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Review

Transient Receptor Potential (TRP) Channels and Functions

Rumeysa Ekim[1], Aylin Kayaaltı[1], Oytun Erbaş[1,2]

ABSTRACT

Transient receptor potential (TRP) is the ion channel protein family expressed in plasma membranes in various cell types, including neurons. They are activated by intracellular and extracellular stimuli. TRP proteins have a lot of physiological and pathological roles. They are involved in critical roles in sensory physiology such as vision, smell, hearing, taste, and touch. The TRP gene was first identified in the fruit fly, Drosophila melanogaster, in the late 1960s and the first human homolog was reported in 1995.TRP channels are not selective against cations but have been reported to be highly sensitive to calcium (Ca^{+2}). Different subgroups of the TRP family are structurally varied by means of N and C terminals. TRP family consists of seven groups such as TRPV (Vanilloid), TRPM (Melastatin), TRPC (Canonical), TRPP (Polycystic), TRPA (Ankyrin), TRPML (Mucolipin), and TRPN (Drosophila NOMPC). The eighth TRP family has recently been identified in yeast and named TRPY. In this review, TRP channels, sub-members, and their physiological effects are mentioned.

Keywords: Biosensor, Ca^{+2} permeability, sensory physiology, transient receptor potential channels.

Transient receptor potential (TRP) channels are one of the subunits of the ion channel called the transient receptor channel. They were discovered in a mutated strain of Drosophila for the first time. Their entire family has been found since the first discovery, and they have around 30 members in the vertebrate. They can be present in a variety of organisms, including yeasts, worms, rats, fish, and humans. The TRP superfamily is generally divided into seven sub-members, and the eighth sub-member, TRPY, consists of yeast TRP's which are remotely associated with other members. TRPC, TRPV, TRPM, and TRPA are classified as Group 1 TRP with the closest similarity to Drosophila TRP.[1] Group 2 TRP channels, including TRPP and TRPML, have a distal relationship with Drosophila TRP.[1] To detect and avoid harmful chemicals, nematodes use TRP channels located at the end of neuronal dendrites in their noses. TRP channels are used by yeasts for the detection and response of hypertonicity.[2] Male mice use these channels as pheromone receptors to distinguish males from females. Additionally, these channels are also used by humans to differentiate between hot and cold, as well as to determine the tastes like bitter, sweet, and umami.

They contribute to lots of different processes in the human body. It is suggested that TRP channels act as integrators for a variety of different sensory stimuli. Due to their exhibition of an effective variety of cation selectivity and specific activation mechanisms, they have a distinct place among other ion channel families.[3] No other protein family has had a wider range of variation in the activation mechanisms than TRPs.

Numerous TRP protein variants have been discovered in almost all large animal groups and several types of cells. The first mammalian TRP protein belonging to the TRPC group was reported in 1995. TRP channels have been shown to be a central component in many physiological systems, and understanding how they act is important for treating some diseases. Basically, different groups of TRP channels differ by their structures. Having

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey
[2]Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey

Correspondence: Rumeysa Ekim. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.

E-mail: rumeysa.ekim.98@gmail.com

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six transmembrane segments and being of N and C terminals on the side of the cytosol are their common points. The transmembrane area constitutes tetrameric complexes. The main difference between different groups is due to the terminals N and C.

Transient receptor potential channels are widely expressed in mammalian tissues. They are activated by numerous physiological stimuli including mechanical stress, temperature, redox signal molecules, and intracellular and extracellular ligands.[4] TRP channels are known to play an important role in hearing. It is considered that TRPN and TRPML3 are crucial for 100% of hearing. TRP channels are found widely in glomerular, tubular, and vascular cells in mammalian kidneys just as they are almost everywhere throughout the body.[4] It is known that TRP channels function as 'biosensors' to detect the changes in the surrounding environment and cellular state.[5] It has been observed that many proteins are subject to redox modification and subsequent signaling. TRPC5, TRPV1, TRPA1, and TRPM2 are known as the redox sensors that are activated by H_2O_2 (hydrogen peroxide), electrophiles, and NO (nitric oxide). TRP channels facilitate a variety of cation flows so that various cellular responses are activated.

Transient receptor potential channels are known as vanguards of sensory systems that respond to osmolarity, temperature, pain, touch, pheromones, and different stimuli but their roles are much broader.[2] Small conformational changes lead to channel opening and allow more than ten million ions per second to flow through each channel.[2] With the temperature-dependent cooperative binding, TRPs can be closed by the second messengers. Ca^{+2} ions are crucial in cellular hemostasis and activity, also the surface of each cell holds thousands of channels that precisely control the timing and entry of Ca^{+2} ions. TRP channels either transmit Ca^{+2} directly or polarize cells to activate other Ca^{+2} permeable channels.[6] It has been reported that intracellular Ca^{+2} levels, growth cone morphology, and membrane precursor vesicles play a triggering role. Ca^{+2} acts as a localized secondary messenger. It triggers many basic cellular events such as secretion, mobility, contraction, cell division, and cell death.

It has been discovered that members of TRP channels expressed in the kidney are involved in the role of maintaining the integrity of the filtration barrier, regulating tubular reabsorption, detecting osmotic stimuli of Ca^{+2} and Mg^{+2}, and sensing the osmotic stimuli. Additionally, mutations in TRP channels have also been linked to kidney disease pathophysiological mechanisms including focal segmental glomerulosclerosis, disturbances in Mg homeostasis, and polycystic kidney disease. Various subtypes of TRP channels are expressed in the renal vasculature. Functional changes in the ion channels expressed in endothelium and the flat muscle of the renal vessels are known to modulate renal vascular resistance and RBF(Renal Blood Flow), therefore renal vascular TRP channels are considered as the potential therapeutic target for the treatment of kidney disease.[4]

Most TRP channels are activated by multiple stimuli in expression systems. The cooperation specific to TRP channels can cause the allosteric connection of different activation alerts and obscure the definition of activator and modulator.[7] The activity of TRP channels is generally divided into three categories. These are receptor activation, ligand activation, and direct activation.

RECEPTOR ACTIVATION

In this type of activation, G-protein-dependent receptors and receptor tyrosine kinases that activate PLC (phospholipase C) can adjust TRP channel activity at least in three ways. These are Hydrolysis of PIP_2 (phosphatidylinositol 4,5-bisphosphate), production of DAG (diacylglycerol), and IP_3 (inositol 1,4,5-triphosphate), and subsequent release of Ca^{+2} from intracellular storage. Among these mechanisms, the most powerful ones are known as PIP_2 and DAG.

LIGAND ACTIVATION

Ligands involved in the activation of TRP channels are generally classified into four categories. These are synthetic compounds and exogenous small organic molecules including natural products such as marrow and capsaicin, endogenous lipids, and lipid metabolism products such as diacylglycerols and phosphoinositides, purine nucleotides and their metabolites, and inorganic ions such as Ca^{+2} and Mg^{+2} that have the most physiological interest. There are few endogenous ligands for TRP channels, such as 2-AG and anandamide.

DIRECT ACTIVATION

Direct activation includes factors like temperature activation and mechanical stimuli. The temperature degrees of each of the different channels can be

different, and it is interesting that they complement each other to give the organism the ability to respond to temperatures physiologically. Protein kinases and A, C, and G have been shown to modulate TRP channel activity, but there is little data indicating its direct phosphorylation and effect on channel activity. Other cellular signaling mechanisms, such as Ca^{+2}/calmodulin regulation, have also been reported to regulate TRP channel activity. For some of the TRP's, the number of functional channels in a given cell is regulated by the penetration of vesicles carrying TRP proteins into the plasma membrane. Signaling cascades that alter and regulate cellular amplification downstream of TRP channels can change the physiological meaning of channel activation.[7]

TRANSIENT RECEPTOR POTENTIAL FAMILY

Transient receptor potential canonical (TRPC)

The TRPC family is a group that has 7 members. This group is the most similar to Drosophila TRP channels. The first TRP variant found in mammals is TRPC1. Mammalian TRPCs are divided into four subgroups based on sequence alignments and functional comparisons. These are TRPC1, TRPC2, TRPC3/6/7, and TRPC4/5. TRPC channels appear as heteromer complexes with other members within the group in some cases. TRPC1 shows a broad expression across different cell types.[8] and generally associated with many physiological functions. TRPC1 is activated by the hormone Orexin-A, which is associated with sleep/wake conditions, alertness, and regulation of appetite.[9] Evidence has been found that TRPC1 can be activated by a reduction in Ca^{+2} receptors and DAG or even a lack of function. TRPC1/TRPC2 channel is activated by GRPCs.[1]

Transient receptor potential canonical 2 is known to be pseudogenic in humans. TRPC2 plays an important role in pheromone detection through VSN (Vomeronasal sensory neurons) in rodents. Mice that are devoid of TRPC2 show abnormal mating behavior due to the role of this channel in pheromone signaling.[2] TRPC2 was detected in the acrosome of the sperm and its role in fertilization was demonstrated.[10] TRPC2 has been detected in the heart, brain, splendor, testicles, erythrocytes, and the main olfactory epithelium. Some members of the TRPC family are expressed in various locations of the human brain. TRPC3 is a multifunctional cellular sensor with a wide range of physiological/pathological functions. TRPC3 is the most exclusively expressed in certain parts of the brain, lungs, and heart.[11] TRPC3 was discovered in brain synaptosomes to interact with TRPC6 and TRPC7, but not with other TRPC members. It is shown as evidence that the TRPC3 channel is operated by a structurally active receptor that can be stimulated by the DAG.[12]

Transient receptor potential canonical 4 is found in various brain parts, ICC (Intestinal battery cells), adrenal glands, kidneys, flat muscle cells, and endothelium. Multiple signals downstream of receptors mediate the activity of TRPC4 homo-/heterotrimeric channels.[1] In mice that lack TRPC4, some defects are seen in agonist-induced vascular regulation and pulmonary microvascular permeability. TRPC4 has been shown to play a role in response to neural injury, neuronal exocytosis, and regulation of neural growth.[13] The silencing of TRPC4 in human kidney epithelial cells disrupts TSP1 (thrombospondin-1) secretion.TRPC5 is basically expressed in brain tissue, especially in the fetal brain.TRPC5 can play an important role in brain development.[14] The TRPC5 is significant due to its amygdala function and fear-related behavior. Increased glutathionylation and activation of TRPC5 through oxidative stress have been reported to contribute to neuronal damage in the striatum. In the central nervous system, TRPC5 can form heteromeric cation channels with TRPC1 and these hetero multimers are located at SOCE (Store-operated Ca^{+2} entry). It plays an important role in the regulation of the vascular endothelial system. It is reported in some studies that TRPC5 is also activated by nitric oxide.[15]

Transient receptor potential canonical 6 is expressed in cardiac neurons, olfactory epithelium neurons, retinal ganglion cells, and some parts of the brain such as the cortex, but its expression in the brain is low compared to other TRPCs. TRPC6 is reportedly playing an important role in brain development and diseases. Its physiological function is related to dendritic overgrowth, excitatory synapse formation, and BDNF (Brain-derived neurotrophic factor) mediated survival of granule cells in the cerebellum. TRPC6 participates in Aβ production in Alzheimer's disease (AD) and many pathological processes, including human glioma cell proliferation. TRPC7 is mainly expressed in the kidney and the pituitary gland. TRPC7 has high sequence homology with TRPC3 and TRPC6. The TRPC7 channel is activated by receptors activated by PIP_2 metabolism and DAG

production via PLC.[12] The TRPC family is generally activated by the stimulation of GRPC and receptor tyrosine kinases.

Transient receptor potential vanilloid (TRPV)

The TRPV family consists of six different members. These are TRPV1, TRPV2, TRPV3, TRPV4, TRPV5, and TRPV6. Since TRPV1, TRPV2, TRPV3, and TRPV4 can be activated by heat, TRPVs activated by vanillin, vanillic acid, and capsaicin in plants are known as thermo-TRP channels. TRPV5 and TRP6 are epithelial calcium ion channels.[16] TRPV1 was identified by cloning the 'hot' pepper-derived vanilloid compound capsaicin as a ligand.[2] The TRPV1 channel is a Ca^{+2} permeable enhanced by temperature (43˚C ≥) and reduced pH and inhibited by intracellular PIP_2. Its thermal sensitivity is increased by bradykinin and nerve growth factor, which appear to act via PLC to hydrolyze PIP_2 by releasing the inhibition of the channel.[2] TRPV1 is mostly expressed in the neuron and has been reported to play a central role in nerve damage associated with chronic and neuropathic pain. It is known that cold stress triggers cardiac hypertrophy by down-regulation of TRPV1. TRPV1 also participates in purinergic signaling mechanically induced by the bladder urothelium. TRPV2 is 50% identical to TRPV1 and it is activated at a higher temperature (52˚C). TRPV2 is expressed in both neuronal and non-neuronal cells. TRPV3 is expressed in the spinal cord, brain, DRG (The dorsal root ganglia) neurons, and trigeminal ganglia. It is activated at temperatures above 34˚C. It is highly expressed in the skin, tongue, and nervous system. TRPV3 has been seen as a cause of Olmsted syndrome and is activated by carvacrol (thyme), eugenol (clove), and camphor.

Transient receptor potential vanilloid 4 is a nonselective cation channel. It is activated by hypoosmotic stimuli, temperatures above 27˚C, mechanical stimuli, endogenous metabolites of arachidonic acid and phorbol esters. It has been reported that it acts as a sensor for osmolyte and mechanical stretching.[1] Deletion of TRPV4 in mice alters CNS (Central nervous system) control of ADH secretion.[6] In a study, it was observed that activation of TRPV4 increased oxidative stress by inhibiting catalase and glutathione peroxidase and increasing nNOS (neuronal nitric oxide synthase) activity.[17] TRPV5 is mainly expressed in renal epithelial cells and plays an important role in the reabsorption of Ca^{+2}. The parathyroid hormone can be regulated by various factors such as 1,25-dihydroxy vitamin D3, dietary Ca^{+2}, and pH change in acid-base state.[18] TRPV6 has some in common with TRPV5. They are expressed together in various tissues such as the kidney, intestine, testicle, and prostate. They also contain a different subfamily of heteromeric and homomeric channels involved in the transport of the intestinal and kidney epithelium. Furthermore, they are known as selective channels of Ca^{+2}. TRPV6 channel is important for male fertility.[1]

Transient receptor potential melastatin (TRPM)

The TRPM family has eight members in mammals. TRPMs are divided into three groups according to the sequence homology. These are TRPM1-3, TRPM4-5, and TRPM6-7. Intracellular membranes contain several TRPMs. TRPM1 is expressed in normal tissues and has been shown to be a prognostic marker for melanoma metastasis. TRPM2 is expressed in different tissues such as the heart, hematopoietic, brain, endothelial cells, and vascular flat muscle. It is regulated by signaling pathways that respond to H_2O_2 and TNF-α (Tumour necrosis factor alpha). TRPM2 acts as a lysosomal calcium release channel in the pancreatic beta-cell and dendritic cells and as a Ca^{+2} permeable channel in the plasma membrane.[19] Activated by moderate temperature and steroid pregnenolone sulfate, TRPM3 forms a Ca^{+2} permeable non-selective channel that is structurally active when expressed as a heterologous. TRPM3 is expressed in the peripheral nervous system, in the islet cells of the pancreas, which regulates insulin secretion, in the brain, neurons, and oligodendrocytes.[20]

The TRPM4 channel is first expressed in the kidney distal collection channel epithelium and central nervous system. It is known as a non-selective cation channel activated by Ca^{+}, which only transmits single-value ions like Na^{+} and K^{+}. It has been reported that it creates a functional channel as a tetramer expressed in a large human tissue and involved in different physiological processes such as T cell activation, neurotoxicity, and allergic reactions.[21] 40% of the amino acid sequence of TRPM5 and TRPM4 is identical. TRPM5 is a single-value selective ion channel. It is a Ca^{+2} activated cation channel that mediates signaling in taste and other chemosensory cells.

The TRPM6 channel is a protein that contains a TRP channel segment that is covalently bound to the α-type serine/threonine-protein kinase. This channel is known to be expressed in the cells of the intestinal and kidney epithelium. A spontaneous

human mutation of TRPM6, together with secondary hypocalcemia, causes familial hypomagnesemia and is therefore thought to be important for Mg^{+2} intake in the kidneys and intestines. TRPM6 and TRPM7 are unique among ion channels, as they also contain functional kinase areas. TRPM7 is inhibited by 0.6 mM intracellular free Mg^{+2}. It is a permeable channel for Ca^{+2} and Mg^{+2}, but in physiological conditions, it passes very little inward current. It has been suggested that the sensitivity of TRPM7 to physiological Mg-ATP levels has a central role in metabolic perception.[22] TRPM8 is activated at temperatures below 28°C. It is a non-selective channel reinforced with 'cooling' compounds such as menthol and icilin. This channel is defined as an upwardly regulated messenger RNA (ribonucleic acid) in prostatic and other cancers. TRPM8 also plays a role in mammalian thermoregulation, so its antagonists have the potential to induce hypothermia in patients. Identification and optimization of different TRPM8 antagonists led to the development of PF-05105679, which has undergone clinical trials and has proven its effectiveness in a cold pressor test comparable to oxycodone, an opioid drug widely used to treat moderate to severe pain.[23,24]

Transient receptor potential ankyrin (TRPA)

Transient receptor potential ankyrin was first named ANKTM1 due to having many repetitions of N-terminal ankyrin. It is known that it is located in a subset of small and medium-sized peripheral sensory neurons, in the same place as TRPV1. There are two TRPA members in C.elegans and four in Drosophila. The only member of the TRPA family in mammals is TRPA1. TRPA1 is located in the plasma membrane of the pain-sensing sensory nerves. It plays a role in activating pain pathways that trigger pathways that promote long-term responses, such as inflammation. It responds to stimuli such as mustard oil, wasabi, and garlic. TRPA1 antagonists such as mustard oil and garlic are known to have the potential to improve neurogenic inflammatory conditions triggered or exacerbated by irritating exposure.[25] Blocking the function of TRPA1 is thought to be a promising way to reduce pain.[1]

Transient receptor potential nomp C (TRPN)

The TRPN channel is not expressed in mammals. It is expressed in organisms such as Drosophila, zebrafish, and C.elegans. TRPN is known as NOMPC (No mechanoreceptor potential C).[26] TRPN is an important channel for mechanical transduction channel sub-units in both vertebrates and invertebrates. Dysfunctional mutations in the gene that encode TRPN almost eliminate mechanical sensory signaling in Drosophila.[26] The TRPN channel is important for tactile and proprioceptive behavior in nematodes and insects and the transmission of vibrating stimuli in zebrafish hair cells.[27]

Transient receptor potential polycystin (TRPP)

Polycystic kidney disease 2 (PDK2, TRPP2), PKD2-like 1 (PKD2L1, TRPP3), and PKD2-like 2 (PKD2L2, TRPP5) are the three human genes that encode the TRPP protein family.[1] Mutations in TRPP1 and TRPP2 lead to autosomal dominant polycystic kidney disease. TRPP2 is a Ca^{+2} permeable non-selective cation channel. All the mammalian orthologues are highly conserved with 90% identification for TRPP2 and TRPP3 and 80% for TRPP5. The TRPP channel is regulated by Polycystin-1 family proteins to form the nucleus of a signal pathway where Ca^{+2} is a second messenger, and they are all combined into receptor-channel complexes.[28]

Transient receptor potential mucolipin (TRPML)

Transient receptor potential mucolipin channel includes three members such as TRMAL1, TRPML2, and TRPML3. They share approximately 75% amino acid similarity among them. TRPML proteins have been discovered as mutated gene products in MLIV (mucolipidosis IV). Mutations in TRPML1 are known to be responsible for lysosomal storage disorder mucolipidosis. Besides, TRPML1 is responsible for iron ions entering the cell from the endosome/lysosome membrane. Mutations of TRPML2 in human or animal models have not been found to be related to any disorder. TRPML3 is basically expressed in the inner ear intracellular. TRPML3 is present in the cytoplasm of hair cells and the plasma membrane of stereocilia. TRPML3 has been proposed as an inward rectifying single-value cation channel printed by H^{+}[29]

Conclusion

There are seven families as the mammalian TRP channel family. These are TRPC, TRPV, TRPA, TRPN, TRPP, and TRPML. TRPs have been shown to be involved in sensory functions such as taste, smell, pain, and hearing. Some TRP channels are activated by oxidative stimuli. TRP channels have become interesting not only in terms of sensory functions

but also in terms of roles they play in different functions. Since TRP channels have the ability to recognize many substances, it has been understood that there is no need to develop several receptors for different stimuli of an organism and this system is very effective.

TRP family sub-members have been shown to play a role in cell physiological functions and abounding diseases. Many diseases such as kidney diseases, chronic pain, brain diseases, and cardiovascular diseases have been linked to abnormalities in TRP channel function, changes in channel properties, and changes in their regulators.

DISCUSSION

Transient receptor potential channels are widely expressed in mammals. There are many variants of these channels. TRP channels are biosensors that detect changes in the surrounding environment and cellular events. Studies show us that more information can be obtained about both protein function and sensory physiology of TRP channels. Interactions such as many ligands and receptors that activate TRP channels provide different opportunities. Many assumptions are presented in this area, but since these assumptions cannot be concluded, many things can be changed. These changes will also affect the knowledge about the different mechanisms for activation and modulation.

The mechanical strength of TRP activation, primary mechanisms, intracellular ligand binding, and temperature will provide clarification on many issues. The role of the TRP family in a wide range means that the channels can have different physiological functions and can contain a lot of information. This indicates that the channels need to be investigated more deeply. Functional inhibition of the TRP family is an important goal in developing drugs for the treatment of various diseases, cancer, and inflammatory diseases. Studies on these channels will reveal many mysteries of TRP channels over time and will become the solution point to many problems.

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