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TRANSIENT RECEPTOR POTENTIAL VANILLOID 1

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Gene Symbol: TRPV1

Other names: Vanilloid Receptor 1 (VR1), Capsaicin Receptor

1. General information

Background and structure

Transient receptor potential vanilloid receptor 1 (TRPV1) is one of 6 members of the subfamily of vanilloid receptors that belongs to the family of transient receptor potential (TRP) channels. TRP channels are an intrinsic part of the mammalian sensory system responding to a broad range of stimuli such as temperature, touch, pain, osmolarity, pheromones, and taste (8). TRPV1, TRPV2, TRPV3 and TRPV4 are all involved in thermoactivation. These channels share a similar structure with 6 putative transmembrane domains, a loop structure between transmembrane regions 5 and 6 believed to be involved in pore formation, ankyrin repeats, and both the N- and C-termini located in the cytoplasm (8, 41).

TRPV1 plays an important role in nociception and was the first of the TRPV family channels to be cloned. TRPV1 was cloned using capsaicin, the pungent component of hot chili pepper, by screening an expression cDNA library of dorsal root ganglia (5). TRPV1 is a non-selective cation channel and can be activated by numerus stimuli such as vanilloids (capsaicin, resiniferatoxin), low pH, elevated temperature (10), endogenous lipoxygenases (leukotriene B_4, 12- or 15-HPETE) (24), endogenous anandamide (40) and ethanol (43). In addition, ethanol can potentiate the effects of capsaicin, protons and heat. TRPV1 is broadly distributed. It is highly expressed in dorsal root ganglia, trigeminal ganglia, in small sensory C fibers and some Aδ fibers. It is also detectable in brain, spinal cord, bladder, kidney, liver, spleen, testis, lung and bowel (17).

The cation selective channel is probably made of a tetrameric quaternary structure (25). Modulation of the activity of TRPV1 is under the control of many intracellular signals that act on the N-terminal and C-terminal portions of the monomer including phosphorylation. Binding of pro-inflammatory agents such as prostaglandins to its receptor induces a cascade of events that lead to activation of cAMP-dependent protein kinase that in turn can phosphorylate TRPV1. Histamine can also activate TRPV1 through phosphorylation by protein kinase C (PKC). Activation of TRPV1 contributes to the release of substance P and CGRP from peripheral terminal of neurons (25).

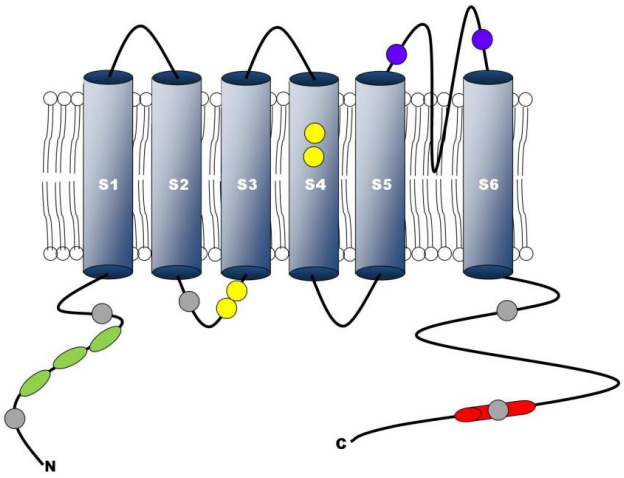

Figure 1. **Model structure of TRPV1.** TRPV1 consists of a cytoplasmic N-terminal region that contains 3 ankyrin domains (green), 6 transmembrane spanning segments (blue cylinders), an intracellular pore forming (P- loop) loop between S5 and S6 and a cytoplasmic C-terminus region that includes a calmodulin and phosphatydylinositol-4,5-biphosphate binding site (red). Colored circles represent amino-acids known to be important in binding the following: H^+ (low pH) (E600, E646), purple; vanilloids (Y511,S512,L547,T550), yellow; protein-kinases (S116,T370,S502,T704,S800), gray.

Function

TRPV1 is activated by a number of agonists (see Table 1) although clear identification of endogenous ligands has been elusive. Increased temperature is a well-established pathological activator of TRPV1 under certain conditions. Local acidification can activate TRPV1 and cause pain and inflammation. There is accumulating evidence for endogenous chemical mediators such as anandamide or leukotrienes in TRPV1 activation.

Intracellular Ca^{2+} is involved in the mechanism of sensitization of TRPV1. Increased intracellular Ca^{2+} results in activation of phospholypase C (PLC) (35) which hydrolyses the membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP_2) into 1,4,5-trisphosphate (IP_3) and diacylglycerol. In an opposing effect, depletion of PIP_2 is responsible for desentization of TRPV1 (35).

Three alternatively spliced TRPV1 mRNAs have been characterized: VR.5'sv (38), TRPV1var (42) and TRPV1β (48). The TRPV1var variant expressed in the kidney encodes the first 248 amino-acids and comprises only one ankyrin domain (42). Another variant called VR.5'sv, expressed in DRG, brain and peripheral blood mononuclear cells is missing most of the N-terminal region and two ankyrin domains (38). Finally, the third alternatively spliced TRPV1 variant known as TRPV1β lacks amino-acids 399 to 408 (before the first transmembrane domain). Interestingly, all these variants can modulate the activity of the canonical TRPV1 protein as demonstrated by coexpression studies of TRPV1 with the variants (38, 42, 48).

The role of TRPV1 in pain sensation has been clearly demonstrated by the advent of TRPV1 knockout mice (4). Knockout mice exhibited impaired thermal sensitivity to pain triggered by heat or capsaicin.

TRPV1 has been implicated in neurogenic inflammation using pharmacological agonists and antagonists in animal models and by genetic approaches comparing severity of insults in wild type or $TRPV1^{-/-}$ (KO) mice. Neurogenic inflammation is characterized by edema, hyperalgesia, vasodilatation and inflammatory cell infiltration caused by nociceptor overstimulation at the site of injury. The role of TRPV1 in a variety

of inflammatory diseases affecting multiple organs has been an active area of investigation.

In some models, activation of TRPV1 plays a central role in the inflammatory response. TRPV1 is expressed in C-fibers innervating the respiratory tract as well as in lung epithelial cells and has been implicated in bronchoconstriction, mucus secretion, cough, and airway irritation. TRPV1 appears to mediate inflammatory tracheal hyperreactivity to carbachol in sensitized mice (3) and cough after RTX and ethanol treatment (15) which either directly activate or lower the activation threshold for TRPV1.

TRPV1 is also involved in acute and chronic inflammation in a model of knee joint injury (26). However, low dose of the TRPV1 agonist RTX produced an analgesic effect and less edema in a knee joint inflammation model (29) possibly through receptor desensitization. TRPV1 is also present in the bladder and and is involved acute bladder inflammation (7). In addition, TRPV1 promotes inflammation in colitis in both rats (27) and mice (28).

Under certain circumstances, TRPV1 activation may confer protection against inflammation. Activation of TRPV1 by agonists (RTX or SA13353) reduced the severity of ishemia/reperfusion-induced renal injury in rats (45) and the severity of LPS-induced rheumatoid arthritis in mice (32). Similar observations were made in a murine model of experimental autoimmune encephalomyelitis (EAE). SA13353 or capsaicin inhibited the production of TNF-α and IL-1β (44). TRPV1 also had a protective effect against the onset of sepsis after endotoxin treatment (LPS) (9) and in rat model of sepsis by cecal ligation and puncture (12). As a member of the acid sensing system, TRPV1 participates in the homeostasis of gastric acid secretion through activation of the sensory nerves and release of CGRP (18-20).

Thus depending upon the cellular environment, TRPV1 may reduce the severity of inflammatory insults or accentuates its effects.

Agent	Metabolites	Reference
Endogenous Activators of TRPV1		
Acid		Tominaga et al., Neuron (1998) 21:531-543
Heat		Caterina et al., Nature (1997) 389:816-824
Anandamide		Zymunt et al., Nature (1999) 400:452-457
N-arachidonoyl-dopamine (NADA)	Arachidonic acid metabolite	Huang et al., PNAS (2002) 99:8400-8405
N-oleoyldopamine	Arachidonic acid metabolite	Huang et al., PNAS (2002) 99:8400-8405
12-hydroperoxyeicosatetranoic acid (HPETE)	Lipoxygenase product	Hwang et al., PNAS (2000) 97:6155-6160
15-HPETE	Lipoxygenase product	Hwang et al., PNAS (2000) 97:6155-6160
Leukotriene B4		Shin et al., PNAS (2002) 99:10150-10155
Endogenous Inhibitors of TRPV1		
PIP2		Prescott and Julius (2003) Science 300:1284-1288
Calmodulin		Chaudury et al., (2011) Molecular Pain 7:34-47
Indirect TRPV1 Activators and Sensitizers	**Receptor**	
Bradykinin	BK2	Chuang et al., Nature (2001) 411:957-962
NGF	TrkA	Chuang et al., Nature (2001) 411:957-962
Prostaglandins	EP and IP	Moriyam et al., Molecular Pain (2005) 17:1-13
Prokineticin	PKR	Negri et al., J. Neuroscience (2006) 26:6716-6727
Proteases	PAR2	Amadesi et al., J. Neuroscience (2004) 24:4300-4312
Serotonin	5-HT receptor	Sugiura et al., J. Neuroscience (2004) 24:9521-9530
Histamine	H1R	Shim et al., J. Neuroscience (2007) 28:2331-2337

Table 1. List of indirect activators/sensitizers of TRPV1 and endogenous activators/inhibitors of TRPV1

2. TRPV1 and the exocrine pancreas

Pancreatitis

Acute pancreatitis is associated with vasodilation, edema, neutrophil infiltration and acinar cell necrosis. Many of these features are manifestations of neurogenic inflammation and there is accumulating evidence that neural factors contribute to the pathogenesis of the disease (30). Using the TRPV1 agonist capsaicin to denervate neonatal rats, Nathan and al. demonstrated that TRPV1 mediated the neurogenic aspect of acute pancreatitis (34). Antagonists such as capsazepine (23) or desensitization of pancreatic primary sensory neurons with RTX (36) ameliorated the severity of caerulein-induced pancreatitis.

TRPV1 activation of primary sensory nerves causes the release of substance P during the inflammatory insult (33). Substance P is a 11 amino-acids peptide that stimulates plasma extravasation (14) and genetic deletion of its receptor (NK1-R) ameliorates caerulein induced acute pancreatitis (16). In the search for the endogenous ligands for TRPV1, Hwang and co-workers (24) demonstrated that products from lipoxygenases such as 12-S-HPETE, 15-S-HPETE and LTB_4 could directly activate TRPV1 (24). Administration of LTB_4 through the celiac artery produced pancreatitis-like inflammation (47). Moreover, blockade of TRPV1 with the TRPV1 antagonist capsazepine or inhibition of the 5-lipoxygenase- activating protein (FLAG) by preteatment with MK886 reduced the severity of the pancreatitis induced by LTB_4 indicating that LTB_4 was an endogenous ligand of TRPV1 and played a role in inducing acute pancreatitis (47).

TRPV1 and pain sensation during pancreatitis

Through retrograde labeling of pancreatic nerves and immunostaining with anti-TRPV1 antibody it has been possible to localize the pancreatic afferents expressing TRPV1 (13). Dorsal root ganglia (T9-T12) had the highest concentration of neurons expressing TRPV1 (65% of the neurons). Some TRPV1 expressing afferents were also detected in the nodose ganglia where 35% of the neurons expressed TRPV1 (13).

TRPV1 mediates pain in acute pancreatitis. Rats subjected to L-arginine-induced pancreatitis exhibited a 2.5 fold increase of *c-fos* expression in spinal neurons suggesting activation of nociceptive pathways and a 3 fold increase in spontaneous abdominal contractions (an indicator of nociceptive sensation). Administration of the TRPV1 antagonist capsazepine reduced both *c-fos* expression and abdominal contractions (49).

TRPV1 activity is potentiated by protease-activated receptor 2 (PAR-2) activation (11, 22). Both TRPV1 and PAR-2 are expressed in the same subset of primary afferent neurons (21). In HEK293 cells co-expressing both TRPV1 and PAR-2, it was demonstrated that PAR-2 could potentiate the activity of TRPV1. Further, it has been demonstrated that PAR-2 activation by the selective agonist SL-NH2 could cause thermal hyperalgesia and mechanical allodynia at a dose that does not produce inflammation (46). Direct infusion of trypsin or PAR-2 agonist in the pancreatic duct of rats induced a nociceptive response as demonstrated by measurement of an electromyographic recording from the acromiotrapezius (21).

TRPV1 mediates hyperalgesia in a TNBS-induced chronic pancreatitis model in the rat (50). A decrease in the response frequency in the Von Frey filament (VFF) test was observed after administration of the TRPV1 antagonist SB-366791 to rats exhibiting chronic pancreatitis after treatment with TNBS. Interestingly, the level of TRPV1 expression and the number of DRG neurons expressing TRPV1 were increased in these rats. TRPV1's effect on hyperalgesia in the TNBS-induced model is mediated by nerve growth factor (NGF) (51). Anti-NGF treatment to rats with chronic pancreatitis reduced their response to the VFF test. In addition, TRPV1 expression in DRG neurons was also reduced

when rats with chronic pancreatitis were subjected to anti-NGF treatment.

Recently, Schwartz and co-authors (39) demonstrated a synergistic effect of TRPV1 and TRPA1 on both pancreatic pain and inflammation in caerulein-induced acute pancreatitis using specific antagonists for TRPV1 and TRPA1. These findings are in agreement with the observation that the cannabinoid agonist, WIN 55,212-2, known to activate TRPA1, attenuated capsaicin-evoked responses (2). Alternatively, TRPV1 can also modulate the TRPA1 response to nociceptive stimuli as exemplified by TRPV1's prevention of mustard oil-induced TRPA1 internalization (1). The interactions between TRPV1 and TRPA1 also have been demonstrated in electrophysiological responses in CHO cells co-expressing TRPV1/TRPA1 and in trigeminal sensory neurons. Both cell types exhibited characteristics suggesting that TRPV1 modulates TRPA1 responses (37).

Finally, TRPV4, another channel of the TRP family that can be activated by changes in osmotic pressure (31), is also present in pancreatic sensory nerves and also contributes to nociceptive sensation in caerulein-induced acute pancreatitis (6).

In summary, TRPV1 expressed in primary sensory neurons is involved in neurogenic inflammation of the pancreas and in nociceptive sensation.

3. Tools available for the study of TRPV1

a. TRPV1 Antibodies

A large number of anti-TRPV1 antibodies are available commercially. Most are polyclonal antisera raised in rabbit, goat or even guinea pig, but some monoclonal antibodies are available. Antibodies have been used to identify TRPV1 in rat, human, mouse, chicken and/or zebrafish. Below, are listed some available antisera.

Polyclonal antisera

- Gp 14100 (Neuromics, Edina, CA). Used in immunohistochemistry (Baiou et al., J Comp Neurol. 2007; 503:334-337).
- Ab63083 (Abcam, Cambridge, MA). Used in immunohistochemistry (Nie et al., Am J Obstet Gynecol 2010; 202: 346. E1-8).
- ACC-030 (Alomone, Jerusalem, Israel). Used in immunohistochemistry, immunoelectron microscopy and western blot (Tominaga et al., Neuron 1998; 21: 531-543).

Affinity purified polyclonal antisera

- P-19 antibody (Santa Cruz Biotechnology, CA; catalog number: sc-12498). Used in Western blots (Vos et al., J Neurochem 2006; 99: 1088-102). Used in immunoprecipitation assay (Stanchev et al., Pain 2009; 143: 26-36).
- N-15 and C-15 antibodies (Santa Cruz Biotechnology, CA; catalog number sc-12500 and sc-12503 respectively). Used in Western blot and immunohistofluorescence (Faussone-Pellegrini et al., (Histochem Cell Biol. 2005; 124: 61-68).
- AB 5370 (EMD-Millipore Calbiochem, Billerica, MA). Used for Western blot, immunohistochemistry and immunoelectron microscopy: Tóth et al., (Brain Res Mol Brain Res. 2005; 135: 162-168).
- PC-420 (EMD-Millipore Calbiochem, Billerica, MA). Used in immunohistochemistry (Zhong et al., Dig Dis Sic. 2008; 53: 194-203).

Monoclonal antibodies

- Y7101-ig (Abcam, Cambridge, MA). Used in immunochemistry (Peng et al., Am J Physiol Renal Physiol. 2008; 295: F1324-1335).
- H00007442-M01 (Novus Biologicals, Littleton, CO). Used in Western blot (El Karim et al., Pain 2011; 152: 2211-2223).

b. cDNA clones

There are three commercial suppliers of TRPV1 cDNA constructs: Genecopoeia (Rockville, MD);

OriGene (Rockville, MD) and DNASU plasmid Repository (ASU-Biodesign Institute, Arizona State University, Arizona). These 3 companies offer human and mouse clones. Rat cDNAs are only offered by Genecopoeia and OriGene

c. Genetically modified mice

Mice with genetic deletion of TRPV1 are available from Jackson Laboratories (catalog number B6.129S4-Trpv1^{tm1Jul}/J).

d. Agonists and antagonists

Compound	Type	Reference	Supplier & catalog number
capsaicin	agonist	Szallasi et al., 1999; Mol Pharmacol 56:581-587	Sigma M2028
RTX	agonist	Caterina et al., 1997; Nature 389: 816-824	Sigma P9983
piperine	agonist	McNamara et al., 2005; r J Pharmacol. 114; 781-790	Sigma W290904
I-RTX	antagonist	Wahl et al., 2001; Mol Pharmacol 59: 9-15	Sigma I 9281
capsazepine	antagonist	Tominaga M& Tominaga T (2005); Pfugers Arch 451: 143-150	Sigma C191
AMG9810	antagonist	Gavva et al., 2005; J. Pharmacol. Exp. Ther. 313: 474-484	Sigma A2731
JNJ-17203212	antagonist	Ghilardi et al., 2005: J. Neurosci. 25: 3126-3131	Sigma J3580
BCTC	antagonist	Valenzano et al., 2003; J. Pharmacol. Exp. Ther. 306: 377-386	Tocris 3875
SB 366791	antagonist	Fowler et al., 2003; Biochem Pharmacol. 66: 757-767	Tocris 1615
SB 452533	antagonist	Rami et al., 2004; Bioorg Med Chem Lett. 14: 3631-3634	Tocris 3265

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