Transient receptor potential ankyrin 1 and calcium: Interactions and association with disease (Review)

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Abstract. Calcium (Ca^{2+}) is an essential signaling molecule in all cells. It is involved in numerous fundamental functions, including cell life and death. Abnormal regulation of Ca^{2+} homeostasis may cause human diseases. Usually known as a member of the transient receptor potential (TRP) family, TRP ankyrin 1 (TRPA1) is the only member of the ankyrin subfamily identified in mammals so far and widely expressed in cells and tissues. As it is involved in numerous sensory disorders such as pain and pruritus, TRPA1 is a potential target for the treatment of neuropathy. The functions of TRP family members are closely related to Ca^{2+}. TRPA1 has a high permeability to Ca^{2+}, sodium and potassium ions as a non-selective cation channel and the Ca^{2+} influx mediated by TRPA1 is involved in a variety of biological processes. In the present review, research on the relationship between the TRPA1 channel and Ca^{2+} ions and their interaction in disease-associated processes was summarised. The therapeutic potential of the TRPA1 channel is highlighted, which is expected to become a novel direction for the prevention and treatment of health conditions such as cancer and neurodegenerative diseases.

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Abbreviations: TRP, transient receptor potential; hTRPA1, human TRP ankyrin 1; CaM, calmodulin; AD, Alzheimer's disease; CYTO, cytoplasm; MITO, mitochondrion; ER, endoplasmic reticulum; SR, sarcoplasmic reticulum; PMCA, plasma membrane calcium ATPase; NCX, sodium calcium exchanger; CaBP, calcium-binding protein; VGCC, voltage-gated calcium channel; SOCC, store-operated calcium channel; IP3R, inositol trisphosphate receptor; SERCA, sarcoplasmic reticulum calcium ATPase; RyR, ryanodine receptor

Key words: transient receptor potential channels, TRPA1 cation channel, calcium, calcium channels, disease progression

Contents

1. Introduction

Calcium ions (Ca^{2+}) are essential electrolytes in the body and have a fundamental role in regulating nerve cell excitation, neurotransmitter release, membrane integrity and muscle contraction. Thus, Ca^{2+}-triggered signalling pathways have an important role in neuron survival, plasticity and nerve transmission.

Over the past decade, transient receptor potential (TRP) channels have attracted increasing attention. TRP ankyrin 1 (TRPA1), a non-selective cation channel permeable to Ca^{2+} ions, is broadly distributed in various parts of the human body and is associated with various physiological and pathological states, such as sensations of cold and pain, as well as itchiness. Numerous studies have explored the role of the channel in the initiation and development of toxicity. The present review summarized the progress of research on the structure, function and distribution of TPRA1, and discussed diseases related to TPRA1 and Ca^{2+}.

2. TRP family

TRP family members are non-selective cation channels that were discovered in the visual system of the fruit fly *Drosophila melanogaster* (1). There are 28 known TRP cation channels with different structures and functions (2). All TRP channels have six transmembrane domains (S1-S6), and both N- and C-termini are located on the cytoplasmic side of the cell membrane. These proteins are thought to function as tetramers. TRP channels allow cations such as Ca^{2+}, Mg^{2+}, Na^{+} and K^{+} to pass through, which leads to cell depolarisation, influx of extracellular Ca^{2+}, release of Ca^{2+} from intracellular Ca^{2+} stores and binding of Ca^{2+} to calmodulin (CaM), ultimately affecting

cell proliferation and apoptosis. The functions of the TRP family are closely related to Ca^{2+}. For instance, TRP cation channel subfamily V member 5 (TRPV5) and TRPV6 are Ca^{2+} uptake channels in epithelial tissues with unique selectivity for Ca^{2+} [permeability (P) ratio P_{Ca}/P_{Na} >100] (3).

In mammals, there are six TRP channel subtypes according to their amino acid sequence homology: The ankyrin TRP TRPA, the canonical TRPC and TRPV, the melastatin TRP termed TRPM, the polycystic TRP known as TRPP and the mucolipin TRP TRPML (4). Although all TRP channels share certain similarities in sequence and structure, there are significant differences in physiological functions, including cation selectivity, ligand binding and sensitivity to temperature and other environmental conditions among family members (5). The members of TRPV subfamily are considered to be heat sensors, nociceptive sensors, mechano-sensors and osmo-sensors (6,7) and the majority of TRPM subfamily members are implicated in taste, gastric hormone secretion and insulin release (7,8). Brain development and vaso-motor regulation have been reported for the TRPC subfamily channels (7-9), while the defining characteristic of the TRPP subfamily is their association with renal development (7-10). Evidence suggests that the TRPML subfamily is associated with endocytosis and the regulation of autophagy (7-9). The TRPA subfamily has been indicated to function as a thermo-sensor, chemo-sensor and olfactory sensor (6,7). The major physiological function of TRP family members in mammals are listed in Table I.

Mutations related to human diseases have been detected in nearly 30 members of the TRP channel family, which highlights their importance in human physiology, and they are likely to continue receiving attention in the future.

3. Structure, distribution and physiological function of TRPA1

Ankyrins are a group of linker proteins located on the membrane cytoskeleton that mediate the attachment of intact membrane proteins to spectrin and actin. TRPA1 was first isolated from human fetal lung fibroblasts in 1999 (11) and was originally called ankyrin-like with transmembrane domains protein 1 (12). It is the only known member of the TRPA subfamily and consists of 119 amino acid residues with a molecular weight of 127.4 kDa.

TRPA1 structure. As all TRP channels, TRPA1 is a tetrameric protein composed of four subunits (119 amino acids) and six transmembrane α-helices (S1-S6), with the pore loop structure located in the hydrophilic region between S5 and 6 (13,14). TRPA1 derives its name from 14-18 ankyrin repeats at the N-terminus (depending on species) in addition to a large number of active cysteine residues (15), which is an unusual structural feature and may be related to its interaction with intracellular components (16).

TRPA1 may be activated by a series of harmful external stimuli and endogenous signals related to cell damage. The latter includes cinnamaldehyde, allicin, allyl isothiocyanate and reactive oxygen species (17,18). The major mechanism of activation is the covalent modification of cysteine and lysine residues at the N-terminus of TRPA1 by highly electrophilic compounds (19). This mechanism promotes local conformational changes, leading to the expansion of the pore loop structure, which increases the permeability to Ca^{2+}. In addition to being activated by reactive electrophiles and oxidants, TRPA1 may also be indirectly activated by the pro-inflammatory factor-mediated phospholipase C signal, in which cytoplasmic Ca^{2+} are an important regulator of channel gating (20). In addition, as TRPA1 is permeable to both univalent and bivalent cations (including Ca^{2+}, sodium and potassium), it is able to depolarise the membrane and activate Ca^{2+} signals (21). The structure of TRPA1 is presented in Fig. 1.

TRPA1 distribution. TRPA1 is a non-selective cation channel present in various tissues and organs, but it is mainly expressed in sensory neurons, such as primary sensory neurons in the lung, skin and brain, and peptidergic neurons (22), particularly those in the mammalian dorsal root ganglion, trigeminal ganglion, nodular ganglion and jugular ganglion (23).

In addition, TRPA1 is also present in several non-nerve cells and tissues, including vascular endothelial cells and chondrocytes (24,25), but the function of this expression has remained largely elusive. The major distribution of TRPA1 in the human body is presented in Fig. 2.

Physiological functions of TRPA1. TRPA1 is a cold-sensitive ion channel that may be activated to generate a stress response to endogenous and exogenous chemical stimulation, cold stimulation, mechanical stimulation and various inflammatory mediators. The activation of TRPA1 is closely related to the conduction and generation of cold sensation, the mediation of pain and analgesia, and the regulation of inflammatory substances.

TRPA1 is not mechanically sensitive under physiological conditions, but it may be activated at temperatures <17˚C (26); hence, it serves as a cold-sensitive receptor that detects changes in temperature in the internal and external environment. In addition to mediating temperature sensation and pain (27), TRPA1 functions in mechanical perception (28) and has a role in certain inflammatory states (29). Furthermore, TRPA1 is also associated with hypersensitivity and overexcitation in certain non-neuronal regions and has an important role in the pathophysiology of asthma, neuropathic pain, chronic itching, migraine, gastrointestinal motility disorders, anxiety and cognitive dysfunction (30-34).

Due to its individual characteristics in different organs, TRPA1 has been actively studied as a potential target for treating various diseases.

4. Ca^{2+} ions

Second messenger is one of the initiating components of intracellular signal transduction. Ca^{2+}, as an ubiquitous second messenger in the cytoplasm, is involved in the regulation of a variety of important physiological processes in cells, such as the synthesis and release of neurotransmitters, regulation of germ cell maturation and fertilization, and regulation of the activities of various enzymes in the body (35). Ca^{2+} is also closely related to hypertension, coronary heart disease, Alzheimer's disease (AD) and numerous other diseases (36-38). The intracellular second messenger Ca^{2+} has been a hot research topic in recent years.

Table I. TRP family members in mammals.

Subfamily	Main physiological function	(Refs.)
TRPV	Thermo-sensation; nociception; mechano-sensation; osmo-sensation	(6,7)
TRPM	Taste; gastric hormone secretion; insulin release	(7,8)
TRPC	Brain development; vaso-motor regulation	(7,9)
TRPP	Renal development	(7,10)
TRPML	Endocytosis and endosomal/lysosomal function; regulation of autophagy	(7,9)
TRPA	Thermo-sensation; chemo-sensing; nociception; olfactory responses	(6,7)

TRP, transient receptor potential channel; V, vanilloid; M, melastatin; C, canonical; P, polycystic; ML, mucolipin; A, ankyrin.

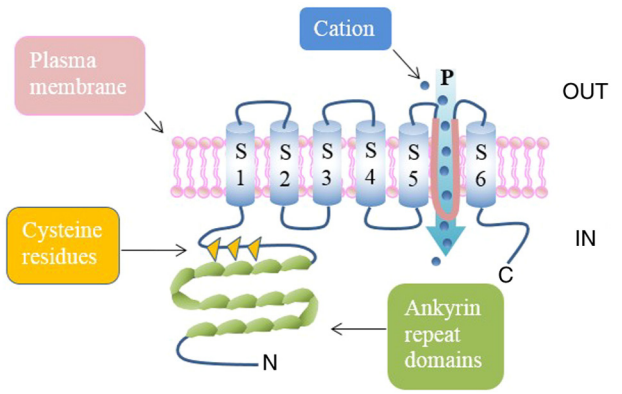

Figure 1. Structure of TRPA1 channel. The schematic diagram displays the six membrane-spanning helices (1-6) of the TRPA1 protein. The intracellular N and C termini are also displayed, along with the pore loop located between helices S5 and 6. TRPA1, transient receptor potential ankyrin 1; P, pore loop.

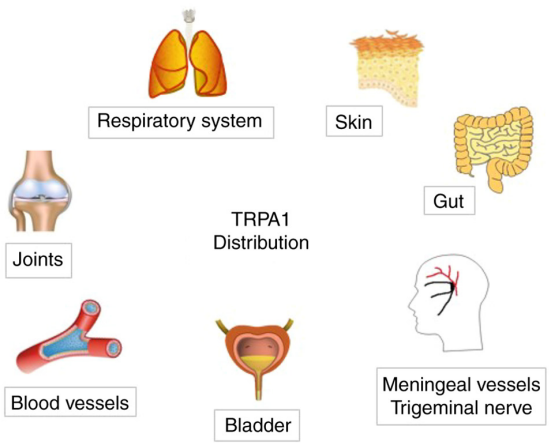

Figure 2. Distribution of the TRPA1 channel in the body. TRPA1 is found in a subset of somatic (dorsal root, trigeminal) and visceral (nodose) primary sensory neurons and it is widely expressed in both neuronal and non-neuronal cells. TRPA1, transient receptor potential ankyrin 1.

The cytosolic free Ca^{2+} concentration in mammalian cells is generally controlled in the range of 100-200 nmol/l, while the Ca^{2+} concentration in extracellular organelles is kept in the order of mmol/l (39). The steep but tightly controlled concentration gradient of Ca^{2+} within and outside the cell membrane, as well as between cytoplasm and organelles, is maintained and dynamically regulated according to cell needs through the cooperative work of a variety of ion channels, ion pumps and transporters (40). The major channels and transporters for intracellular Ca^{2+} cycling are presented in Fig. 3.

Abnormality of any link may cause instability of Ca^{2+} homeostasis. Ca^{2+} homeostasis is essential for cell maintenance; under pathological conditions, Ca^{2+} homeostasis is altered, with increased cytoplasmic Ca^{2+} concentrations. Ca^{2+} channels are a basis for revealing the regulatory laws of Ca^{2+} homeostasis and vital processes. Certain cation channels, including TRP family members, promote the influx of Ca^{2+}. For instance, although TRPA1 has high permeability to Ca^{2+}, Na^{+} and K^{+}, it has high Ca^{2+} selectivity. The PCa/PNa is 6 when the channel opens spontaneously and increases to 9 when the channel is activated by an electrophilic reagent (41).

5. Coupling TRPA1 with Ca^{2+} ions

TRPA1 mediates Ca^{2+} internal flow. Compared with most other TRP channels, TRPA1 has higher Ca^{2+} permeability. The N-terminus of TRPA1 contains two helical Ca^{2+}-binding motifs and the permeation pathway involves two major contraction sites (15), with an aspartate (D918 in mouse, D915 in human) within the pore loop that is critical for Ca^{2+} permeability (13). Total internal reflection fluorescence and confocal microscopy revealed that the signal generated by Ca^{2+} influx from a single TRPA1 channel in endothelial cells is at least 200 times that of L-type Ca^{2+} channels (42). This is because TRPA1 channels exist in the plasma membrane of endothelial cells with a tight binary structure. When one of a pair of channels is opened, afferent Ca^{2+} is able to bind to the Ca^{2+}-sensitive EF-Hand protein domain at the N-terminus, thereby triggering the adjacent channel (43).

There is a highly conserved structural motif in the TRPA1 channel that is the key site of intracellular Ca^{2+} elevation caused by Ca^{2+} storage (44), which explains various Ca^{2+}-dependent processes, including sensitisation, desensitisation and coupling with metabolic receptors. TRPA1-mediated Ca^{2+} influx is involved in various biological processes such as factor secretion (45) and gene transcription (46). TRPA1 is able to induce apoptosis in cardiomyocytes (47), oligodendrocytes (48) and hippocampal neurons (49) by regulating the Ca^{2+} concentration. Increasing evidence indicates that TRPA1-mediated Ca^{2+} influx has a role in determining the pathophysiological state.

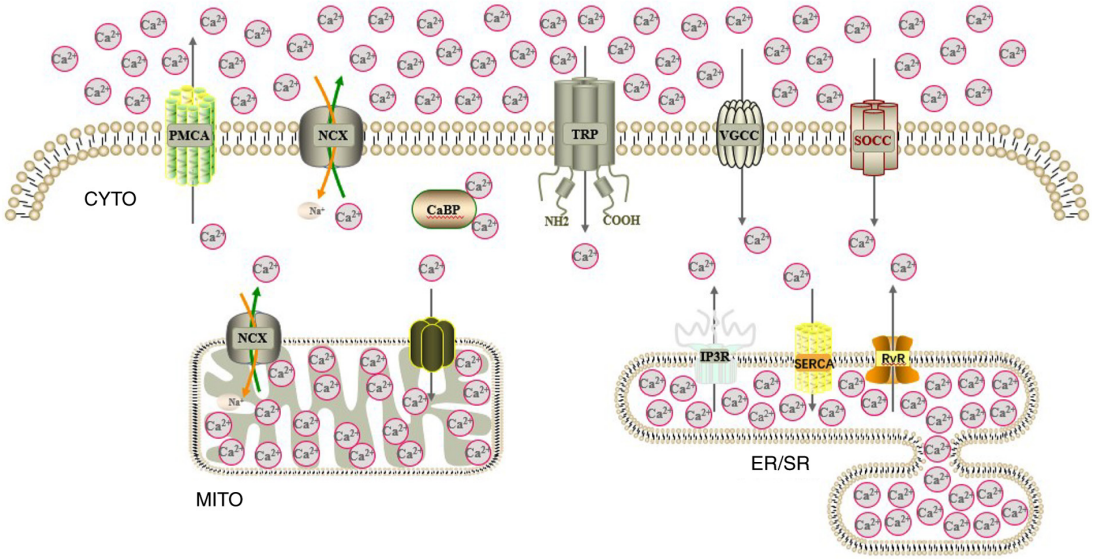

Figure 3. Pattern of mammalian cell Ca^{2+} metabolism. The main channels and transporters for intracellular Ca^{2+} cycling are displayed. Ca^{2+}, calcium; CYTO, cytoplasm; MITO, mitochondrion; ER/SR, endoplasmic reticulum/sarcoplasmic reticulum; PMCA, plasma membrane Ca^{2+} ATPase; NCX, sodium Ca^{2+} exchanger; CaBP, Ca^{2+}-binding protein; TRP, transient receptor potential channel; VGCC, voltage-gated Ca^{2+} channel; SOCC, store-operated Ca^{2+} channel; IP3R, inositol trisphosphate receptor; SERCA, sarcoplasmic reticulum Ca^{2+} ATPase; RyR, ryanodine receptor.

Electrical stimulation of TRPA1 in adult mouse cardiomyocytes may lead to activation of the calmodulin-dependent kinase II signalling pathway (45), thereby regulating the availability and manoeuvrability of intracellular Ca^{2+}. TRPA1 is also the major contributor to the increase in Ca^{2+} in oligodendrocytes caused by ischemia; 70% of the Ca^{2+} increase may be attributed to TRPA1 (50), indicating a key role of the mediation of Ca^{2+} influx in myelin injury. The molecular basis by which TRPA1 regulates nociceptive neurons is also related to Ca^{2+}; TRPA1 induces local Ca^{2+} influx at nerve endings, promotes membrane depolarisation and causes the release of neuropeptides from large dense core vesicles through Ca^{2+}-dependent exocytosis, resulting in further amplification of nociceptive sensation, recruitment of immune cells, vasodilation and neurogenic inflammation (51).

Ca^{2+} regulates TRPA1 activity. Ca^{2+} ions are the most important endogenous regulators of TRPA1 and they enhance and inhibit the activity of this channel under chemical stimulation. Ca^{2+} binds to the Ca^{2+} binding domain at the C-terminus of the molecule, which opens the ion channel. The high permeability of TRPA1 to Ca^{2+} not only triggers the influx of extracellular Ca^{2+}, but also promotes the release of Ca^{2+} from intracellular stores, such as the endoplasmic reticulum (52). Ca^{2+} activation may enhance the responses to other stimuli and desensitise ion channels through a variety of signaling pathways, which in turn regulate the activity of TRPA1.

The opening kinetics of TRPA1 are strongly affected by divalent cations. When Ca^{2+} binds to the channel, the binding of monovalent cations to the channel is hindered. Under the spontaneous opening state, ~17% of the TRPA1 current is Ca^{2+} current (41). Ca^{2+} is able to directly activate TRPA1, which is not only important for the basic reaction of TRPA1 at low Ca^{2+} concentrations (<1 mM), but may also rapidly inactivate TRPA1 at high Ca^{2+} concentrations (>1 mM) (53). Therefore, Ca^{2+} has dual and opposite effects on TRPA1. In addition to direct interaction with TRPA1, indirect interactions occur via cytoplasmic Ca^{2+} binding proteins, among which CaM is the most prominent. TRPA1 binds CaM to form a Ca^{2+}-sensing channel complex, a key Ca^{2+} receptor that responds differently to different Ca^{2+} signals (54). Extracellular Ca^{2+} activates and/or enhances TRPA1 at low concentrations but quickly inactivates TRPA1 following channel activation. This process is called desensitisation or rapid analgesia (55) and this contrasting effect is the result of Ca^{2+} regulating TRPA1 through CaM. Both the N- and C-terminal regions may be important for these interactions. A direct effect for Ca^{2+} on purified human TRPA1 (hTRPA1) independent of CaM has been demonstrated (56); Ca^{2+} is able to directly activate hTRPA1 and cause structural changes by directly interacting with binding sites other than the N-terminal ankyrin protein repeat domain of hTRPA1.

Furthermore, thermal activation of TRPA1 in chameleon, chicken and rat snake depends on extracellular Ca^{2+} binding to negatively charged amino acids near the outer surface of channel pore cells, while other divalent cations cannot activate the heat-evoked current (57). Although TRPA1 is a hypothermic receptor, certain researchers assume that harmful hypothermia does not directly activate TRPA1, but rather that the cold environment stimulates the release of intracellular Ca^{2+} stores (58), activating TRPA1, a Ca^{2+}-dependent ion channel.

6. Interaction between TRPA1 and Ca^{2+} in disease progression

TRPA1 is a neuronal redox-sensitive Ca^{2+} internal flow channel that is overexpressed in human cancers. It upregulates Ca^{2+}-dependent anti-apoptosis pathways and promotes resistance to reactive oxygen species (59). Triclosan, an antibacterial agent, was indicated to induce activation of TRPA1 and Ca^{2+} influx in human prostate cancer stromal cells, resulting in the secretion of VEGF and the growth of prostate cancer epithelial cells (60).

TRPA1 serves as a physiological medium for inflammatory signals and appears to perform a functional role in promoting myoblast migration, fusion and potential activation of human satellite cells. Thus, it may provide a novel target for treating muscle injury or muscle-related diseases via the formation of Ca^{2+}/calmodulin complexes (61).

The inflammatory factor interleukin (IL)-1β increases the functional expression of TRPA1, which leads to Ca^{2+} overload and a significant decrease in mitochondrial membrane potential. Inhibition of TRPA1 has a protective effect on mitochondrial dysfunction and even apoptosis of rat chondrocytes induced by IL-1β (62). Furthermore, the TRPA1 channel may protect against intestinal fibrosis by mediating Ca^{2+} mobilisation, in addition to its anti-inflammatory actions (63).

A considerable amount of research has focused on the role of TRPA1 in nervous system regions and suggests that TRPA1 has a promising prospect in both peripheral and central nervous system regions (64-66).

Current therapies of multiple sclerosis mainly focus on pathological immune responses, but they cannot prevent the progression of clinical symptoms (67). TRPA1 regulates the functions of astrocytes by increasing the intracellular Ca^{2+} concentration (24).

Organophosphate-induced delayed neurotoxicity refers to a series of neurological symptoms that occur within 1-3 weeks after the ingestion of organophosphorus compounds (68). A study from the Shanghai Institute of Pharmacy, Chinese Academy of Sciences, discovered that TRPA1 is the major mediator of delayed neuropathy (69). In the same study, verapamil (an L-type Ca^{2+} channel blocker that effectively relieves the symptoms of the disease) was indicated to have a neuroprotective role by inhibiting TRPA1-mediated Ca^{2+} influx.

There is evidence to suggest that excessive Ca^{2+} in astrocytes may influence synaptic function, and regulating TRPA1 channel activity in astrocytes may provide a novel target for blocking early dysfunction in AD (70).

7. Conclusions and perspectives

After years of in-depth research, TRPA1 has attracted extensive clinical attention due to its function as a chemical sensor for irritation and cell damage, and its relationship with various diseases. For instance, hydrogen sulphide-mediated vasodilation is due to an increase in Ca^{2+} concentration in trigeminal ganglion neurons activated by TRPA1 (71). In addition, TRPA1 is an important subject of toxicology research and is actively studied by pharmaceutical companies (72). However, the functional regulatory mechanisms of TRPA1 remain poorly understood and further investigations may lead to novel protective strategies. In our opinion, areas worthy of further research include the following: i) Unveiling the specific mechanism of the interaction between TRPA1 and Ca^{2+}; ii) exploring the therapeutic potential of TRPA1 in the treatment of pain and airway respiratory diseases through clinical studies; iii) assessing the potential of TRPA1 antagonist as a therapeutic target; and iv) investigating the mechanisms by which TRPA1 regulates Ca^{2+} in different diseases.

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Authors' contributions

FH: Writing-original draft preparation, review and editing. XS: Conceptualization. DL: Supervision, funding acquisition and manuscript revision. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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