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Gene Section
Review

TRPV1 (transient receptor potential cation channel, subfamily V, member 1)

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Identity

Other names: DKFZp434K0220; VR1

HGNC (Hugo): TRPV1

Location: 17p13.2

Local order: Colocalized with another transient receptor potential channel gene (TRPV3).

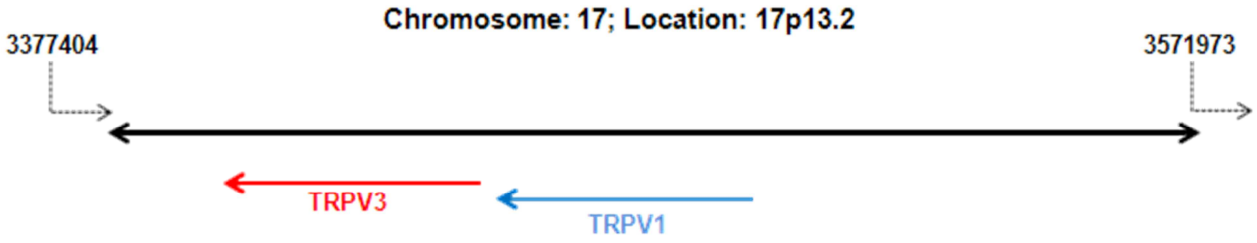
DNA/RNA

Description

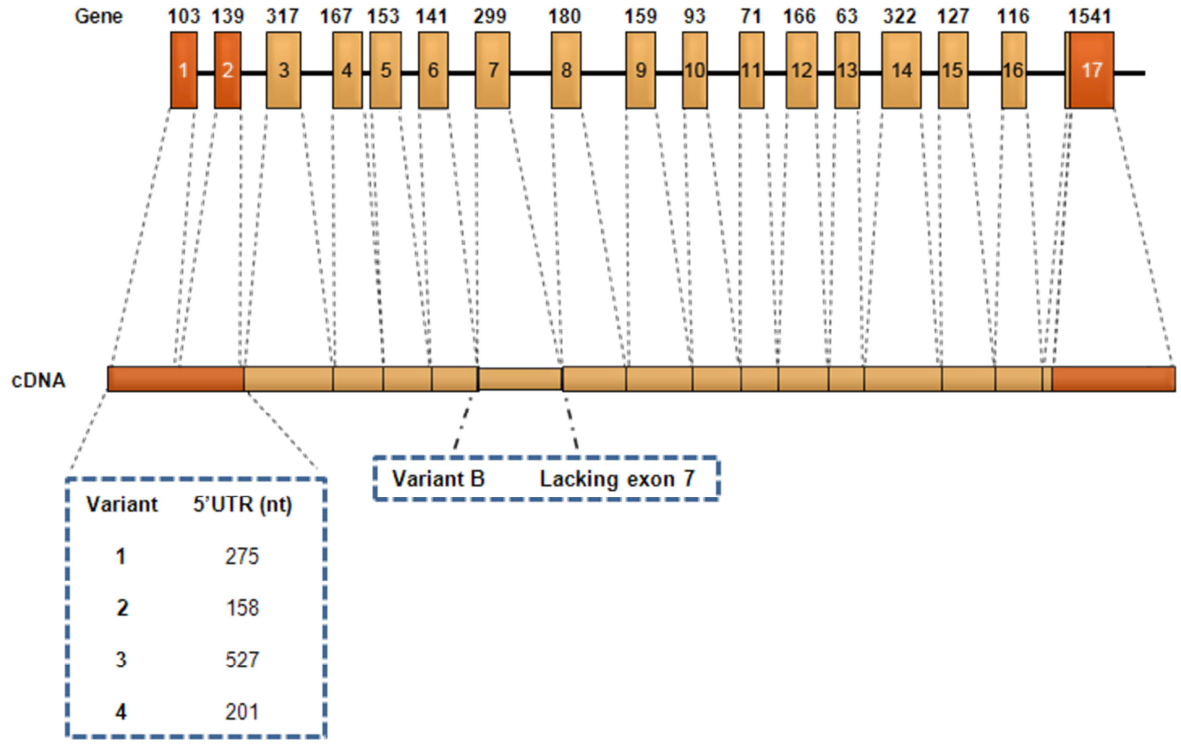
TRPV1 gene consists of 17 exons and 17 introns including a coding region and a 5' and a 3' non-coding region.

Transcription

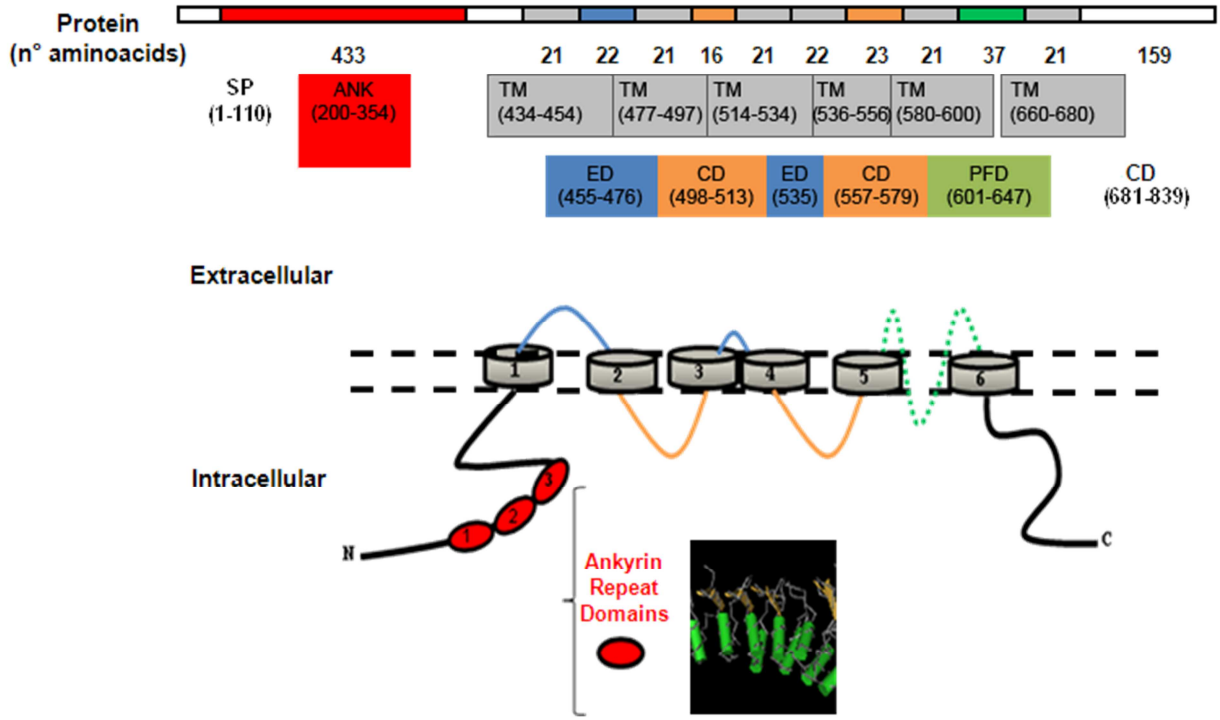
There are four transcript variants encoding the same protein, but with different segments in the 5' UTR (var.1, var.2, var.3, var.4) and one alternative splice variant lacking exon 7 (TRPV1b). TRPV1 gene transcription was demonstrated in different cells and tissues, but no data are available on TRPV1 variant expression profiles.



Schematic representation of human TRPV1 gene and neighbouring family gene.



Genomic structure of human TRPV1. In gene the exon number and relative length in bp are shown. In cDNA, the coding region is shown by open bars. The non-traslated regions are shown by black filled bars. The different 5' UTR TRPV1 splice variants with relative 5' UTR length are described in table. The TRPV1 splice variant (TRPV1b) is described in table. Hyperlink to FASTA nucleotide sequences of all TRPV1 cDNAs are inserted.



Schematic representation of TRPV1 protein. Double broken line is representative of cellular membrane, transmembrane domains are numbered. Red spot indicates the position of the three ankyrin repeat domains and a representative image of the structural ankyrin repeat unit containing two antiparallel helices and a beta-hairpin, with repeats that are stacked in a superhelical arrangement is shows in black box (from NCBI Conserved Domains), N and C (-terminal domains). SP (signal peptide region), ANK (ankyrin regions, red box), TM (trasmembrane domain, grey box), ED (extracellular domain, blue box), CD (cytoplasmatic domain, orange box), PFD (pore forming domain, green box). An association domain (AD) in 685-713 region has been found necessary for self-association.

Protein

Description

The canonical form comprises 839 aa (MW~96 kDa) and is composed of six transmembrane spanning domains and a pore forming region between transmembrane domains 5 and 6. The N-terminal and C-terminal tails are in cytoplasmatic side. Three N terminal ankyrin (ANK) repeats are present in N-terminal tail. The variant form TRPV1b is identical to TRPV1 except for the partial deletion of the third ankyrin repeat domain and adjoining polypeptide sequence. Aminoacid modifications has been found (according to Swiss-Prot) in different residues (Table 1). The N-terminal intracellular domain appears to play a pivotal role in intracellular activation of TRPV1, in fact, by mutagenesis analysis a loss of sensitivity to capsaicin has been found related to residue Tyr-511 (Gavva et al., 2004). Modification of a single N-terminal cysteine altered activation of TRPV1 by pungent compounds ranging from onions to garlic (Salazar et al., 2008). The N-terminal intracellular domain also interacts with adjacent modulatory proteins and with the C-terminal intracellular domain. In the closed state, the N-terminal domain is likely exposed to the binding of ATP and a C-terminal region residues interact with PIP-2, facilitating channel activation. In contrast, a desensitized state may be promoted through the interaction of the N- and C-terminal domains through modulatory action involving calcium-calmodulin interacting regions. Moreover, the ankyrin repeat domains residing within the N-terminal intracellular domain forming a region of three repeats spanning amino acids participating in protein-protein (subunit) interactions (Bork, 1993). The presence of concave binding surfaces for ATP within the ANK regions suggest a role of ANKs in modulating channel activation and function (Lishko et al., 2007).

Aminoacid	Residue modification
117	Phosphoserine
145	Phosphoserine
371	Phosphoserine
502	Phosphoserine
604	Glycosylation
705	Phosphoserine
775	Phosphoserine
801	Phosphoserine
821	Phosphoserine

Table 1. Aminoacid number and type of putative modification in TRPV1 protein.

Expression

TRPV1 has also been found in different brain region, such as in dopaminergic neurones of the substantia nigra, hippocampal pyramidal neurones, hypothalamic neurones, neurones in the locus coeruleus, and in various layers of the cortex as in small to medium diameter primary afferent fibres, In non-neuronal cells TRPV1 has been found in keratinocytes, bladder urothelium, smooth muscle, liver, polymorphonuclear granulocytes, pancreatic beta-cells, endothelial cells, lymphocytes, thymocytes and macrophages. Moreover by expression profile studies more cells and tissues has been analyzed for TRPV1 expression.

Localisation

TRPV1 is expressed in discrete spots in the plasma membrane and cytosol of different cell types (e.g. urothelial cells). Moreover, dorsal root ganglion (DRG) neurons express ectopic but functional TRPV1 channels in the endoplasmic reticulum (ER) (TRPV1(ER)).

Function

TRPV1 agonists. TRPV1 is a non-selective cation channel, belonging to the superfamily of TRP channels. TRPV1 agonists are of exogenous and endogenous origins. Exogenous agonist are of natural, semi-synthetic and synthetic origin. The natural compounds include dietary derived compounds as: capsaicinoids, capsinoids, piperine, allicin, alliin, eugenol and gingerol or non dietary plant compounds as resiniferatoxin, Δ9-tetrahydrocannabinol, cannabidiol and venom from animal origins (Pertwee, 2005; Vriens et al., 2009). Moreover, other environmental irritants as well as noxious heat (> 43-45 °C) has been found to act as TRPV1 agonist. The existence of endogenous vanilloid agonists, a class of compounds referred to as endovanilloids, as TRPV1 channels modulators as been also investigated. TRPV1 has been found to be activated by biogenic amines like N-arachidonylethanolamine (AEA, anandamide), N-arachidonoyldopamine (NADA), N-oleoylethanolamine (OLEA), N-arachidonolylserine, and various N-acyltaurines and N-acylsalsolinols. Various lipids from the fatty acid pool have also been identified as TRPV1 activators, as inflammatory compounds such as bradykinin, products of the lipoxygenases (12-HPETE and leukotriene B4, 5(S)-HPETE (hydroperoxyeicosatetranoic acid) and/or leukotriene B4) (Van Der Stelt and Di Marzo, 2004). Also nerve growth factor (NGF), an inflammatory mediator is known to activate/sensitize TRPV1 through the TrkA receptor, act primarily through phosphoinositide-3- kinase (PI3K) and mitogen activated protein kinase (MAPK) signaling pathways (Chuang et al., 2001).

TRPV1 antagonists. Natural TRPV1 antagonists are actually restricted to two plant derived compounds, the thapsigargin that is the irritant principle of Thapsia garganica L. and yohimbine, an indole alkaloid from the tree Corynanthe yohimbe K. The endogenous TRPV1 antagonists discovery up to now are dynorphins, adenosine, various dietary omega-3 fatty acids like eicosapentaenoic and linolenic acids, the endogenous fatty acid amide hydrolase (FAAH) and different polyamines as putrescine, spermidine, and spermine permeate. The most active non-natural compound that act as TRPV1 antagonist are capsazepine and 5-iodoRTX.

Ligand-binding site. By comparative analysis of the primary structure of theTRPV1 and by mutagenesis studies has been revealed a critical role for Tyr511 and Ser512 (between the second intracellular loop and TM3), confirming that the vanilloid binding site is located intracellulary, moreover a third critical residue in the putative TM4 segment (Leu547) was indicated as relevant in ligand-binding.

The effect of extracellular protons (as Ca^{2+}), acts primarily by increasing channel opening, rather than interacting directly with the vanilloid binding site.

Related TRPV1 intracellular signaling pathways

EGFR (epidermal growth factor receptor). TRPV1 has been found to down-regulate epidermal growth factor receptor (EGFR) expression. Interaction of TRPV1 terminal cytosolic domain with EGFR induces EGFR ubiquitination and degradation. Moreover, by transfection of TRPV1 in HEK293 cells a decreased EGFR protein expression was observed (Bode et al., 2009).

Fas/CD95. Activation of TRPV1 with capsaicin, in low-grade urothelial cancer cells, induced a TRPV1-dependent G0/G1 cell cycle arrest and apoptosis by inducing transcription of pro-apoptotic genes Fas/CD95, Bcl-2 and caspases, and by activation of the DNA damage response pathway. Moreover, CPS stimulation induced a TRPV1-dependent redistribution and its clustering with Fas/CD95. In addition, an involvement of capsaicin in activation of the ATM kinase/p53 pathways was found (Amantini et al., 2009).

PKA (protein kinase A). TRPV1 are found phosphorylated by PKA in the amino terminus Ser116 and Thr370 and involved in desensitisation while phosphorylation of Ser116 by PKA inhibits dephosphorylation of TRPV1 caused by capsaicin exposure (Mohapatra and Nau, 2003).

PKC (protein kinase C). Several inflammatory mediators, like ATP, bradykinin, prostaglandins and trypsin or tryptase activated Gq coupled receptors and induced PKC-dependent phosphorylation of TRPV1 (Moriyama et al., 2003).

PKC dependent phosphorylation of TRPV1 potentiates capsaicin- or proton-evoked responses and reduces temperature 'threshold' for TRPV1 activation. Direct phosphorylation of TRPV1 by PKC has been located at Ser502 and Ser800 (Bhave et al., 2003).

IGF-I (insulin growth factor I). Insulin and IGF-I increase translocation of TRPV1 to the plasma membrane via activation of IGF receptors, which, in turn, induced PI(3) kinase and PKC activation (Van Buren et al., 2005).

CdK5 (cyclin-dependent kinase 5). CdK5 can directly phosphorylate Thr407 in TRPV1, while inhibition of CdK5 activity decreases TRPV1 function and Ca^{2+} influx (Pareek et al., 2007).

Homology

86% identity with Mus musculus TRPV1, 85% with Rattus norvegicus TRPV1, 65% with human TRPV3.

Implicated in

Bone cancer

Note

Bone cancer leads to osteoclast activation, which promotes acidosis and consequently TRPV1 activation in sensory fibers. The correlation between TRPV1 activation and bone cancer pain was demonstrated by the evaluation of the RTX analgesic effects of pharmacological blockade of TRPV1. So, TRPV1 activation plays a critical role in the generation of bone cancer pain, and bone cancer increases TRPV1 expression within distinct subpopulation of DRG neurons (Niiyama et al., 2007).

Skin cancer

Oncogenesis

TRPV1 is highly and specifically expressed in both premalignant (leukoplasia) and low-grade papillary skin carcinoma, whereas its expression is substantially absent in invasive carcinoma. Recently, TRPV1 has been found to exhibit tumor suppressive activity on skin carcinogenesis in mice because of its ability to down-regulate epidermal growth factor receptor (EGFR) expression; conversely, loss of TRPV1 expression resulted in marked increase in papilloma development. TRPV1 by interacting with EGFR through its terminal cytosolic domain, facilitates Cbl-mediated EGFR ubiquitination and subsequently its degradation via the lysosomal pathway. In addition, ectopic TRPV1 expression in HEK293 cells resulted in decreased EGFR protein expression, and higher EGFR levels were observed in the skin of TRPV1 deficient mice (TRPV1-/-) as compared to wild-type control animals (Marincsák et al., 2009; Hwang et al., 2010).

Urothelial cancer

Oncogenesis

Changes in the TRPV1 expression occur during the development of human urothelial cancer. Thus, transitional cell carcinoma (TCC) show a progressive decrease in TRPV1 expression as the tumor stage increases. Treatment of low-grade RT4 urothelial

cancer cells with a specific TRPV1 agonist, capsaicin (CPS) induced a TRPV1-dependent G0/G1 cell cycle arrest and apoptosis. These events were associated with the transcription of pro-apoptotic genes including Fas/CD95, Bcl-2 and caspases, and with the activation of the DNA damage response pathway. Moreover, stimulation of TRPV1 by CPS significantly increased Fas/CD95 protein expression and more importantly induced a TRPV1-dependent redistribution and clustering of Fas/CD95 that co-localized with the vanilloid receptor, suggesting that Fas/CD95 ligand-independent TRPV1-mediated Fas/CD95 clustering results in death-inducing signaling complex formation and triggering of apoptotic signaling through both the extrinsic and intrinsic mitochondrial-dependent pathways. Moreover, we found that CPS activates the ATM kinase involved in p53 Ser15, Ser20 and Ser392 phosphorylation. ATM activation is involved in Fas/CD95 up-regulation and co-clustering with TRPV1 as well as in urothelial cancer cell growth and apoptosis. Finally, the role of TRPV1 mRNA down-regulation as a negative prognostic factor in patients with bladder cancer has been reported. By univariate analysis, cumulative survival curves calculated according to the Kaplan-Meier method for the canonic prognostic parameters such as tumor grade and high stage (pT4), lymph nodes and distant diagnosed metastasis, reached significance. Notably, the reduction of TRPV1 mRNA expression was associated with a shorter survival of urothelial cancer patients (P=0.008). On multivariate Cox regression analysis, TRPV1 mRNA expression retained its significance as an independent risk factor, also in a subgroup of patients without diagnosed metastasis (M0). These findings may be particularly important in the stratification of urothelial cancer patients with higher risk of tumor progression for the choice of therapy options (Amantini et al., 2009; Kalogris et al., 2010).

Glioblastoma

Oncogenesis

TRPV1 mRNA and protein expression was evidenced in normal astrocytes and glioma cells and tissues. Its expression inversely correlated with glioma grading, with a marked loss of TRPV1 expression in the majority of grade IV glioblastoma tissues. TRPV1 activation by CPS induced apoptosis of U373MG glioma cells, and involved rise of Ca^{2+} influx, p38MAPK activation, mitochondrial permeability transmembrane pore opening and transmembrane potential dissipation, and caspase-3 activation (Amantini et al., 2007).

Pancreatic cancer

Oncogenesis

Human pancreatic cancer, significantly expressed increased levels of TRPV1 mRNA and protein. However, resinferatoxin (RTX), a potent TRPV1 agonist, induced apoptosis by targeting mitochondrial respiration, and decreased pancreatic cancer cell growth in a TRPV1-independent manner (Hartel et al., 2006).

Cervical cancer

Oncogenesis

TRPV1 expression has been reported in human cervical cancer cell lines and tissues, and the endocannabinod anandamide (AEA) induced TRPV1-dependent tumor cell apoptosis. In addition, TRPV1 stimulation completely reverted the cannabidiol (CBD)-mediated inhibitory effect on human cervical cancer cell invasion by blocking CBD-induced increase of TIMP-1, a MMP inhibitor both at mRNA and protein levels, and ERK1/ERK2 and p38MAPK activation (Contassot et al., 2004a; Contassot et al., 2004b).

Prostate cancer

Oncogenesis

A functional TRPV1 channel is expressed in human prostate cancer cells (PC3 and LNCaP) and in prostate hyperplasic tissue. Moreover, increased TRPV1 mRNA and protein expression was found in human prostate cancer tissues as compared to prostate hyperplastic and healthy donors, and this increase correlated with degree of malignancy. CPS induced a growth inhibition and apoptosis of PC3 prostate cancer cells, but in TRPV1-independent manner, through ROS generation, mitochondrial inner transmembrane potential dissipation and caspase-3 activation. Moreover, CPS or the specific antagonist capsazepin inhibited tumor growth in vivo, in a xenograft human prostate PC3 cancer model. By contrast, in androgen-responsive LNCaP prostate cancer cells, CPS was found to stimulate TRPV1-dependent cell proliferation. CPS effects were attributable to decreased ceramide levels and to activation of Akt/PKB and ERK pathways, and were associated with increased androgen receptor expression (Sanchez et al., 2005).

Pheochromocytoma

Oncogenesis

TRPV1 expression has been also demonstrated on the plasma membrane of rat pheochromocytoma-derived PC12 cell line. PC12 stimulation by CPS resulted in TRPV1-dependent nitric oxide synthase (iNOS) expression. CPS exposure triggered Ca^{2+} influx, which in turn enhanced mitochondrial Ca^{2+} accumulation and promoted NO generation, events that have been associated with tumor progression (Qiao et al., 2004).

Hepatocarcinoma

Oncogenesis

Hepatocarcinoma patients show high TRPV1 expression that is associated with increased disease-free survival (Miao et al., 2008).

Digestive tract diseases

Note

TRPV1 sensitive sensory nerves are densely distributed in the gastrointestinal system, and one of the important roles of these nerves is the preservation of the tissues integrity from the exposed to aggressive compounds, such as protons and activated enzymes. Moreover, activation of TRPV1 either by endogenous or by exogenous agonists exerts hypotensive effects or protective effects against gastrointestinal injury. Therefore, TRPV1 is not only a prime target for the pharmacological control of pain but also a useful target for drug development to treat various gastrointestinal diseases. The function of TRPV1 visceral sensitivity and hypersensitivity tends to be well established. It was shown the involvement of TRPV1 in the regulation of gastrointestinal motility and absorption, visceral sensation and visceral hypersensitivity (Holzer, 2010).

Respiratory system diseases

Note

TRPV1 is expressed on vagal afferent C fibers in the lungs and may be activated by intense heat, acidic solutions, endocannabinoids, metabolites of arachidonic acid, capsaicin and ROS.The role of TRPV1 in respiratory system is correlated to date indicating that acidic solutions as other TRPV1-inducing stimuli lead to C-fiber-mediated respiratory reflexes and activation of these fibers leads to bronchoconstriction, mucus secretion, bradycardia and hypotension, in addition to cough and airway irritation (Taylor-Clark and Undem, 2006).

Bladder diseases

Note

The role of TRPV1 in overactive (irritable) bladder disease has been shown in TRPV1 knockout mice where differences in their response to bladder injury when compared to their wild-type counterparts. TRPV1 knockout mice didn't develop bladder overactivity during acute bladder inflammation, suggesting a role for TRPV1 in bladder inflammatory states. Moreover, in patients diagnosed with neurogenic detrusor overactivity (NDO), higher levels of TRPV1 immunoreactivity in the urothelium and in the number of nerve fibers were found, compared to control (Apostolidis et al., 2005).

Diseases of the basal ganglia

Note

TRPV1 plays a role in dopaminergic mechanisms associated with schizophrenia and Parkinson's disease. Exposure of mesencephalic dopaminergic neurons to the TRPV1 agonist capsaicin triggers cell death, while exposure to TRPV1 antagonists prevents these effects. In addition, schizophrenic patients tend to display reduced pain sensitivity and a diminished skin flare response to niacin, suggesting a defects in TRPV1-expressing afferent nerve fibers (Blumensohn et al., 2002).

Cardiovascular diseases

Note

TRPV1 is expressed in cardiac spinal sympathetic sensory fibers. During cardiac ischemia these fibers are essential for the sympathoexcitatory reflex, which is associated with increased blood pressure and chest pain. Acidosis TRPV1 activation and ischemia provides the organism with a mechanism, which relays painful information to the brain. Conversely, the release substance P (SP), neurokinin A (NKA) and CGRP by the nerve fiber itself has beneficial effects, which helping to reduce the effects of ischemia and acidosis. Some data indicated that spinal cord stimulation (SCS) used to improve peripheral blood flow in selected populations of patients with ischemia is mediated via VR-1 containing sensory fibers. Treatment of patients with the TRPV1 agonist RTX result in a SCS-induced vasodilation indicating a cardioprotective role for TRPV1 (Wu et al., 2006).

Diabetes

Note

A fundamental role for insulin responsive TRPV1+ in pancreatic sensory neurons in controlling islet inflammation and insulin resistance function and diabetes pathoetiology has been demonstrated. Infact, eliminating these neurons in diabetes-prone NOD mice prevents insulitis and diabetes. In type 2 diabetes administration of capsaicin and RTX which desensitize TRPV1 result in improved glucose tolerance through enhancement of insulin secretion and decreased plasma insulin levels. So ablation of TRPV1-expressing neurons which innervate the pancreas through neonatal capsaicin treatment prevents the insulitis and pancreatic beta-cell destruction that normally occurs in these animals (Gram et al., 2007; Razavi et al., 2006).

Itch

Note

TRPV1 is expressed on the "pruriceptor subpopulation" of mechano insensitive fibers and the itch-selective sensory afferents respond to capsaicin.

Itch sensation can be modulate by changing skin temperature and pH, to common TRPV1 activator stimuli. Therefore, TRPV1 may function as a 'central integrator' molecule in the itch pathway (Yosipovitch et al., 2005; Ghilardi et al., 2005).

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