Wu, Zagranichnaya et al. 2004, Numaga, Wakamori et al. 2007). In Dahl salt-sensitive rats, TRPC7 mRNA expression was increased in the failing myocardium (Satoh, Tanaka et al. 2007). TRPC7 mRNA was also expressed in cultured rat microglia (Ohana, Newell et al. 2009).

TRPC7 protein was observed in rat striatal cholinergic interneurons (Berg, Sen et al. 2007), and had a strikingly high level of expression in the neuropil in the rat globus pallidus (GP) (Chung, Kim et al. 2007).

TRPC7 mRNA was not detected in freshly isolated rat renal resistance vessels, glomeruli, and aorta (Facemire, Mohler et al. 2004), in rat distal pulmonary arterial smooth muscle (Wang, Shimoda et al. 2004), and in rat dorsal root ganglia (DRG) neurons (Wu, Huang et al. 2008). (Table 2).

In rabbit, Immunocytochemical studies demonstrated preferential TRPC7 expression in the plasmalemma of the freshly dispersed rabbit coronary artery myocytes (Peppiatt-Wildman, Albert et al. 2007). Saleh et al. (2008) and Ju et al. (2010) reported that TRPC7 protein was expressed in Portal vein myocytes. To date rabbit TRPC7 mRNA detection was not reported.

The channel protein including structural aspects

TRPC channels share sequence similarity and transmembrane topology with voltage-gated K^+ and Na^+ channels, and by analogy to these channels, functional TRPC are predicted to form tetramers. TRPC7 protein contains four N-terminal ankyrin repeats, six transmembrane spanning domains, a putative pore region located between transmembrane domains 5 and 6, and a highly conserved TRP box consisting of the EWKFAR motif and a proline-rich region (Dietrich, Mederos y Schnitzler et al. 2005) (Figure 1).

Interacting partners and regulation

TRPC7 along with other TRPC channels have been proposed to constitute the pore-forming units of store-operated calcium entry (SOCE) channels (Worley, Zeng et al. 2007, Cheng, Ong et al. 2013). However, the more recent discovery of STIM1 and Orai1 as the *bona fide* molecular correlates of the SOCE pathway has challenged this earlier view. STIM1 is the Ca^{2+} sensor residing in the endoplasmic reticulum (ER) while Orai1 is the SOCE channel at the plasma membrane mediating the highly Ca^{2+} selective Ca^{2+} release-activated Ca^{2+} (CRAC) current (Potier and Trebak 2008). Nevertheless, STIM1 was shown to bind to TRPC1, TRPC2, TRPC4 and TRPC5 but not to TRPC3, TRPC6 and TRPC7, suggesting a more general role for STIM1 in regulating various ion channels at the plasma membrane (Worley, Zeng et al. 2007). DeHaven et al showed that TRPC7-mediated currents are receptor-activated and were not dependent on either STIM1 or Orai1 expression (DeHaven, Jones et al. 2009), questioning the requirement for STIM1 in TRPC channel function. Regardless of whether STIM1 is involved in TRPC channel regulation, it is widely accepted that TRPC7 is activated downstream stimulation of PLC-coupled receptors in a manner independent of store depletion, presumably through production of dicylglycerol (DAG); DAG analogs such as 1-oleoyl-2-acetyl-sn-glycerol (OAG) applied in bath solutions can activate TRPC7 currents in a PKC-independent manner (Okada, Inoue et al. 1999). TRPC3 and TRPC6 channels are also activated by a similar mechanism involving DAG produced downstream PLC activity (Hofmann, Obukhov et al. 1999, Trebak, St et al. 2003, Trebak, Vazquez et al. 2003, Putney, Trebak et al. 2004, Vazquez, Wedel et al. 2004). It is unclear how DAG activates TRPC7 and its closest homologues, TRPC3 and TRPC6 and whether

DAG acts directly on these channels or through some intermediary proteins. In the cell-attached configuration, TRPC7 channels expressed in HEK293 cells could be activated by OAG, but OAG failed to activate TRPC7 channels in excised patches suggesting that DAG action on TRPC7 channels is not a direct one and requires cytosolic proteins or factors lost in excised patches (Lemonnier, Trebak et al. 2008).

The inositol 1,4,5-trisphosphate (IP₃) receptor is one of the major proteins that was shown to interact with TRPC7 to positively regulate its activity (Vazquez, Bird et al. 2006, Zhang, Inoue et al. 2008, Ju, Shi et al. 2010). Polyphospho-inositides (PIPs) were shown to interact with and regulate a number of TRP channels, including TRPC channels (Lemonnier, Trebak et al. 2008, Trebak, Lemonnier et al. 2009). PIPs are positive modulators of TRPC7 channels whereby inhibition of PIPs synthesis inhibits the ability of OAG to activate TRPC7 currents (Lemonnier, Trebak et al. 2008). In excised inside-out patches, TRPC7 channels can be activated by application of phosphatidylinositol-4,5 biphosphate (PIP₂) or ATP, but not by inositol 1,4,5-trisphosphate (IP₃) (Lemonnier, Trebak et al. 2008). Using ectopic expression of a voltage-sensing PIP phosphatase gene from zebrafish, Imai et al showed that dephosphorylation of PIPs robustly inhibited TRPC7 currents induced by either the muscarinic agonist carbachol (CCh), OAG or the DAG lipase inhibitor RHC80267 (which causes endogenous DAG accumulation) (Imai, Itsuki et al. 2012). These authors showed that that depletion of PIP₂ using the voltage-sensing PIP phosphatase inhibits TRPC3/C6/C7 channel activity. These data suggest that while PIP₂ degradation is necessary for TRPC3/6/7 channel activation by producing DAG, PIP₂ degradation is also necessary for the closing of TRPC3/6/7 channels, in agreement with previous studies documenting the complex nature of PIPs in the regulation of TRPC channels (Lemonnier, Trebak et al. 2008, Trebak, Lemonnier et al. 2009). A study by Ju et al used inhibitory antibodies against TRPC in inside-out patch clamp recordings and co-immunoprecipitations to conclude that in portal vein myocytes, noradrenaline-activated native cationic currents are mediated by TRPC6/TRPC7 heteromultimers (Ju, Shi et al. 2010). They also showed that PIP₂ inhibited OAG-induced native TRPC6/TRPC7 activity and this inhibition by PIP₂ could be normalized by IP₃ acting independently of IP₃ receptors (Ju, Shi et al. 2010). This study is in stark contrast to the data described above indicating a positive regulation of TRPC7 channels by PIP₂. This discrepancy might be due to the heteromeric nature of the TRPC6/TRPC7 channels identified in portal vein myocytes by Ju et al (Ju, Shi et al. 2010).

TRPC7 channels are negatively regulated by Ca²⁺ through a direct extracellular action, and *via* Ca²⁺/calmodulin (CaM)- and protein kinase C (PKC)-dependent mechanisms (Shi, Mori et al. 2004, Lemonnier, Trebak et al. 2006). The negative regulation of TRPC7 channels by PKC also extends to its closest homologues, TRPC3 and TRPC6 and PKC phosphorylates a C-terminal site, Ser712 on TRPC3 (Trebak, Hempel et al. 2005) and Ser714 on TRPC6 (Kim and Saffen 2005). TRPC7 inhibition by Ca²⁺ is due to Ca²⁺ entry through TRPC7 channels themselves and this negative feedback by Ca²⁺ is mediated by calmodulin and attenuated under physiological conditions by the presence of closely associated SERCA pumps, which buffers Ca²⁺ to the endoplasmic reticulum (Lemonnier, Trebak et al. 2006). Shi et al reported whole cell and single channel data suggesting voltage-dependent inhibitory actions of extracellular Ca²⁺ on TRPC7 currents likely mediated through Ca²⁺ interaction with an extracellular site capable of sensing the membrane potential. The same authors also

reported a concentration-dependent inhibitory effect of intracellular Ca^{2+} on TRPC7 currents mediated by calmodulin (Shi, Mori et al. 2004).

Lussier et al used yeast two-hybrid screen, GST pull-down and co-immunoprecipitation assays to show that a member of the dynamin superfamily, MxA interacts with TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, and TRPC7; the interaction of MxA with TRPC6 involved the second ankyrin-like repeat domain of TRPC6 and co-expression of MxA and TRPC6 enhanced agonist-activated and OAG-activated calcium entry, suggesting a positive regulatory role of MxA on TRPC channel activity. MxA mutants defective in GTP binding marginally potentiated OAG-induced TRPC6 channel activity, suggesting that MxA positive regulation of TRPC channels is dependent on GTP binding. (Lussier, Cayouette et al. 2005). A subsequent study by the same group used a similar approach to reveal that RNF24, a new membrane RING-H2 finger protein, interacted with the ankyrin-like repeat domain of TRPC6 and interacted with all TRPCs (Lussier, Lepage et al. 2008). The significance of this RNF24/TRPCs interaction is not clear as RNF24 did not affect receptor-activation of TRPC channels. The authors proposed that RNF24 interacts with TRPCs channels in the Golgi apparatus, thus likely impacting TRPC intracellular trafficking (Lussier, Lepage et al. 2008).

Yuasa et al investigated the potential regulation of TRPC7 channels by cyclic GMP (cGMP) and cGMP-dependent protein kinase (cGK) using ectopic expression in HEK293 and COS-7 cells. They found that TRPC7 has three putative cGK phosphorylation sites and using in vitro and in vivo kinase assays they revealed that the cytosolic cGK-I α isoform specifically phosphorylates mouse TRPC7 on threonine 15 without any effect on mouse TRPC3. This cGK-I α -mediated phosphorylation of TRPC7 caused a significant reduction in carbachol-activated calcium signaling and phosphorylation of the transcription factor, CREB (Yuasa, Matsuda et al. 2011). In the same report, Yuasa et al used co-immunoprecipitation assays and showed interaction between cGK-I α and TRPC7 N-terminal ankyrin repeat region (Yuasa, Matsuda et al. 2011).

Sinkins et al reported differential association between TRPC channel isoforms and immunophilins. Using immunoprecipitations assays in cells co-expressing different TRPC and immunophilin isoforms, they showed that TRPC3, TRPC6, and TRPC7 interact with FKBP12, whereas TRPC1, TRPC4, and TRPC5 interact with FKBP52. Similar results were found with membrane lysates from the rat cerebral cortex and in both cases the association of immunophilins with TRPC channels could be displaced by FK506 (Sinkins, Goel et al. 2004). Finally, in HEK293 cells stably expressing TRPC6 channels, FK506 disrupted the interaction between TRPC6 and immunophilins and inhibited TRPC6 activation by the muscarinic agonist carbachol, suggesting a role of immunophilins in the receptor-activation of all TRPC channels (Sinkins, Goel et al. 2004).

A biophysical description of the channel function, permeation, gating

When ectopically expressed in HEK293 cells, TRPC7 forms a non-selective cation channel with reversal potentials around $\sim 0\text{mV}$ and permeability ratios $P_{\text{Cs}}:P_{\text{Na}}:P_{\text{Ca}}:P_{\text{Ba}}$ of 1:1:1.9:3.5 for the spontaneous current and 1:1.1:5.9:5.0 for the ATP-activated current (Okada, Inoue et al. 1999). Lievremon et al. (2005) reported that in TRPC7-deficient avian B-lymphocytes

DT40 cells, Ba^{2+} entry induced in response to either OAG or muscarinic receptor stimulation was significantly inhibited, suggesting that TRPC7 channel permeates Ba^{2+} ions. When expressed in HEK293 cells, the typical current voltage (I/V) relationship of mouse or human TRPC7 currents is almost linear with a slight flattening around the reversal potentials (Fig. 2, **left panel**). Mouse TRPC7 single channel conductance is 24.8 pS and 24.3 pS (Fig. 2, **right panel**) under bath solutions containing 1mM Ca^{2+} and 10 mM Ca^{2+} , respectively (Shi, Mori et al. 2004).

As discussed above, TRPC7 is a receptor-activated non-selective cation channel activated through PLC-mediated metabolism of PIP_2 and production of DAG (Okada, Inoue et al. 1999, Trebak, Vazquez et al. 2003). Okada et al. (1999) showed that heterologously expressed mouse TRPC7 behaves as a receptor-activated cation channel not activated by store depletion. Earlier reports on human TRPC7 described its activation by the SERCA pump inhibitor thapsigargin, suggesting that at least under certain expression conditions TRPC7 could behave as a store-operated channel (Riccio, Mattei et al. 2002, Lievremon, Bird et al. 2004). However, subsequent studies on native TRPC7 in DT40 cells and on TRPC7 ectopically expressed in HEK293 cells have questioned the role of human TRPC7 in store-operated Ca^{2+} entry and demonstrated that human TRPC7 forms a store-independent receptor-activated channel (Lievremont, Numaga et al. 2005, DeHaven, Jones et al. 2009). Currently, there are no specific pharmacological modulators of TRPC7. Okada et al showed 100 μ M lanthanum (La^{3+}) and 25 μ M SKF96365 are more efficient at inhibiting ATP-activated Ca^{2+} entry in HEK293 cells expressing mouse TRPC7 than 100 μ M Gadolinium (Gd^{3+}) (Okada, Inoue et al. 1999). Riccio et al. (2002) used 250 μ M Gd^{3+} , 250 μ M La^{3+} , and 25 μ M SKF96365 to completely block the Ca^{2+} entry in cells expressing human TRPC7. Amiloride at 300 μ M was also used to inhibit constitutively activated TRPC7 currents (Okada, Inoue et al. 1999) and the drug 2-Aminoethoxydiphenyl borate (2-APB) originally described and IP_3 receptor blocker partially inhibited TRPC3, TRPC6 and TRPC7 channels at concentrations of 10–100 μ M by a mechanism not involving IP_3 receptors (Lievremont, Bird et al. 2005). (Table 3)

Physiological functions in native cells, organs, organ systems

Using ectopic expression, Hofmann et al (2002) showed that TRPC channel isoforms can heteromultimerize with preferential associations between members of the TRPC3/6/7 subfamily and several investigations suggested widespread TRPC channel heteromultimerization in native tissues (for review (Eder and Groschner 2008). Wu X et al. (2010) reported that the activity of the TRPC3/6/7 subfamily was inhibited in the heart of cardiac-specific transgenic mice that express dominant-negative TRPC4, suggesting that coordinated TRPC heteromultimers might occur between different TRPC subfamilies under native conditions. Although this has not been described specifically for TRPC7 channels, studies have reported associations between TRPC1 and a member of the vallinoid family of TRP channels, TRPV4 in vascular endothelial cells (Ma, Qiu et al. 2010). Most data currently available on TRPC7 and its involvement in various native conditions is correlative. TRPC7 mRNA is upregulated in human myometrium obtained from pregnant women at term active labor when compared with samples from non-pregnant patients (Dalrymple, Slater et al. 2004). Anantamongkol et al showed rat mammary tissues from pregnant and

lactating rats upregulated the expression of TRPC1, TRPC5 and TRPC7 while downregulating that of TRPC3 and TRPC4 in the early lactating period (Anantamongkol, Charoenphandhu et al. 2010). A study by Ben-Mabrouk et al. (2010) suggested that substance P activates TRPC3 and TRPC7 channels to enhance respiratory rhythm regularity. These authors suggested that in mouse brainstem slices containing the pre-Bötzinger complex, TRPC3/7 underlie the rhythmic inward non-specific cation current necessary for pacemaker activity (Ben-Mabrouk and Tryba 2010).

Lessons from knock outs

Xue et al (2011) reported the existence of an intrinsic component of the eye pupillary light reflex in nocturnal and crepuscular non-primates mammals that was dependent on the pigment melanopsin and PLC β 4 isoform. TRPC6^{-/-} and TRPC7^{-/-} double knockout mice showed abrogated light response in the M1 subtype of melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (M1-ipRGCs) but had a normal intrinsic pupillary light reflex. These authors concluded that in M1-ipRGCs, the depolarizing light response is presumably generated by cation entry through heteromeric TRPC6/TRPC7 channels activated downstream of PLC, while there is no role for either TRPC3/6/7 or TRPC1/4/5 in light-induced contraction of the sphincter muscle. Shortly after, a study by Perez-Leighton et al. (2011) reported that TRPC3^{-/-} and TRPC7^{-/-} single knockouts showed no effect on the light response of intrinsically photosensitive retinal ganglion cells, while the TRPC6^{-/-} knockout mice displayed smaller light responses compared to wild type mice. The reasons for the discrepancy between the results obtained by these two independent groups are unknown. Xue et al. (2011) suggested in a post-scriptum that the differences could be attributed to their use of the perforated-patch clamp recording technique as opposed to the classical whole-cell configuration adopted by Perez-Leighton et al. (2011).

Role in hereditary and acquired diseases

Miyagi et al. (2009) showed data suggesting heteromeric associations between a novel TRPP2 mutant and either TRPC3 or TRPC7. These heteromultimeric channels are involved in enhanced receptor-activated Ca²⁺ entry potentially leading to dysregulated cell growth in autosomal dominant polycystic kidney disease. Miyagi et al identified a TRPP2 frameshift mutant with a 17-amino acid addition after glutamic acid residue 697 from a family with symptoms of autosomal dominant polycystic kidney disease. In HEK293 expression system, this TRPP2 mutant showed predominant plasma membrane localization and increased muscarinic receptor-activated Ca²⁺ influx in cells co-expressing either TRPC3 or TRPC7. Biochemical studies showed a direct association between the TRPP2 mutant, but not wild type TRPP2, and either TRPC3 or TRPC7. This TRPP2 mutant induced a depolarizing shift of reversal potentials and an enhancement of single-channel conductance of muscarinic receptor-activated currents. These data suggest that heteromultimers of TRPP2 mutant and either TRPC3 or TRPC7 can enhance receptor-activated Ca²⁺ entry responsible for disruption of cell growth in autosomal dominant polycystic kidney disease (Miyagi, Kiyonaka et al. 2009). Alvarez et al. described a potentially pathological role of TRPC3/7 channels in ventricular cardiomyocytes. These authors proposed that TRPC3/7 heteromultimers mediate Ca²⁺ entry upon activation of the purinergic receptor P2Y₂ by

ATP/UTP. The sustained receptor-activated TRPC3/7 currents could cause depolarization, thus inducing cell automaticity and arrhythmias in response to the ATP/UTP release that occurs during early infarcts (Alvarez, Coulombe et al. 2008). In the failing myocardium of Dahl salt-sensitive rats, Satoh et al reported increased TRPC7 expression, suggesting that TRPC7 might mediate pathological Ca^{2+} signaling and causing myocardial apoptosis (Satoh, Tanaka et al. 2007). Wu et al suggested a role of TRPC in cardiac hypertrophy as inhibition of TRPC channel expression using a dominant negative strategy in transgenic mice or in cultured neonatal cardiomyocytes inhibited NFAT transcriptional activity and pathological cardiac hypertrophy (Wu, Eder et al. 2010). In light of the established role of SERCA2 gene mutations in Darier's disease (for review see Hovnanian et al (2004)), the study by Lemonnier et al (2006), demonstrating that the maintained activation of TRPC7 channels depends on closely associated SERCA pumps, might indicate an involvement of TRPC7 channels in the clinical manifestations of Darier's disease.

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Fig. 1. Domain structure of TRPC7

TRPC7 contains 6 transmembrane domains (S1–S6) with the pore region between S5 and S6. N-terminal obtains 4 ankyrin-like repeats (ANK1–4). C-terminal obtains a highly conserved TRP box containing the EWKFAR motif and a proline-rich region.

Fig. 2.

Current–voltage relationship and single channel conductance of carbachol-stimulated TRPC7 channel currents in HEK293 cells. Nystatin-perforated whole-cell recordings (left panel) were performed in HEK293 cells expressing TRPC7, the pipette solution contained (in mM): 140 CsCl, 2 MgCl₂, 10 Hepes, 10 glucose (pH=7.2, adjusted with Tris base), Ca²⁺-free external solution contained (in mM): 140 NaCl, 5 KCl, 1.2 MgCl₂, 1 EGTA, 10 Hepes, 10 glucose (pH=7.4, adjusted with Tris base), for Ca²⁺-containing external solution, 1mM CaCl₂ was added to Ca²⁺-free solution with the omission of EGTA. For Cell-attached (C/A) configuration single channel recording (right panel), cells were bathed in high potassium solution with the following composition to null the transmembrane potential (in mM): 140 KCl, 2 EGTA, 2 MgCl₂, 10 Hepes (pH=7.2, adjusted with Tris base), the pipette solution contained (in mM): 140 NaCl, 5 TEA-Cl, 1.2 MgCl₂, 0.1 CaCl₂, 10 Hepes, 10 Glucose, 0.1 carbachol (CCh) (pH=7.4, adjusted with Tris base) Taken from (Shi, Mori et al. 2004).

Table 1

TRPC7 gene in different species

Species	Chromosomal Location	Splicing	mRNA(bp)	aa	Exon
Human	5q31.1	hTRPC7-001	2987	862	12
		hTRPC7-002	2603	380	11
		hTRPC7-003	2239	746	9
		hTRPC7-004	2022	261	8
		hTRPC7-005	2404	801	10
		hTRPC7-006	2422	807	10
		hTRPC7-007	817	?	4
		hTRPC7-008	414	?	2
		hTRPC7-201	2752	801	11
		hTRPC7-202	2587	746	10
Mouse	13 B2	mTRPC7-001	3483	862	12
		mTRPC7-002	3519	861	12
		mTRPC7-003	3502	451	13
		mTRPC7-004	2424	807	11
		mTRPC7-005	2024	261	9
		mTRPC7-006	2406	801	11
		mTRPC7-008	2241	746	10
		mTRPC7-009	2605	380	12
Rabbit	3	ND	4077	862	12
Rat	1/p14	ND	3055	862	12

Table 2

Expression of TRPC7

Species	mRNA	Protein
Human	Lung tissue ^P (Finney-Hayward, Popa et al. 2010) Differentiated IMR-32 neuroblastoma cells ^P (Nasman, Bart et al. 2006) HaCaT cells ^P (Beck, Zholos et al. 2006) Undifferentiated gingival keratinocytes ^P (Cai, Fatherazi et al. 2005) HEK293 cells ^P (Zagranichnaya, Wu et al. 2005) Coronary artery endothelial cells ^{P, ISH} (Yip, Chan et al. 2004) Pregnant women myometrium and myometrial cell lines ^P (Dalrymple, Slater et al. 2002; Yang, Gupta et al. 2002) Central nervous system (CNS) and pituitary gland, kidney, intestine, prostate and cartilage ^P (Riccio, Medhurst et al. 2002)	HEK293 cells ^W (Zagranichnaya, Wu et al. 2005)
Mouse	Brain, testis, lung, liver, heart, kidney, and DRG ^P (Jang, Lee et al. 2012) MnPO Glutamatergic Neurons ^P (Tabarean 2012) Melanopsin-expressing ganglion cells ^P (Perez-Leighton, Schmidt et al. 2011) MC3T3 osteoblasts ^P (Abed, Labelle et al. 2009) Embryonic brain and cortex of E13 C57BL/6J mice ^P (Boisseau, Kunert-Keil et al. 2009) Retinas ^P (Warren, Allen et al. 2006; Hartwick, Bramley et al. 2007; Sekaran, Lall et al. 2007) Smooth muscle cells ^P (Walker, Hume et al. 2001) Heart, lung, eye, brain, spleen, and testis ^N (Okada, Inoue et al. 1999)	Cerebellum and ventral respiratory group island ^W (Ben-Mabrouk and Tryba 2010)
Rabbit	Not determined	Portal vein and mesenteric artery ^{IP} (Ju, Shi et al. 2010) Portal vein myocytes ^W (Saleh, Albert et al. 2008) Coronary artery myocytes ^I (Peppiatt-Wildman, Albert et al. 2007)
Rat	Mammary tissues ^P (Anantamongkol, Charoenphandhu et al. 2010) Hypocretin/orexin neurons ^P (Cvetkovic-Lopes, Eggermann et al. 2010) Cultured rat microglia ^P (Ohana, Newell et al. 2009) Failing myocardium of Dahl salt-sensitive rats ^P (Satoh, Tanaka et al. 2007) Striatal cholinergic interneurons ^{ISH} (Berg, Sen et al. 2007) Hippocampal H19-7 cells ^P (Wu, Zagranichnaya et al. 2004; Numaga, Wakamori et al. 2007) A7r5 vascular smooth muscle cells ^P (Maruyama, Nakanishi et al. 2006) Myometrium ^P (Babich, Ku et al. 2004)	GH4C1 pituitary cells ^W (Lavender, Chong et al. 2008) Neuropil in globus pallidus (GP) ^I (Chung, Kim et al. 2007) Striatal cholinergic interneurons ^I (Berg, Sen et al. 2007) Hippocampal H19-7 cells ^W (Wu, Zagranichnaya et al. 2004; Numaga, Wakamori et al. 2007) A7r5 vascular smooth muscle cells ^W (Maruyama, Nakanishi et al. 2006) Ganglion neurons ^I (Buniel, Schilling et al. 2003) Brain ^W (Goel, Sinkins et al. 2002)

^I Protein detected by immunostaining,

^{ISH} mRNA detected by in situ hybridization,

^N mRNA detected by northern blotting,

^P mRNA detected by RT-PCR,

^W Protein detected by western blotting,

^{IP} immunoprecipitation

Table 3

Activation and inhibition of TRPC7 channels

	Activation	Inhibition
Human TRPC7	CCh, TG (Riccio, Mattei et al. 2002) TG, MeCh (Lievremont, Bird et al. 2004) TG, MeCh (Lievremont, Bird et al. 2005) CCh, ATP (Beck, Zholos et al. 2006) ET-1 (Horinouchi, Terada et al. 2011) ATP, OAG (Nishioka, Nishida et al. 2011) OAG, PIP ₂ (Lemonnier, Trebak et al. 2008)	La ³⁺ , Gd ³⁺ , SKF96365 (Riccio, Mattei et al. 2002) 2-APB, SKF96365 (Lievremont, Bird et al. 2005, Zagranichnaya, Wu et al. 2005) TG/Ca ²⁺ (Lemonnier, Trebak et al. 2006) Cilostazol (Nishioka, Nishida et al. 2011)
Mouse TRPC7	DOG, OAG, ATP (Okada, Inoue et al. 1999) Constitutive active (Okada, Inoue et al. 1999) CCh, GTP γ S, OAG (Shi, Mori et al. 2004) CCh (Yuasa, Matsuda et al. 2011) CCh, OAG, RHC80267 (Imai, Itsuki et al. 2012)	La ³⁺ , SKF96365, Amiloride (Okada, Inoue et al. 1999) DrVSP (Imai, Itsuki et al. 2012)
Rabbit TRPC7	OAG, IP ₃ (Ju, Shi et al. 2010)	PIP ₂ (Ju, Shi et al. 2010)
Rat TRPC7	AVP, Ang II (Maruyama, Nakanishi et al. 2006) CCh (Satoh, Tanaka et al. 2007)	SKF96365 (Satoh, Tanaka et al. 2007)

CCh, carbachol; TG, thapsigargin; MeCh, methacholine; ET-1, endothelin-1; ATP, Adenosine-5'-triphosphate; SKF96365, 1-[beta-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl]-1H-imidazole hydrochloride; 2-APB, 2-aminoethoxydiphenyl borate; DOG, 1,2-dioctanoylsn-glycerol; OAG, 1-oleoyl-2-acetyl-sn-glycerol; AVP, arginine vasopressin; Ang II, angiotensin II; DrVSP, *Danio rerio* voltage-sensing phosphatase; RHC80267, 1,6-bis (Cyclohexyloximinocarbonylamino)hexane; DiC8-PIP₂, a water-soluble PIP₂ analogue;