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TRP super family ion channels: A review

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Abstract

TRP super family includes certain ion channels that is permeable to a range of ions like calcium, sodium, potassium and magnesium either actively or passively and are involved in affecting various physiological functions of the body due to their wide distribution in various cells of the body. This review article will provide a comprehensive knowledge regarding the classification and distribution of these ion channels throughout the organ systems with their physiological effects that will provide a basic concept of the ion channels and can help the researchers in designing their future experiments.

Keywords: TRP, ion channels, classification, effects

Introduction

The transient receptor potential (TRP) super family first identified by Cosens and Manning (1969) [5] and named as “TRP” by Minke *et al.* (1975) [20] is a large protein family that is multimodal ion channel widely distributed in animal tissues with variety of roles to play (Zhang *et al.*, 2023) [34]. The nomenclature as “TRP” was on the basis of its electrophysiological phenotype that oscillates between Ca^{2+} transporting and non-transporting states (transient state). In mammals, it comprises of atleast six subfamilies viz; TRPC (canonical), TRPM (melastatin), TRPP (polycystins), TRPA (ankyrin), TRPML (mucopolin) and TRPV (vanilloid) (Montell *et al.*, 2002) [22]. TRP channels have six transmembrane spanning domains (S1-S6), with a pore-forming loop between S5 and S6, and both the C and N termini are located intracellularly (Wu *et al.*, 2010) [30].

Classification of TRP channels

In mammals, based on amino acid sequence and topological differences, it has been divided into two groups viz; group 1 and group 2. Group 1 with four subfamily members (TRPC, TRPV, TRPM and TRPA), and group 2 with two subfamilies (TRPP and TRPML) of seven subfamilies have multiple roles in animal body.

TRPC (canonical)

These channels are first to be identified in TRP family. These are non-selective cation channels (Feng, 2017) [8] with a molecular weight ranging from ten to few hundred kilodaltons (Latorre *et al.*, 2009) [16]. Based on amino acid sequence, seven TRPC proteins (1-7) have been identified till date (Montell *et al.*, 2002) [22]. They have a wide distribution in animal tissue and involved in various functions like receptor-activated Ca^{2+} entry, increase intracellular Ca^{2+} level, smooth muscle contraction, endothelial cell function, neuron differentiation and also act as sensors for mechanical stretch in vasculature and oxidative stress.

TRPV (vanilloid)

The TRPV subfamily can be divided into 4 groups: TRPV1/2, TRPV3, TRPV4, and TRPV5/6. TRPV1 to TRPV4 are non-selective cation channels that can be activated by a number of different stimuli, such as second-messenger binding, heat and cold, and chemical and/or mechanical stress. These channels are modestly permeable for Ca, whereas the other 2 members of the family, TRPV5 and TRPV6, are highly selective for Ca and tightly regulated by intracellular Ca^{2+} concentration (Vanoeven *et al.*, 2011) [27]. TRPV5 and TRPV6 share about 75% homology at the amino acid level.

The main sequence differences are located in the N-and C-terminal tails. TRPV5 and TRPV6 reveal only 30-40% homology with other members of the TRP family, and possess unique properties that distinguish them from other TRP channels in that they have a constitutively activated Ca^{2+} permeability at physiological membrane potentials while other TRP channels need activation by receptor stimulation. In general TRPV5 is the major isoform in kidneys, whereas TRPV6 is highly expressed in the small intestine (Dekker *et al.*, 2003) [6].

TRPM (melastatin)

It is the largest member of TRP super family and consists of eight members (1-8). They are involved in numerous physiological functions like cell proliferation, temperature sensing, development of blood vessels, cancer progression, neurological disorders, endothelial dysfunction, type-II diabetes, etc. (Zhang *et al.*, 2023) [34].

TRPA (ankyrin)

TRPA consists of only one member (1) with numerous N-terminal ankyrin repeats. TRPA1 is a sensor for diverse noxious external stimuli such as intense cold, irritating compounds, mechanical stimuli, reactive chemicals, and endogenous signals associated with cellular damage (Naert *et al.*, 2021) [23]. It is heavily linked to chronic pain, neuropathic pain, migraine, asthma, and respiratory inflammation.

TRPP (polycystins)

It the most primitive type and consists of three members (TRPP2, TRPP3 and TRPP5) and act as non-selective Ca^{2+} permeable cation channels. TRPPs act as sensors for external mechanical forces, such as fluid shear stress in the renal tubule, involved in osteogenesis and preventing bone loss. Mutation in the protein leads to PCKD (Polycystic kidney disease) leading to formation of fluid filled cysts in the kidney (Li, 2017) [17].

TRPML (mucopolin)

It includes three members (1-3). They are non-selective cation channels and are involved in lysosomal acidification, membrane trafficking, autophagy, and lysosomal exocytosis, chemokine secretion, modulates inflammatory responses, hair cell function in the cochlea and melanocytes (Flores and Garcia, 2011) [9].

Effects of TRP channels on organ systems

Several factors are responsible for activation and inhibition of TRP channels in animal body like heat or cold stimuli, changes in osmolarity, proton gradients, noxious and irritant compounds, several natural products, herbs and compounds of plant origin (Vincent and Duncton, 2011) [29]. Based on the agonist and antagonist activity, some compounds have also been used in clinical trials and drug designing to treat certain diseases either by inhibiting or activating the expression patterns of TRP channels. These channels are widely distributed throughout the organ systems with unique effects.

Nervous system: TRP channels are widely distributed in the neuronal and neuroglial cells of the brain and are involved in regulating various neurological disorders. Activation of TRPC1, TRPC3 and TRPC4 and down regulation of TRPC5

helps in neuron protection (Kim *et al.*, 2006) Activation of TRPV6 reduces the risk of hemorrhagic stroke, neuronal death and survival in ischemic stroke and reduces neuro-toxicity and apoptosis by increasing the Ca^{2+} influx (Huang, 2017) [11]. TRPV1 regulate the microglia and enhance autophagy and phagocytosis. Activation of TRPV2 induces the release of nerve growth factor (NGF) and regulated blood-brain barrier (BBB) function, which may be associated with ischemic stroke (Lu *et al.*, 2019) [18]. TRPV4 alleviates ischemic injury by increasing glutamate and overloading Ca^{2+} , thereby reducing neurotoxicity. The TRP channel may represent a promising therapeutic strategy for neurological disorders with special emphasis on the TRPC channel because it is more widely distributed in the nervous system.

Respiratory system: TRP channels are widely distributed in the lungs and hence can be targeted for treatment of respiratory disorders. It has been reported that in cough (a reflex mechanism to clear the upper airways), TRPV1 channels are mostly involved. Therefore; inhibition of TRPV1 expression can minimize the cough symptoms (Anderson, 2004) [2]. Use of TRPV1 and TRPV6 antagonists can reduce the symptoms of asthma as arachidonic acid is released in lungs during asthma attacks and have a stimulatory effect on TRPV1 (Hwang *et al.*, 2000) [12]. Rahaman *et al.* (2014) [24] reported that TRPV4 activity was up-regulated in lung fibroblasts in lung fibrosis. TRPV4 also plays an important role in the formation of pulmonary edema and acute lung injury.

Cardiovascular system: Vasoconstriction leads to hypertension in patients with cardiovascular disorders. It has been reported that activation of TRPV1 channels can reduce vasoconstriction by inducing the release CGRP (Calcitonin Gene-Related Peptide) leading to potent vasodilatation (Zygmunt *et al.*, 1999) [36]. TRPV4 and TRPM4 have also been reported to have regulatory effects on systemic blood pressure suggesting their vasoprotective effect (Earley *et al.*, 2009) [7].

Uro-genital system: TRPC6 is expressed in glomerular podocytes and its up-regulation may lead to certain kidney disease like glomerulosclerosis and membranous nephropathies (Moller *et al.*, 2007) [21]. TRPV1 is highly expressed in lining epithelium of the urinary bladder in patients with bladder disorders (Zhang *et al.*, 2015) [33].

Digestive system: It has been reported that activation of TRPV4 receptors in the GI tract can trigger inflammation. Inflammation in mouse colitis models can be alleviated by the activation of TRPM8 as reported by Vergnolle (2014) [28]. Activation of TRPV1 increases energy metabolism and prevents the accumulation of visceral fat (Ma *et al.*, 2011). TRPV6 channels are actively involved in absorption of calcium from gut epithelium (Ranjan *et al.*, 2020) [25].

Integumentary system: On the skin, TRPs act as interesting pharmacological targets because they allow for topical treatment and may reduce the risk of severe harmful effects (Koivisto *et al.*, 2022) [15]. TRP channels are widely expressed in various skin cell types, including keratinocytes, melanocytes, nerve endings, and immune cells (Ho and Lee, 2015) [10]. Their functions involve hair growth, wound

healing, skin cell proliferation and differentiation, immunity, skin barrier function, skin inflammation and pruritis (Toth *et al.*, 2014) [26].

Endocrine system: TRP channels have been expressed in a number of cancers like prostate cancer, breast cancer, colorectal and gastric cancers as these TRP channels play a role in tumor cell growth and proliferation (Zeng *et al.*, 2010) [32]. TRP channels have also been reported to be expressed in adipose tissues and reduce obesity by increasing thermo genesis (Yoneshiro and Saito, 2013) [31]. In diabetes, it has been observed that TRPC4 was up regulated and TRPC1 and TRPC6 was down regulated in blood vessels of diabetic patients (Chung *et al.*, 2009) [4]. TRPV4 further, has been reported to influence the release of insulin from pancreatic beta cells (Billert *et al.*, 2017) [3].

Musculo-skeletal system: Expression of TRPA1 has been reported in osteoarthritis and inflammation (Zsombok and Derbenev, 2016) [35]. These channels upon activation lead to influx of sodium and calcium ions that causes depolarization of nerve endings leading to propagation of pain stimulus. Koh *et al.* (2014) [14] reported that down regulation of TRPA1 expression reduced the development of mechanical, thermal, and cold sensitivity. Apart from this, TRPV1 co-expression has also been reported to contribute towards mediating acute and chronic pain modulated by inflammatory mediators (Abbas, 2020) [1].

Conclusion

TRP ion channels have been reported to express in almost all the organ systems of the body influencing various physiological functions either by up-or down regulations. Hence, these ion channels have become a target structure for various drug trials. Drugs either in the form of agonist or antagonists are being used or under trial against various diseases. Selective application of drug molecules to act on the targeted ion channels are required to prevent any cross reaction against the activation of depression of multiple TRP channels.

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