REVIEW PAPER

Molecular Determinants, Distribution, Physiology, and Toxicological Significance of TRPA1 Channels

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ABSTRACT

Transient receptor potential ankyrin 1 (TRPA1) is a non-selective cation channel, known to be a polymodal sensor of oxidative, thermal, and chemical signals. TRPA1 is the first member of the TRP superfamily shown to be an ankyrin-rich protein and proven as one of the significant ways of cell's response to stimuli. These aspects render TRPA1 as a redox sensitive signaling because of its non-structural features which entails numerous repeating ankyrins and reactive cysteine residues. It is particularly sensitive to the electrophilic compounds and the reactive oxygen species. TRPA1 is widely expressed in non-neuronal tissues such immune cells, cardiovascular tissues and epithelial cells and in sensory neurons - dorsal root and trigeminal ganglia. Physiologically, it helps in vascular regulation, neurogenic inflammation, thermos-sensation and nociception. In addition to the sensory roles, it has a mounting body of evidence that it is involved in pathological processes such as chronic pain, inflammatory disorders, respiratory ailments, loss of metabolic functions and toxicant-induced tissue destruction. TRPA1 controls cellular reactions to environmental irritants, air pollutants, products of cigarette smoking and industrial toxins, thus gaining the special attention in the field of toxicological research. A better understanding of TRPA1 signaling pathways is the need of time for the development of targeted treatment regimens and improved evaluation for overdose, organophosphate, endogenous and exogenous toxicants.

Keywords: TRPA1 channel, Polymodal sensor, Ankyrin, Cellular response, Toxicants

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1. Introduction:

The electrical activity in cells is definitely one of the most interesting tales of biology that have been investigated. The facts about electrical properties of living tissues must have been almost mystic, tending to rely as they do on amounts that cannot be felt, and which were difficult to measure until this century. Scientists who had an excellent understanding of the physics of their time, but do not appear to have been awe-stricken about the subject, contributed critical passages in the tale. In 1872, Hermann had an insightful idea of the requirements of electrical transport in nerve fibers, which he applied with a correct concept with the cable equations. The pivotal understanding of Nernst (1888) with respect to diffusion potentials was that the voltage difference due to a difference in ion concentration could exist. Making of a voltage, not only demanded a concentration gradient, but necessitated that one of the ions of a salt be more diffusible than the other. To give an example, Cl- will pass ahead of Na+ when the speed of C1- diffusion is higher than Na+ and in this case, the concentration wave in front will have a negative value. At this juncture Bernstein came up with a great idea, that a resting cell membrane excludes the diffusion of all but K +, thus creating an extreme form of a Nernst diffusion potential. Moreover, a postulation of the loss of selective K+ permeability of the membrane simultaneously could have been made to produce a voltage change (Bernstein, 1902). Similarly, at a slightly later period, Overton (1902) has identified that Na+ plays a vital role towards ensuring the excitability of muscle fibers. Even more shocking than it evokes the fact that cell theory was not yet so established, the bilipid membrane was proposed more than 20 years later (Armstrong, C. M. 1999, Armstrong, 1999). These are that ion channels that are large transmembrane proteins that just offer a route by which ion can explosively diffuse across the cell membrane in accordance with their electrochemical potential. The action potentials of the excitable cells are the fast closing and opening of voltage activated Na+ and K+ structure determination

selective channels influenced by variations of the transmembrane. During the past few decades, the knowledge of ion channels has been increased tremendously due to the three-dimensional s using X-ray crystallo-graphy and completing the dynamical motions of the atoms using computational methods as a time dependency (Roux, 2017)

The light-sensing mechanism of fruit fly Drosophila melanogaster is a rhodopsin-based mechanism that is connected to phospholipase-C (PLC) by a GTP-binding (G)-protein. Light leads to the closing of cyclic nucleotide-gated channels of the vertebrates and to an eventual hyperpolarising membrane potential of photoreceptor cells, and to the depolarising membrane current of Drosophila in PLC-mediated opening of membrane channels. TRP channels were identified when a mutation of Drosophila was identified that had a temporary rather than long response to light. The mutant photoreceptor cells were then measured to be in a plateau-like receptor potential which came to be known as trp (transient receptor potential). In 1989, the trp gene was cloned (Pedersen et al., 2005). The first characterization of transient receptor potential (TRP) channels was done in Drosophila where mutations in trp genes in photoreceptors resulted in a transient voltage response to prolonged light. Unlike TRP channels, most ion channels are grouped based on their homology, but not on the functional use or selectivity of the ligand due to the heterogeneous nature of their functions and poor knowledge of them. They can be termed as store operated channels (SOCs) which is abstract and an occurrence that is not clearly understood. Functions that are known are diverse. Hypertonicity is sensed and responded to in the TRP channel in yeast. Their noses have tips of neuronal dendrites that have TRP channels that are utilized by the nematodes to detect and intercept any harmful chemicals. TRP channel that detects pheromones is menace in male mice to differentiate between males and females. The use of TRP channels enables human beings to experience a taste of sweetness or bitterness as well as umami (amino acid) and the perception of warmth, heat and cold. In both of them, the mediator role of TRPs in the process of sensory transduction is not only classical in a traditional charity, but also of the particular cell. The genes of the TRP channel are virtually known to be present in all mammals (Clapham, 2003)

The discovery of TRPA1 as a broadly expressed (it is present in most tissues) and ankyrin-rich TRP channel to chemical irritants and thermal stimuli has directed extensive research on its role in sensory transduction and pathology. TRPA1 attracted attention due to its occupation as a polymodal sensor to harmful chemicals and temperature that have a direct compulsion between environmental stimuli and pain and inflammation. The first studies proved that TRPA1 can be activated by environmental irritants, electrophilic compounds and even inflammatory mediators so it is a significant molecular sensor of cell injury and harmful stimuli. Its ubiquitous presence in neurons and non-neurons, as well as the demonstration of the relationship of it to the perception of pain, thermosensation, inflammation and oxidative stress, further highlighted its physiological and pathological importance. Moreover, it was the revelation that TRPA1 is species-specifically thermosensitive and evolved in response to its required functions that allowed it to be used as a valuable instrument in the investigation of the biology of sensory in a variety of organisms. TRPA1 (wasabi receptor, ankyrin-like with transmembrane domains protein 1, ANKTM1) got its name because of the numerous ankyrins repeat domains (ARKTMs) in the N-terminus. It was firstly cloned in 1999 in human fibroblasts, and appears in band 8q13 on human chromosome 8. TRPA1 is a nonselective cation nonselective homotetrameric cation channel where every monomer contains six transmembrane domains (S1-S6) each of which has cytoplasmic N- and C- terminals and the loop of pore is between S5 and S6. TRPA1 is very abundant in many tissues and organs and occurs in neuronal cells such as dorsal root ganglion (DRG) neurons, trigeminal ganglia (TG) neurons, nodose ganglia neurons and non-neuronal cells such as astrocytes, hair cells, ventricular cardiomyocytes, pulmonary epithelial cells and other immune cells (H. Zhang et al., 2022)

2. Methodology:

A comprehensive e-database search was performed on PubMed, Scopus, Web of Science, and Google Scholar was conducted to in order to retrieve relevant experimental, mechanistic, preclinical, clinical and translational articles related to identify the molecular determinants, distribution, physiological roles, toxicological significance and future prospects of transient receptor potential ankyrin 1 (TRPA The literature search was limited to only those articles that were published within the last 2 decades, that is, 2000-2025. The following MeSH (Medical Subject Headings) and free-text terms were used in the literature search: TRPA1 channel, transient receptor potential ankyrin 1, polymodal receptor, ankyrin repeat domain, redox signaling, reactive oxygen species, electrophilic activation, nociception, neurogenic inflammation, ion channel physiology, oxidative stress, environmental toxicants, air pollutants, cigarette smoke, and industrial chemicals. To gain mechanistic information, pathway-related terms related to calcium signaling, MAPK signaling, NF-κB pathway, oxidative stress pathways, and inflammatory signaling were included in the literature search. Eligible studies comprised original research articles, referred and cited review articles written in English containing information for the provided mechanistic, structural, physiological, or toxicological insights into TRPA1 channel function. Such selected studies and claims were employed to carry out a qualitative synthesis aimed

at identifying common molecular mechanisms of TRPA1 activation, its tissue-specific distribution, physiological functions, and its involvement in pathological and toxicological processes. This integrative approach enabled the identification of key signalling pathways, functional correlations, and potential therapeutic implications associated with TRPA1 channel activity.

3. Discovery of TRPA1 channels

The explanation of Transient Receptor Potential Ankyrin 1 (TRPA1) channels has been the subject of much development since the discovery of the entire TRP family in 1969 in Drosophila. The particular scientific path of TRPA1 started in 1999 when it was first cloned and discovered in human fibroblasts, it was then known as ANKTM1. In the next few decades, much characterization was done to identify its importance as a polymodal sensor especially in chemical nociception, airway chemo-sensation, and detection of irritants. As a unique covalently activated ion channel, TRPA1 has received a lot of interest not only as a central mediator in pathophysiological states (including pain, inflammation, and respiratory diseases) but also as one of the most promising therapeutic targets. Moreover, it has lately grown to be relevant to other areas other than human health, with its orthologs in other species, such as Spodoptera frugiperda, as new molecular targets in agricultural pest management approaches. Table 1 summarizes the important chronological events of discovery and functional characterization of TRPA1 channels.

Table 1: The discovery of TRPA1 channels

Year	Discovery	References
1969	First identification of TRP channels in Drosophila (basis for later TRP family research)	(Jordt & Guimaraes, 2006)
1999	First cloning/identification of TRPA1 (then named ANKTM1) from human fibroblasts in a screen for transformation-sensitive proteins.	(Caspani & Heppenstall, 2009)
2006	TRPA1 role in chemical nociception and activation mechanisms characterized further	(Taylor-Clark et al., 2008)
2008	TRPA1 involveme4nt in airway chemo sensation and irritant sensing highlighted.	(Bessac & Jordt, 2008)
2015	TRPA1 is a unique covalently activated ion channel with strong genetic, pharmacological, and pathological evidence supporting it as a promising therapeutic target for pain, respiratory, itch, and inflammatory diseases, although key mechanistic and translational challenges remain.	(J. Chen & Hackos, 2015)
2017	A key mediator of OPIDN is TRPA1 (Transient receptor potential cation channel, member A1).	(Viswanath et al., 2023a)
2020	TRPA1 recognized as a therapeutic target in pain, inflammation, chronic cough, and respiratory disorders; pharmacology explored.	(Viswanath et al., 2023b)
2023	Identification the complete TRP gene repertoire in Spodoptera frugiperda and demonstrated that SfruTRPA1 functions as both a thermal and chemical sensor, highlighting its potential as a novel molecular target for pest control strategies.	(Y. Zhang et al., 2024)

4. Classification of TRPA1 channel:

Transient receptor potential (TRP) channels are polysensory receptors that are classified into seven subfamilies as shown in fig.1: TRPC, TRPM, TRPV, TRPA, TRPP, TRPML, and TRPN (Yang et al., 2025). They are divided into two broad groups, based on sequence and topological variation: Group 1 TRPs (TRPC, TRPV, TRPM, TRPA, and TRPN): The group has the greatest homology of sequence with the Drosophila TRP prototype. Such channels are characterized by six transmembrane segments, a pore loop, and highly conserved TRP boxes 1 and 2. Although mammals lack TRPN proteins, mutations in other members can result in human diseases. e.g., TRPC6 mutations result in glomerulosclerosis, and TRPM6 mutations cause hypomagnesemia. Group 2 TRPs (TRPP and TRPML): These channels do not have a close sequence relationship with Group 1, but have a broad loop between the first two transmembrane domains. As a possible, more ancient evolutionary group, their first proteins were reported to be mutant gene products that cause autosomal dominant polycystic kidney disease (ADPKD) and mucolipidosis type IV (MLIV).TRP channels typically act as non-selective cation channels in the plasma membrane, depolarizing cells to a wide variety of sensory stimuli including taste, smell, light and Mechanosensation, and so controlling many pathophysiological states (Andersson, 2024).Among the wider superfamily, the TRPA1 channel is a calcium-permeable, temperature-sensitive receptor that is specific to detecting harmful signals, such as extreme cold and reactive chemicals (David E. Clapham 2003).

Electrophiles, including mustard oil (MO), acrolein, and allyl isothiocyanate (AITC) cause massive activation of TRPA1 by covalently modifying particular cysteine residues in its cytoplasmic domain (Y. Zhang et al., 2024). TRPA1 is highly expressed in primary sensory nerve terminals, CD4+ T lymphocytes, and non-neuronal cells of the skin, making activation of TRPA1 a causative event of cutaneous inflammation, which increases proinflammatory cytokines such as Interleukin-1 (IL-1). The pharmacological loss or inhibition of TRPA1, therefore, effectively reduces inflammation of diseases such as atopic dermatitis (Wu et al., 2022)

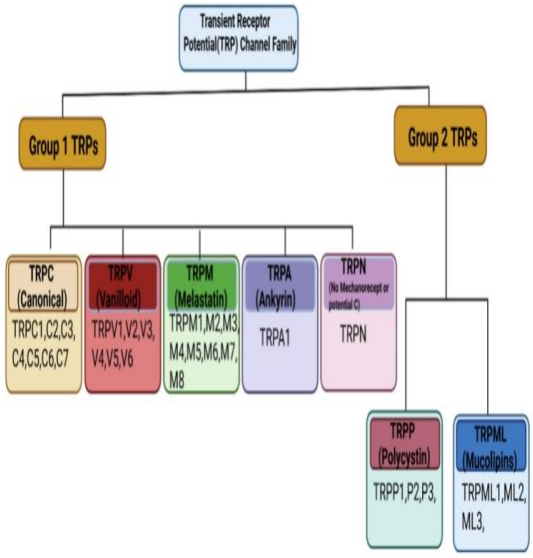


Figure 1: Classification of TRPA1 channel

Based on structural and functional traits, the diagram shows how the Transient Receptor Potential (TRP) channel family is divided into two main categories. TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), and TRPN are the five subfamilies of Group 1 TRPs, also referred to as classical TRP channels. The TRPA subfamily in mammals is represented by a single member, TRPA1, whereas the TRPC, TRPV, and TRPM subfamilies have several members. Non-mammalian organisms typically contain TRPN channels. The TRPP (polycystin) and TRPML (mucolipin) subfamilies make up Group 2 TRPs, often known as non-classical TRP channels. In general, the diagram draws attention to the variety of TRP channels and the distinct role that TRPA1 plays within the TRPA subfamily.

5. Molecular Structure of TRPA1 Channels:

TRPA1 is a protein of the TRPA family, but it contains a unique N terminal repeat ankyrin repeats (ARs) sequence, without which interaction with molecular chaperones and ligands is not possible. On the contrary, C-terminus of TRA1 is a nonselective cation channel with high Ca2+ permeability due to the presence of six transmembrane widths and a pore that is formed between TM5 and TM6 as shown in fig.2. TRPA1 has been identified as a temperature-sensitive TRP channel in many species. The mammalian TRPA1 has been shown to be a cold receptor in rodent and a natural bidirectional temperature sensor in people (Qian et al., 2025).

The homotetrameric nonselective cation channel TRPA1 has six transmembrane domains (S1-S6) and cytoplasmic N- and C-terminals. The pore loop is found between S6 and S5. TRPA1 can be found on non-neuronal cells such as astrocytes, hair cells, ventricular cardiomyocytes, pulmonary epithelial cells, and in various immune cells and in neuronal cells such as in the dorsal root ganglion (DRG), trigeminal ganglia (TG) and nodose ganglia neurons. TRPA1 is widely found in numerous tissues and organs. Transient Receptor Potential (TRP) ion channels are multimodal cation channels that participate in many physiological and pathological conditions (Close et al., 2025)

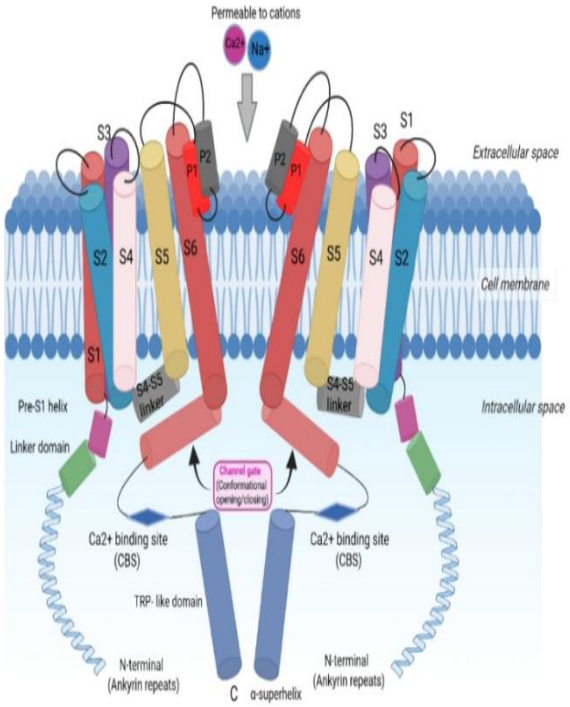


Figure 2: Structure of TRPA1 channel

The TRPA1 ion channel, a tetrameric, non-selective cation channel that spans the cell membrane with separate external and intracellular sections, as seen in the diagram. Each subunit has six transmembrane helices (S1–S6). The major ion-conducting channel that permits Ca2+ and Na2+ inflow is formed by the S5–S6 segments and related pore loops (P1 and P2). While the pre-S1 helix and linker domain link cytoplasmic components to the membrane region, the S1–S4 region serves as a sensor domain. Transmitting conformational changes during channel gating (opening and closing) depends on the S4–S5 linker. On the intracellular side, TRPA1 has a lengthy N-terminal

domain containing ankyrin repeats, a TRP-like domain, Ca2+ binding sites (CBS) for regulatory control, and a C-terminal α-superhelix, all of which support signal detection, channel stability, and ion permeability modulation.

6. Tissue Distribution of TRPA1 channel:

TRPA1 was first identified as a hypothetic transduction channel in the inner ear (organ of Corti), and which played a role in hearing, and a nociceptive channel that is expressed in sensory cells in the dorsal root ganglia (DRG), trigeminal ganglia (TG) and nodose ganglia which detects cold and pungent compounds. However, there is accumulating evidence that TRPA1 is a widely expressed channel that is expressed in numerous tissues and organs as shown in fig. 3 (Nilius et al., 2012)

6.1 Sensory neurons and peripheral nervous systems

TRPA1 is also found in small myelinated (A -) and unmyelinated (C) axons in TG, and is seldom identified in large myelinated axons. Non-peptidergic neurons were turned out to be isolectin B4 (IB4; ~45) and more than one-quarterth (25-percent) of the neurons were found to contain TRPA1. The DH and trigeminal caudal nucleus (Vc) terminals of the superficial laminae are highly expressed (Nilius et al., 2012).

The TRPA1 is very much expressed in the pelvic nerve (PN) neurons that innervate the colon. These neurons have axons that originated at DRG, thoracolumbar (TL) and lumbosacral (LS).TRPA1 has been implicated in the expression in the bladder afferents of the lumbosacral plexus which serves the bladder (DRG level L6-S1 DRG) that causes hyperreflexia the afferent path C-fiber.TRPA1 occurs in prostate nerves that are positive to CB1, CB2, CGRP, nitric oxide synthase (NOS) or vesicular acetylcholine transporter (VAChT). Its gene has been reported to be expressed in diverse tissues in multiple species (rats and mice) which include the dorsal root ganglion (DRG) and trigeminal ganglion (TG) sensory neurons as well as in some cells (keratinocytes, macrophages and neutrophils) (Kudsi et al., 2022)

6.2 Central nervous system

One can see that TRPA1 is expressed by the central nervous system (CNS). As the hippocampus develops, TRPA1 is linked with the opening of the cannabinoid receptor CB1. Also, it is expressed in the neurons of the nucleus supraopticus. TRPA1 is involved in the regulation of glutamate release and can be found in the visceral afferent path in the brain stem. The expression of TRPA1 could be linked with the regulation of the inhibitory synapses in astrocytes which is involved in forming as well as functioning of the synapses. The activation of TRPA1 causes frequent and strongly localized, so-called spotty Ca2+ membrane-near microdomains. The GABA transport of TRPA1 channels caused the decrease in the astrocyte resting Ca2+ concentrations, resulting in reduced efficiency of the interneuron inhibitory synapses, which increased the contents of extracellular GABA (Nilius et al., 2012)The distribution of TRPA1 channels at the tissue, cellular, and subcellular levels in the human body is depicted in the diagram. TRPA1 is found in neurons and is widely expressed in sensory systems, such as the trigeminal and

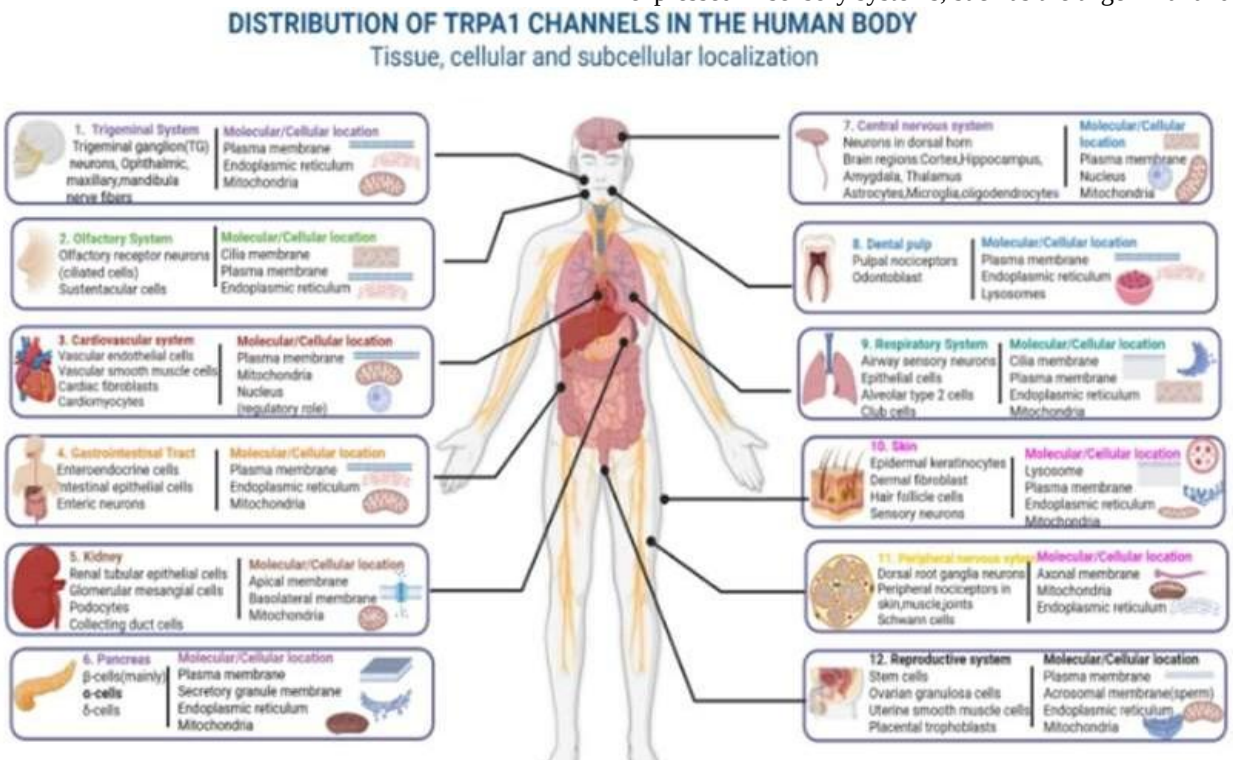


***Figure 3**: Distribution of TRPA1 channels in the human body*

olfactory systems, where it is linked to chemical and pain perception. Major organ systems like the kidneys (tubular and glomerular cells), pancreas (α, β, δ cells), gastrointestinal tract (enteroendocrine and epithelial cells), and cardiovascular system (endothelial cells, cardiomyocytes) all include it. Furthermore, TRPA1 is expressed in the skin (keratinocytes, fibroblasts, sensory neurons), dental pulp, peripheral nervous system, reproductive system, respiratory system (airway neurons and epithelial cells), and central nervous system (neurons and glial cells). TRPA1 is mainly found in the plasma membrane at the subcellular level, but it is also present in organelles like the endoplasmic reticulum, mitochondria, lysosomes, nucleus, and cilia, suggesting that it plays a variety of roles in cellular signaling, sensory transduction, and physiological regulation across various body systems.

6.3 Inner ear

The unique ARD-structure of TRPA1 implied that it could be an inner ear mechanosensitive channel. TRPA1 is expressed in the stria vascularis, the organ of Corti and the outer and inner hair cells (OHCs and IHCs) of the cochlea (Nilius et al., 2012). The spiral ganglion nerve fibers and those of the OHCs and IHCs were found to have immunoreactivity to TRPA1 but none was seen in the spiral ganglion cell and the lateral wall of the cochlea. The VHCs were found to be immunoreactive to TRPA1 in the sensory hairs in the vestibular end organs. Nerve fibers were observed in the VHCs, and were immunofluorescent (Cao et al., 2012)

6.4 Kidney

Ca2+ permeability is influenced by the nonselective transmembrane cation channel known as transient receptor potential ankyrin 1 (TRPA1). Neuronal TRPA1 functions as a molecular integrator of cellular stress, including ROS, and a sensor of harmful signals. Recent research has shown that renal epithelial tubular cells, among other non-neuronal cell types, express TRPA1. One of TRPA1's primary roles in non-neuronal cells is to promote inflammation [24]. For instance, cigarette smoke, a significant oxidant, stimulates lung epithelial cells, increasing the synthesis of IL-8 through TRPA1. Cigarette smoke-induced lung inflammation in mice is mediated via epithelial TRPA. However, it is still unknown if TRPA1 contributes to the inflammation and damage caused by IR in the kidney. Recent research has shown that TRPA1 may prevent IR injury caused by sepsis or Ang II by regulating mitophagy and mitochondrial biogenesis or by preventing inflammation mediated by macrophages (Nilius et al., 2012)

6.5 Cardiovascular system

TRPA1 activity has shown links with the responses of endothelium-derived hyperpolarizing factor (EDHF) in vascular endothelial cells. TRPA1 channels located on perivascular neurons mediate vasodilatation of peripheral and cerebral arteries in response to chemical agonists by the release of CGRP. TRPA1 is mainly located at the endothelium at myoendothelial junction. It requires the presence of small and intermediate conductance Ca2+-activated K+ channels in order to stimulate endothelium dependent smooth muscle cell hyperpolarization, as well as, vasodilatation (Nilius et al., 2012)

Numerous medical professionals are not quite familiar with cardiac complications associated with organophosphate and carbamate poisoning. The majority of them are noted within the initial couple of hours of exposure. These complications have hypoxemia, acidosis and electrolyte derangements as the key predetermining factors. Once the condition is diagnosed, the patient is supposed to be rushed into an intensive/coronary care unit where she is supposed to be well monitored and provided with resuscitative units. The secrets to the effective management of such cases are intensive supportive treatment, care in terms of respiration and administration of Singapore Med J 2004 Vol 45(8) : 389 atropine in good doses very early in the course of the illness (Karki et al., 2004)

6.6 Pancreas

TRPA1 is highly expressed at rat pancreatic islets. Both 15-deoxy-Delta [12, 14]-prostaglandin J2 (15dPGJ2) and allylisothiocyanate significantly promoted Ca2+ influx in 8 cells, and the results of electrophilic stimulation are inhibited by some TRPA1 inhibitors. TRPA1 collaborates with intestinal odorant receptors (ORs) of the colon and small intestine. Enterochromaffin cells are also relatively highly expressed with TRPA1 in the GI tract. TRPA1 agonists have been shown to emulate serotonergic mechanisms to delay stomach emptying in vivo (Nilius et al., 2012).

TRPA1 channel was found in mouse dorsal root ganglion (DRG), pancreatic (Pan) and pancreatic islets (Isl) and absent in a hamster pancreatic alpha cell line, INR1G9 (Fig. 1a) using RT-PCR technique. Western blot test revealed that the traces of TRPA1 protein are present in RIN cells (Fig. 1b). Moreover, immunohistochemistry assays revealed that TRPA1 was strongly and selectively expressed in pancreatic islets and insulin stained the TRPA1-positive cells in the rat pancreatic islets (Fig. 1c). Specificity of the antibody association was confirmed by preabsorption of antibody through incubating the antibody with TRPA1 blocking peptide (Cao et al., 2012)

6.7 Gastrointestinal tract

TRPA1 interacts with intestinal odorant receptors (ORs) on

the colon and the small intestine mucosal. TRPA1 is also relatively expressed in enterochromaffin cells located in the GI tract. Agonists of TRPA1 have been shown to induce serotonergic pathways to delay stomach emptying in vivo (Nilius et al., 2012)

In response to RT-PCR and immunostaining, the expression of TRPA1 has been examined in stomach-labelled DRGand nodose neurons and afferent nerve terminals of the gastric wall. TRPA1 has been observed to be expressed in the nodose neurons in the labelled rat duodenum. There was also a lot of co-expression between TRPA1 and TRPV1 which was evident in the stomach. TRPA1 mRNA and protein were identified in mouse colonic afferent neurons in DRG neurons at the thoracolumbar and lumbosacral levels. They generally co-express with TRPV1, and they have substance P and CGRP (Yu et al., 2015)

6.8. Respiratory system

TRPA1 is mainly located in different nonneuronal cells that constitute the pulmonary system where it is not essential to the functioning of normal airways but rather plays a critical role when acquired diseases are present. Studies show that the activation of TRPA1 could affect the secretion of chemokines of inflamed airways (Nilius et al., 2012)

Interestingly, biophysical and pharmacological properties of TRPA1 bear some resemblance to the hypothetical reactive airway irritant receptor. Firstly, imaging and electrophysiological studies have shown that TRPA1 is expressed in a sub-group of TRPV1- expressing C-fiber neurons and is open to calcium ions. This finding is in agreement with past reports that indicated that reactive airway irritants stimulate calcium ion influx on a subgroup of capsaicin sensitive neurons. Second, ruthenium red is a TRPA1 antagonist that was reported able to prevent bronchoconstriction by irritants. Third, pretreatment of capsaicin makes C-fibers unresponsive to mustard oil and chemical irritants of the airways. Fourth, mustard oil is already a potent irritant of the upper airways, as the sushi enthusiasts can attest when they enjoy the nosebleeding experience of wasabi. Taken together, these facts provoked a further investigation of the role of TRPA1 in the chemical sensing of the airways (Bessac & Jordt, 2008)

6.9 Skin

The activation of TRPA1 in non-neuronal skin cells, e.g., in human keratinocytes and fibroblasts, participates in the regulation of the secretion of eicosanoids, encompassing prostaglandin E2 (PGE2) and leukotriene B4 (LTB4), and in the induction of a sustained local erythema. There is also co-location of TRPA1 and the melanocyte marker pMel-17 in the basal epidermis. Research has revealed that TRPA1 in melanocytes can regulate the activity of the proinflammatory cytokines; that is, interleukin-1a, interleukin-1b (IL-1a, IL-1b) (Bernd Nilius et al 2012).

The expression and contribution in non-neuronal cells, including skin cells like keratinocytes and melanocytes, mast cells, dendritic cells or endothelial cells over the last few years have been of imminent importance. TRPA1 seems to play a critical role in a chain of physiological processes of the skin, including formation and regeneration of physico-chemical barriers of the skin, skin cells and tissue growth and differentiation. TRPA1 also appears to play a role in different immunological inflammatory diseases and skin cancer, atopic and allergic contact dermatitis, psoriasis, bullous pemphigoid, cutaneous T-cell lymphoma, and melanoma, all appear mechanistically to involve [TRPA1] (Maglie et al., 2021)

6.10 Dental pulp

Activation of TRPA1 promotes the release of the eicosanoids, prostaglandin E2 (PGE2), and leukotriene B4 (LTB4) in non-neuronal skin cells, including human keratinocytes and fibroblasts, leading to the occurrence of a prolonged local erythema. Also, the melanocyte marker, pMel-17, and TRPA1 co-localize in the epidermal basal layer. The studies have determined that TRPA1 influences the release of proinflammatory cytokines such as interleukin-1 alpha and beta (IL-1 a, IL-2 b) in melanocytes (Nilius et al., 2012)

TRPA1 has been reported to be expressed in cells of dental pulp, odontoblasts18,19 and induced in inflamed or damaged pulp18. The functionality of TRPA1 channels has been shown to be regulated by cariesinduced inflammation, which may be a potential cause of inflammatory hyperalgesia. A majority of their recent studies have shown that dentin hypersensitivity which develops after dentin exposure and is mechanically aroused is linked to opening of the TRP channels and consequently, to the activation of the intradental nerve (C. Chen et al., 123 C.E.)

6.11 Stem cells

Epidermal epidermal neural crest-like stem cells of newborn mice may grow into Schwann precursor cells, pigmented melanocytes, chondrocytes or functioning sensory neurons bearing TRPA1 and voltage-gated silicon channels (Nilius et al., 2012)

It turned out that TRPA1 positively impacts the maturing of CMs. Knockdown of TRPA1 resulted in nascent cell architecture, impaired Ca2+ homeostasis and electrophysiological functions, and slower metabolic rate in ESC-CMs. The mitochondrial biogenesis and fusion were linked to ESC-CMs that had been perturbed by TRPA1 knockdown to be immature. Mechanistically, it is established that the most important transcriptional coactivator associated with mitochondrial biogenesis and metabolism, peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 alpha) was reduced by

TRPA1 knockdown (Ding et al., 2023)

6.12 Urogenital tract:

The suggestion of a role in the pathogenesis of a range of diseases of the male and female urogenital tract such as neurogenic bladder dysfunction, cystitis and vulvodynia, is suggestive, but to date has not been followed through with regard to the characterisation of TRPA1 in human genital tissues. Because of the findings, the hypothesis was put forward that TRPA1 has a role in the mechanism of sensory (afferent) transduction, which depends on the NO/cyclic GMP pathway, in the vagina and in the regulation of secretory (also mediated by cyclic GMP) activity of the tissue of seminal vesicles glandular tissue (Ückert et al., 2017)

Vaginal wall was found to have transcriptional and protein levels of TRPA1. The evidence of TRPA1 being expressed in nerve fibres and epithelial cells, which too express CGRP and nNOS, indicate that the cation channel protein can potentially contribute to the activation of normal sensory (mechanoafferent) transduction in the vagina. Its findings suggest that a process like this is also dependent on the availability of the nitric oxide/cyclic guanosine monophosphate when using isolated vaginal smooth muscle and compounds known to excite TRPA1) may show whether or not TRPA1 appears to mediate the keeping of vaginal function (Ückert et al., 2015)

7 Mechanisms of Activation of TRPA1 channel:

The transient receptor potential (TRP) channel superfamily are polymodal cell-membrane receptors involved in sensory transduction in response to numerous stimuli. They can be activated by direct ligand interaction, depletion of intracellular stores of Ca2+, Ca2+/calmodulin mediated activation, and osmotic stress, temperature changes, pheromones, taste, mechanical stimulation and other stimuli. Even though TRPA1 is a cold sensor and triggered by various strong compounds, some of which include allyl isothiocyanate (AITC), its sensitivity to temperature in mammals remains controversial. Among the stimuli that activate TRPV1, there are high temperatures (>43 o C), acids, and capsaicin that is present in spicy chili peppers.Initially TRPA1 was considered a thermal channel that is activated by low temperatures. What remains unclear is the how TRPA1 acts mechanosensoryly and the influence of TRPA1 on mechanical sensitivities of sensory neurons. TRPA1 is mechanosensitive, being activated by hypertonic solution (HTS), but not by hypotonic solutions. Electrophilic substances stimulate TRPA1 to generate large inward currents and largely abolish outward rectification (Bb). Conversely, outward rectification is also observed during the activations of TRPA1 by non-electrophilic compounds. The cause of such variations still needs to be identified. The abundance of extracellular Ca2+ ([Ca2+] e) affects the TRPA1 currents. TRPA1 currents decrease (decay, desensitization C) in the presence of [Ca2+], and current activation and current decay are prolonged in the absence of agonists. The N terminal of the channel covalently contains the cysteine amino acid, which is altered by the electrophilic agonists such as AITC to activate the channel. Non-covalent agonists of TRPA1 work on Carvacrol (Miho Hashimoto et al 2023)

7.1 Electrophilic activation

TRPA1 has a wonderful gating promiscuity. Nucleophilic cysteine and lysine residues in the N-terminus of the channel are modified by the environmental, dietary or endogenous electrophilic TRPA1 ligands. MO allyl isothiocyanate is one of the most efficient electrophilic activator of TRPA1. Also, cells generate hydrogen peroxide (H2O2), which is a household and factory chemical that triggers TRPA1 to generate pain as described in fig.4. TRPA1 is as a rule activated by reactive oxygen species (ROS) resulting in cysteine oxidation or disulfide formation, reactive nitrogen species (RNS) such as nitric oxide (NO) which mediate S nitrosylation, and reactive carbonyl species (RCS) such as electrophilic prostaglandins (PG) and 0/H unsaturated aldehydes that. And group of DRG neurons respond to endothelium tetrahydrobiopterin (BH4), an essential co-factor in NO production, by the activation of TRPA1. DRG neurons become sensitive to near ultraviolet (UVA) light by TRPA1. UVA radiation activates TRPA1 currents in the membrane-delimited and wavelength-dependent way. TRPA1 is a possible molecular candidate in the occurrences that cause painful or a burning sensation during photodynamic therapy or after the local application of hydrogen peroxide since light-induced activation of TRPA1 is instigated by increased ROSs and presents another method of activation.

Some molecules of tear gasses, such as dibenz oxazepines, 1 H-dibenz azepines (morphanthridines), and methyl isocyanate, activate TRPA1. Stimulation of TRPA1 is possible by ozone, but TRPV1 is resistant. Also, the cells also generate hydrogen peroxide (H2O2), a frequently used domestic and industrial chemical that triggers TRPA1 to generate discomfort. Powerful TRPA1 activators are such release factors of tissue damage in the form of 4-hydroxynonenal (4-HNE) and some other endogenously produced alkenal, 4-oxononenal in exposed workers. The analgesic drugs are often tested on animal models due to the fact that formaldehyde and its aqueous form formalin are direct activators of the TRPA1. A nonspecific cysteine alkylating agent, iodoacetamide, elicits painful reactions due to its ability to activate TRPA1.

Additionally, disulfiram (Antabuse), a medication used to treat alcoholism, and chlordantoin, an antifungal medication, activate TRPA1 (Bernd Nilius et al 2012).

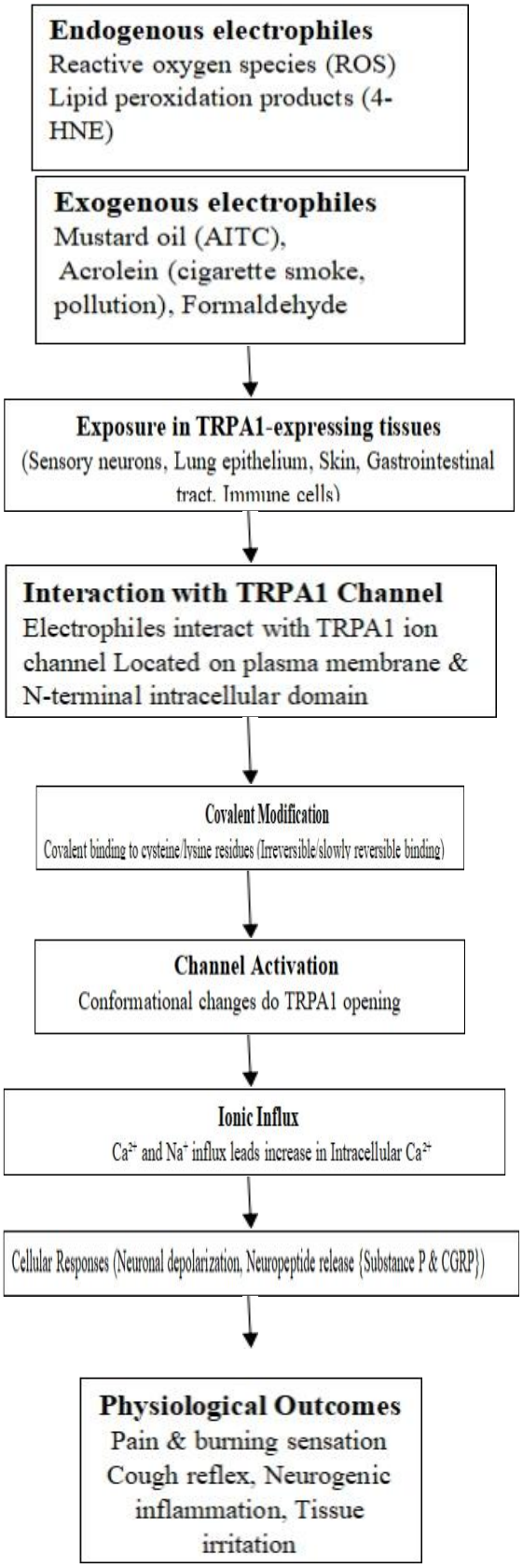


Figure 4: Electrophilic activation of TRPA1 channel

7.2 Non-electrophilic activation

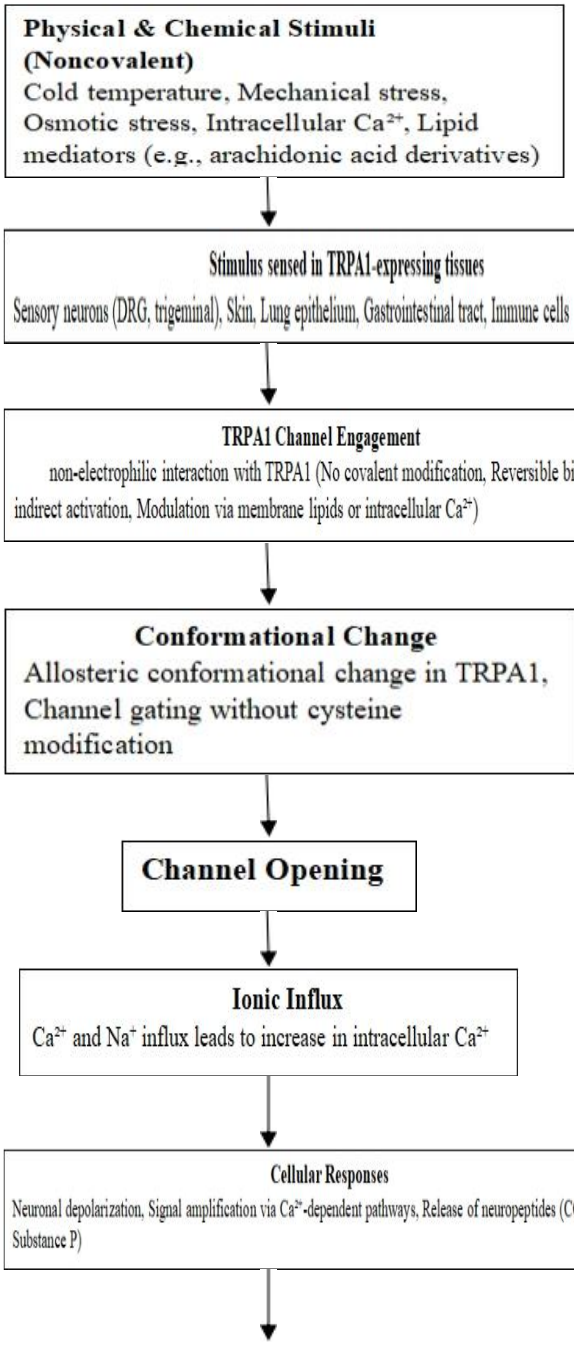
Besides the enormous number of electrophilic activators, there are also other substances that are unlikely to induce covalent changes of the channel proteins that can affect TRPA1.TRPA1 is mostly paradoxically activated and sensitized due to anesthetics. Anaesthetic propofol or 2,6-diosopropylphenol is an intravenous drug of excruciating discomfort when administered. TRPA1 is largely involved in triggering sensory neurons with propofol. Intravenous and inhalation GAs activate sensory neurons by a specific activation of TRPA1, which are known as clinical doses of toxic drugs. Local anaesthetics (LA) stimulate the irritant receptor TRPA1. Lidocaine blocks neuronal excitability, but may act as a TRPA1 agonist in a concentration-dependent manner, by blocking Na + channels of voltage-gated channels. Moreover, TRPA1 may also be sensitised and activated by fenamate nonsteroidal anti-inflammatory drugs (NSAIDs).

Many no electrophilic NSAIDs (including flufenamic, niflumic, and mefenamic acid) and flurbiprofen, ketoprofen, diclofenac and indomethacin are reversibly activated by TRPA1. TRPA1 antagonists inhibit the response to fenamate agonists. Also, TRPA1 activators like electrophilic compounds are potentiated by fenamate NSAIDs. Metabolism of non electrophilic substances to electrophilic products may affect the TRPA1 functionality. N-acetyl-p-aminophenol, or paracetamol, acetaminophen or APAP is the most widespread antipyretic/analgesic drug in the world. One of the products of APAP 2 N-acetyl-p benzoquinoneimine (NAPQI) is a potent liver toxin, which leads to severe liver poisoning in case of an overdose. NAPQI is an electrophilic chemical provoking TRPA1, as other TRPA1 agonists do, leading to neurogenic airways inflammation. Dicarboxyles of p-hydroxybenzoate (e.g., parabens), a type of alcohol frequently employed as antibacterial in food, cosmetics, and drugs can also act as TRPA1 activators.

Primary alcohols cause irritation of the skin, eyes or nose by activating TRPA1. Higher alcohols, such as 1-butanol, 1-hexanol, or more, activate TRPA1 regarding the length of the carbon chain; that is, the strength increased with the increase of carbon chain length. Interestingly, Cys665 and His983 in the N-terminal part of TRPA are also required in the process of activation by primary alcohols. Caffeine is a species-specific activator of TRPA1. Caffeine of Coffea arabica in mice activates TRPA1, but in humans, the same is inhibited. Topical nicotine, used to aid in nicotine replacement therapy, irritates the skin and mucosa due to the activation of TRPA1 since nicotine activates this receptor. An increased concentration, in turn, occludes the channel. Inhibiting the activation of TRPA1 is expected to aid in developing smoking cessation therapies with minimal side effects.

Antifungal/amoebicidal drug Clioquinol (CQ) was withdrawn due to its association with a subacute myelo-optico-neuropathy (SMON) outbreak. Clioquinol is an ionophore and a Cu/Zn chelator to generate its anti-parasitic activities. Local injections of CQ result in mechanical hyperalgesia and cold hypersensitivity by

stimulating TRPA in a zin2 dependent fashion. When the intracellular face of removed inside-out patches is directly exposed to Zn 2, TRPA1 is activated. Consequently, it leads to the activation of TRPA1 by Zn2+ ionophores such as CQ that increase intracellular Zn2+ levels. TRPA1 is an intracellular Zn2+ sensor. Similar to zinc, two other heavy metals, copper and cadmium, also stimulate TRPA1, and activate pulmonary sensory neurons directly as shown in fig.5 (Bernd Nilius et al 2012).



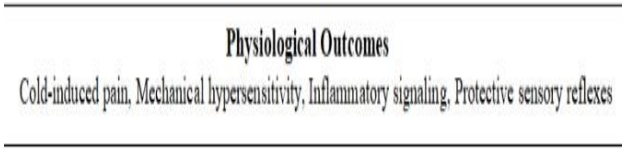


Figure 5: Non-electrophilic activation of TRPA1 channel

8. Physiological Functions of TRPA1 channel:

8.1. Pain: Transient receptor potential (TRP) A1 (non-selective cation channel found predominantly on sensory neurone expressing TRPV1) is necessary in triggering the sensory nerves and pain behaviours induced by a vast array of reactive irritants and mediators of inflammation and tissue damage. TRPA1 can be stimulated with reactive electrophilic compounds which covalently modify cysteine residues in the cytosolic N-terminus of the protein (T. E. Taylor-Clark et al 2008). TRP channels have been found to be the potential targets and multimodal gauges of pain and irritant signals. Also, TRP channels can collaborate in order to encode a specific pain signal. As an illustration, the role of TRPV1, TRPM3 and TRPA1 would have to work together in the example of unpleasant heat.

The role of TRPA1 in peripheral neuropathic pain, that is not triggered by mechanical pathology, and includes neuropathy pain associated with diabetes, has been established. Peripheral neuropathy is one of the common consequences of diabetes mellitus causing painful skin pain often of a burning nature. A very recent discovery in a mouse model of induced metastatic cancer pain through injection of melanoma-forming cells into the hind paw showed that oxidative stress and TRPA1 are important in the development of mechanical and cold allodynia with genetic deletion/pharmacological antagonists of either TRPA1 or antioxidants reducing pain-like responses. Several lines of evidence can be viewed as supporting the implication of TRPA1 models of disorders where the dysfunctional pain is located. After stimulating neurons of the primary sensory ganglion in a mouse model of migraine by injecting with glyceryl trinitrate, it has been established that blocking the TRPA1 channel or deleting it in the periorbital region, such as the primary sensory neurons, turns off periorbital mechanical allodynia. Migraine may be a therapeutic target via the channel, as the stimulation of TRPA1 can lead to the release of CGRP which is one of the triggers of migraines, some medications used in the treatment of migraine may desensitise or inhibit TRPA1. With plenty of evidence that direct stimulation of TRPA1 in nociceptors is the determinant of the acute pain responses, recent studies have aimed at TRPA1 expressed in glial cells as the critical element required to sustain chronic pain (Daniel Souza Monteiro de Araujo et al 2020)

The role of TRPA1 in pain disorders has been discovered because of the human genetic research. In the first study, TRPA1 has been associated with the autosomal-dominant familial episodic pain syndrome (FEPS), a rare pathological pain illness characterized by an upper body crippling pain episodes triggered by fasting and physical stress. Conversely, the oxidative and nitrative stress by-products, under different pathophysiological situations,

have been reported in human beings and experimental animals at a higher level as compared to that required to open up the TRPA1. Hence, it is much more likely that blockage of TRPA1 can bring to light the role of TRP-ergic pathways in acute nociception, allodynia and hyperalgesia than blockage of TRPV1. Recent studies in multiple animal models have indicated that TRPA1 might be a cause of numerous neuropathic types of pain. The hypothesis that TRPA1 plays an important role in the hypersensitivity to chemical, thermal and mechanical stimuli that characterizes models of neuropathic pain, such as nerve injury, diabetic neuropathy and neuropathy, is gathering momentum as shown in fig.6. TRPA1 Channel TRPA1 is the trigger of Inflammatory and Neuropathic Pain and Migraine by a wide range of chemotherapeutic drugs. Data supporting information has been collected using both pharmacological and genetic means (Romina Nassini et al 2014).

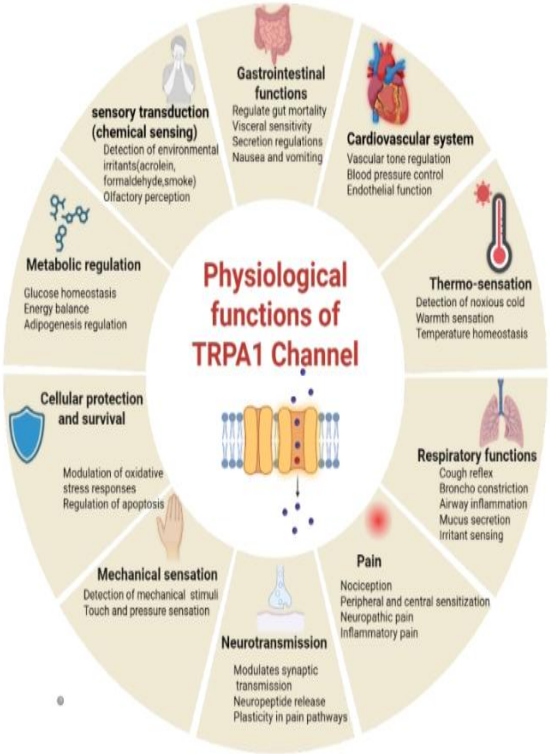


Figure 6: Physiological Functions of TRPA1 channel

The physiological roles of the TRPA1 channel in several systems are depicted in the diagram. TRPA1 is essential for sensory transduction; it detects environmental irritants and contributes to mechanical perception, thermosensation, and pain (nociception). It supports cardiovascular processes including blood pressure regulation and vascular tone as well as respiratory processes like cough and airway irritation. It affects visceral sensitivity, secretion, and gut motility in the gastrointestinal tract. Furthermore, TRPA1 contributes to cellular defense by controlling oxidative stress and apoptosis, affects neurotransmission through synaptic signalling and neuropeptide release, and is involved in metabolic regulation, including glucose homeostasis and energy balance.

8.2. Inflammation: TRPV1 is sensitized after the neuronal receptors of bradykinin, prostaglandins, histamine, purines, proteases, NGF, chemokines and most other pro-inflammatory factors are activated. Similar to TRPV1, Trpa1 is activated and sensitized through the pathways of inflammatory receptors. TRPA1 response to bradykinin or histamine receptors can be studied both in cultured heterologous cells, and native sensory neurons cultured out of trigeminal ganglia.

Without TRPA1 the mice were incapable of developing thermal and mechanical hyperalgesia following bradykinin injections in the hind paw, indicating that TRPA1 is an influential target of the inflammatory signalling pathways in vivo.

TRPA1 is one of the less specific polymodal channels indicating by its activation by a broad spectrum of natural and exogenous chemical irritants, including reactive oxygen species and other products generated during inflammation. Noxious cold also activates TRPA1 and is involved in Mechan transduction in critical functions (Bret F. Bessac and Sven-Eric Jordt 2008).

TRPA1 has been found in peripheral nerve cells and very thin cells (Schwann cells) and corneal epithelium, stromal keratocytes and inflammatory cells corneas, in both human and mouse. It is calcium dependent low temperature activated. Nonetheless, when in high temperature TRPA1 can be activated, and lead to inflammation when it is in a calcium-free environment. The TRPA1 signal is reported to induce the inflammation through either enhancement of the production of interleukin-1 (IL-1) or prostaglandin E2 in the keratinocytes. In contrast, this signal downregulates inducible Nos2 or Tnf in monocytes and macrophages. Consequently, these findings indicate that TRPA1 activation leads to the either up- or down-regulation of genes with both proand anti-inflammatory impacts (Shu-ichiro Sasakia et al 2025).

The number of TRPA1 nociceptors in the mouse TG is abundant. These neurons also express the mRNAs of the inflammatory mediators like neuropeptides (SP, CGRP), cytokines and chemokines. Additionally, a healthy portion of these co-expressing neurons with TRPA1 mRNA in conjunction with the mRNAs of other nociceptors and the proteins that trigger signals to various stimuli. The implication of these findings is that TRPA1 might be a major regulator of corneal nerve activity to thermal, mechanical, and acidic stimuli (Tiffany Migeon et al 2025)

TRPA1 has been found to facilitate healing of stromal wounds of the eye in mice after laceration of the tissue. The phenotype was linked to collagen-type I expression, keratocyte-myofibroblast transformation, TGFb signalling in stromal cells, and a decrease in the production of repair

Schwann cells.[46] The body's primary chemo sensor is TRPA1. The three types of compounds that directly interact with channels of TRPA1 are agonists (both electrophilic and no electrophilic), antagonists, and modulators with a bimodal effect (Yu. A. Logashina et al 2019).

8.3. Respiratory Functions: The TRPA1 can generally be primarily located in the nociceptive neurons (small-diameter) of primary sensory afferent nerves, which cover the entire respiratory tract. Exposure of the mammal to the upper respiratory causes alteration in the usual exhalation pattern and it retards the respiration rate. This slowing of respiration rate has been used as a response to sensorimotor irritation, and at least TRPA1 plays a role in it. Some of the endogenous inflammatory mediators, which are augmented in respiratory disease, include PGE2 and BK. One of the primary "effector"of tussive response to these agents is TRPA1 that can be found on respiratory vagal C fibres, and usually in combination with TRPV1. The response to PGE2 and BK in the tussis is blocked by TRPA1 blockers and TRAP1 is likely to be one of the most interesting drug development targets of anti-tussives. Asthma is an inflammatory disease that arises because of exposures of the airway to allergens and chemical irritants such as cigarette smoke, chlorine, aldehydes and scents. Endogenous TRPA1 agonists, ROS and lipid peroxidation products are other powerful initiators of the asthma-induced airway inflammation triggered by allergens. Inhibiting allergen induced airway infiltration of leukocytes, TRPA1 reduces the synthesis of cytokines and mucus and almost entirely prevents airway hyper reactivity to contractile stimuli in the murine ovalbumin model. Since this pattern of effects is also induced by TRPA1 antagonists, TRPA1 may enable finding a promising pharmacological target in the treatment of asthma and other inflammatory diseases could be treated with antagonists of TRPA1.

The pathogenesis of chronic obstructive pulmonary disease (COPD) also takes part in TRPA1. TRPA1 is present in human lung fibroblasts and pulmonary alveolar epithelial cell and upon its stimulation results in release of a chemokine IL-8 which is blocked with TRPA1 selective antagonists. On the other hand, it has been shown that the level of electrophilic compounds in the pollen itself is extremely high which in turn would suggest that the activation of TRPA1 by small molecule electrophilic compounds naturally present in the pollen would add to the damage to the allergenic offense by proteins of pollen (Bret F. Bessac and Sven-Eric Jordt 2008). Recent studies have revealed a key role of TRPA1, a TRP ion channel of the sensory neurons in airway chemo sensation and inflammation. TRPA1 opens in response to chlorine, reactive oxygen species, as well as noxious smoke and smog components and causes irritation and airway reflex. TRPA1 also has the potential to contribute to chemical hypersensitivity, chronic cough and airway inflammation in asthma, COPD and syndrome of reactive airway dysfunction in combination with the capsaicin receptor, TRPV1 (Bret F. Bessac and Sven-Eric Jordt 2008)

8.4. Gastrointestinal functions: TRPA1 participates in the gastric accommodation (or gastric relaxation) response which reduces the increase in gastric pressure following meals and thus can prevent the emergence of dyspeptic symptoms. The pretreatment of TRPA1 with agonists increases the gastric tone via TRPA1-mediated gastric cholinergic neuronal pathway and therefore meal induced gastric accommodation is inhibited. Satiety effect may as well be partly connected to TRPA1 activation. Selective TRPA1 agonists of spicy origin may work in the cranial visceral afferent systems which mediate satiety and aid in reducing the quantity of food consumed in reference to a spicy diet. GI motility is also affected by TRPA1. TRPA1 agonists produce secretory effects. Agonists secretion of Cl- and HCO3 - was also induced in a concentration-dependent manner by mucosal application but not by serosal application. TRPA1 activation results in the release of anions through synthesis of PG, without neural pathways in the colon, and triggered by the EP4 subtype of the PG receptor. The activation of the TRPA1 in colonic epithelial cells also involves in the host defence mechanism through secretion of anions rapid, as well. Serotonin is present in high amounts in the GI, most of the stores are located in enterochromaffin (EC) cells located on the mucosal surface. The EC cells are secreting the serotonin which activates the intrinsic and extrinsic nerves leading to diverse physiological and pathophysiological responses, including GI contractions. TRPA1 is highly expressed on EC cells. TRPA1 agonists stimulate EC cell functions by promoting an intensified release of serotonin which consequently leads to ileum contraction via serotonin receptor. Thus, TRPA1 is an EC cell sensor molecule, which regulates GI functioning.

The CGRP and substance-P neuropeptides emitted by extrinsic sensory neurons, are important in experimental colitis. The activation of TRPA1 in the colitis model segment leads to discharging of colonic substance-P and CGRP. TRPA1 cysteine and lysine residues are covalently activated by the inductor of inflammation TNBS ((Bernd Nilius et al 2012).

A gastrointestinal tract is one of the most studied internal organs in the context of the contribution made by TRPA1 to the visceral inflammation and nociception. Mechanical hypersensitivity to colonic distension was found to be mediated by the TRPA1 in the chemically induced colitis (Daniel Souza Monteiro de Araujo et al 2020).

8.5. Thermosensation: The transient receptor potential (TRP) channel superfamily is made up of polymodal cell-membrane receptors that mediate sensory transduction to a collection of various stimuli. They can be activated by direct binding of the ligand, depletion of the intracellular

storage of Ca2+, Ca2+/calmodulin depended activation and osmotic stress, temperature change, pheromones, taste, mechanical stimuli, and other stimuli. It is calcium ion-dependent and triggered by low temperatures.23. Conversely, TRPA1 is able to trigger at higher temperature and induce inflammation without the presence of calcium (Shu-ichiro Sasakia et al 2025).

The essential role of TRPA1 in both chemical and temperature perception has attracted much interest. Though it stimulates avoiding high temperatures between 28 and 35 C and minimizes damage at high temperatures, it can be turned on by low temperatures between 18 and 24 C (Yutong Zhang et al 2024).

It is not known when TRPA1 became a thermosensor and whether or not the original TRPA1 protein had unusual sensitivity to temperature. The possibility that the channel transduces an even earlier modality is however brought to the fore by the reality that most of the other members of the TRPA family are equally sensitive to temperature. Eighty The ubiquitous expression of thermosensitive TRPA1 channels and the strong species-to-species difference in documented activation thresholds suggests that the temperature sensitivity of TRPA1 is a topic of evolutionary attention and has gone through various changes throughout evolution to adapt to particular environmental situations.

Cloning of the Drosophila melanogaster ortholog (dTRPA1) of cold activation of mouse TRPA1.81 came soon after the first reports. The EC50 of the insect TRPA1 is larger than the mammalian counterparts, but the channel is sensitive to electrophilic compounds, such as the mouse channel.82. It is interesting to note that heat stimulation of dTrpa1 expressed in Xenopus oocytes was demonstrated to have an activation threshold of approximately 2789 °C and was heat activated instead of cold activated.81,83 There are also reports of heat-activated TRPA1 in silkworm Bombyl mori and mosquito Anopheles gambiae81-86. In vivo tests supported the heat-activation of dTrpa1, and demonstrated the importance of the protein to thermotaxis and temperature preference in larvae88 and adult flies. It is interesting to note that it was proposed that evolution of endothermism was not necessarily followed by a change of heat sensitivity to cold sensitivity (or insensitivity).136 As endothermic animals, chicken (Gallus gallus domesticus) maintain a body temperature of 41-42 °C. The endotherm-derived TRPA1 was closer to green anole TRPA1 82% than to other endotherms This channel is activated by heat ramps of approximately 39 °Cin response to heat gradients that may be visible.The first account of TRPA1 as a thermosensor was observed in the case of a study using the mouse ortholog that thermally activated the sub-TRPM8 region (<17 °C). Trpa1 appears to retain its physiological use as both a heat and chemical sensor in vertebrate ectotherms. The non-pit-bearing snakes (2), frog (Western Clawed Frog) and lizards have orthologous channels, which are temperature sensitive; in each case thermal activation is identifiable at about 40 C, 34 °C, and 37°C, respectively. It is an exception on the part of the zebrafish, however. The two paralogs of TRPA1 in zebrafish can be electrophilically activated, though lack heat activation and do not seem to be involved in behavioural responses to adverse temperatures (Willem J Laursen et al 2015).

Recent Investigations:

A promising and practical approach to treating asthma is to target the TRPV1 and TRPA1 ion channels, especially when using Chinese herbal medicines (CHM). The authors show that TRPV1/TRPA1 are essential for neurogenic and immune-mediated airway inflammation, hyperresponsiveness, and remodelling, and that deregulation of these channels plays a major role in the pathophysiology of asthma by combining data from 134 investigations. Crucially, through multi-target and synergistic pathways, CHM and its bioactive metabolites can affect TRPV1/TRPA1 via inhibition, desensitization, or downregulation, reducing pulmonary inflammation and enhancing airway function. CHM-derived molecules provide a solid basis for the development of new asthma medications because of their structural diversity, previous clinical use, low toxicity, and ability to operate on several pathogenic pathways at once.

To overcome translational and regulatory obstacles and fully realize the therapeutic promise of TRPV1/TRPA1-modulating CHM in asthma management, the review also highlights the need for more precise identification of active metabolites, mechanistic validation, and solid clinical data (Xiang Yao et al 2025).

By interfering with the proper growth, shape, and migration of human embryonic stem cell (hESC) colonies through the activation of TRPA1 and TRPM8 ion channels, menthol, a frequent component in electronic cigarette products, might negatively impact early human embryonic development. Menthol changed calcium homeostasis, increased cell mortality, elongated colony shape, and boosted colony motility—all essential processes for effective gastrulation—even at nanomolar amounts that are expected to occur in the blood of pregnant women who vape. The biological plausibility of menthol-induced developmental toxicity is strengthened by these mechanistic findings, which are in line with epidemiological evidence that links the use of menthol-flavoured e-cigarettes during pregnancy to an increased risk of fetal death.

The conclusion that inhaling menthol- or mint-flavoured e-cigarettes during pregnancy causes a serious risk to the embryo and should be avoided is highly supported by the available research (Shabnam Etemadi et al 2025)

An unsaturated fatty acid called phialomustin-B (PHL-B) was extracted from the endophytic fungus. Phialophora mustea is a naturally occurring TRPA1 ion channel

inhibitor that is strong, selective, reversible, and has minimal cytotoxicity. The authors show that PHL-B inhibits TRPA1 with micromolar potency while exhibiting no appreciable off-target effects on other thermo-TRP channels, such as TRPV1, TRPV4, and TRPM8, using complementary fluorescence-based calcium imaging, whole-cell and single-channel electrophysiology, molecular docking, and site-directed mutagenesis. Mechanistically, PHL-B interacts with important residues in the distal S5 region and S4–S5 linker of TRPA1, particularly I860 and K868, suggesting a binding mode different from that of known synthetic antagonists. All of these results point to PHL-B as a unique natural TRPA1 antagonist and a potential lead scaffold for the creation of targeted antinociceptive treatments for TRPA1-mediated pain disorders (Priyanka Yadav et al 2025)

In the green peach aphid Myzus persicae, the TRPA1 channel is crucial for controlling temperature perception and preference. MperTRPA1(A) and MperTRPA1(B), two TRPA1 splice variants, were shown to have different heat sensitivity and to be broadly expressed, especially in chemosensory organs. Both variants are activated by rising temperatures, according to functional investigations, although MperTRPA1(B) has a lower activation threshold and significantly higher thermos sensitivity than MperTRPA1(A). Crucially, aphid thermotactic behaviour was markedly changed by RNA interference-mediated knockdown of MperTRPA1, which caused them to favor higher temperatures. In addition to highlighting TRPA1 as a crucial thermal sensor involved in behavioural adaptation to ambient temperature, these findings collectively clarify the molecular mechanism underlying temperature preference in M. persicae. These findings may have implications for comprehending aphid ecology and creating temperature-based pest management strategies (Lulu Yang et al 2025).

In human skin, TRPA1 ion channel activation has a potent, context-dependent regulatory influence on gene expression, which is especially advantageous in psoriatic lesions. The authors show that pharmacological activation of TRPA1 by mustard oil results in a broad anti-inflammatory and homeostatic transcriptional shift, whereas TRPA1 blockade has negligible effects, consistent with low basal TRPA1 activity in skin, using ex vivo full-thickness human skin biopsies and RNA-sequencing analysis. TRPA1 activation significantly down-regulates important inflammatory pathways in lesional psoriatic skin, such as circadian clock-associated genes, senescence-associated secretory phenotype (SASP) genes, and IL-4/IL-10/IL-13 signaling, all of which are linked to chronic inflammation and disease persistenceTogether, these results demonstrate TRPA1's role as a balancing and protective regulator of cutaneous immune responses and point to TRPA1 activation as a potentially effective therapeutic approach for improving psoriasis pathogenesis and restoring skin homeostasis (Agnes Kemény et al 2025)

The TRPA1 ion channel has a modulatory role in chronic airway inflammation and is functionally expressed in both human and animal lung macrophages. It is markedly increased by exposure to cigarette smoke. The authors demonstrate that cigarette smoke-induced TRPA1 upregulation coincides with significant alterations in macrophage-driven inflammatory responses, including a time-dependent transition from pro-inflammatory (M1) cytokines toward anti-inflammatory and tissue-remodeling (M2) cytokines, especially TGF-β, using in vivo mouse models and physiologically relevant human 3D lung spheroids. The lack of TRPA1 changed cytokine profiles and macrophage infiltration, highlighting its regulatory role in immunological balance and lung structural damage following long-term smoking exposure. All things considered, these results point to TRPA1 as a crucial mediator connecting cigarette smoke to macrophage-dependent airway inflammation and emphasize it as a possible therapeutic target for smoking-related chronic lung diseases, calling for additional research in human lung tissues and sophisticated organoid models (Anita Steib et al 2025)

Zinc is a very important trace element to life. It is the dependency of more than 300 proteins in terms of their structure or functionality, and its role in cell signalling is increasingly recognized. Nevertheless, overexposure to zinc may lead to irritation and inflammation via an unknown mechanism, and high levels of zinc are deadly. The zinc activates nociceptive somatosensory neurons, and produces nociception in mice through TRPA1, a cation channel recently shown to mediate the pungency of cinnamon and wasabi as a result of cysteine mutations. Zinc activates TRPA1 through a specialized mechanism which requires the entry of zinc by TRPA1 channels and subsequent stimulation by some intracellular cysteine and histidine residues. The sensitivity varies at low nanomolar concentrations, so TRPA1 is highly sensitive to intracellular zinc since it is activated at low concentrations.These results highlight TRPA1 as a key target for zinc's sensory effects and lend credence to zinc's developing function as a signalling molecule that might alter sensory transmission (Hongzhen Hu et al 2008)

9. Toxicological Significance of TRPA1 ion channel:

9.1 Environmental & Air-Pollution Toxicology: The extravasation of plasma proteins and other neurogenic inflammatory reactions triggered by TRPA1 stimulation by unsaturated aldehydes in cigarette smoke (CS) may represent an early defense mechanism against the harmful effects of CS on lung tissue and airways (Eunice Andrè et al 2008).

Examples of 4-hydroxy-trans-2-nonenal (4HNE) and acrolein (propenal), crotonaldehyde (butenal), formed by

the oxidation of 1,3-butadiene, are 4-hydroxy-trans-2-nonenal (4HNE) 4-hydroxy-trans-2-nonenal and acrolein The principal overall physiological role of TRPA1 is to limit pulmonary (and systemic) exposure of airborne toxins as shown by its localization in the pulmonary airways and its role in the protective physiological response called respiratory braking in response to inhaled toxins (Daniel J. Conklin et al 2017)

Diesel exhaust particulate matter (DEP) makes asthma and other diseases worse and irritates and inflames the lungs. These effects may be due to the activation of transient receptor potential ankyrin-1 (TRPA1) (Cassandra E. Deering-Rice et al 2019).

9.2 Foundational TRPA1 Toxicology: Since acrolein (and the corresponding crotonaldehyde) is a strong electrophile, it readily disbursed to make irreversible covalent complexes with biological nucleophiles like cysteine-rich proteins and glutathione (GSH). Due to this tendency, acrolein and crotonaldehyde are good agonists of TRPA1.29 Acrolein interacts with intracellular cysteines of TRPA1 and is likely to lead to the opening of the cation channel, which causes the release of calcium and neuronal activation as well as the release of tachykinin peptides SubP and CGRP. These peptides increase local tissue inflammation, blood flow, vascular permeability and edema in addition to enhancing pain signalling (in dorsal root ganglia) (Daniel J. Conklin et al 2017)

TRPA1 mediates acute respiratory responses to electrophilic and oxidizing environmental pollutants, such as as acrolein and crotonaldehyde, and to H2O2 and HOCl. Other modes of activity of TRPA1 include the release of non-electrophilic compounds and particle-associated electrophiles and mechanical perturbation of insoluble components, leading to activation of TRPA1. TRPA1 activation in pulmonary C-fibers mechanochemically propagates neurogenic inflammation. Moreover, TRPA1 is also expressed by some airway and alveolar epithelial-type cells and the activation of this protein may alter the expression of pro-inflammatory cytokines and chemokines and other toxicologically relevant responses (Cassandra E. Deering-Rice et al 2019).

The high concentrations and the continuous action of endogenous ligands and pro-inflammatory mediators may maintain the activity of TRPA1, long-term. This aligns with the TRPA1 KO mouse phenotype in the allergen induced asthma model and the CS model displaying reduced airways leukocyte infiltration and reduced production of cytokines and mucus through its inhibition of leukocyte entry into the airways and production of cytokines and mucus during the modelss (Indranil Mukhopadhyay, et al 2016)

9.3 Immune & Macrophage-Mediated Toxicity: Immune cells express many regulators of intracellular Ca2+ homeostasis such as purinergic receptors and CRAC channels. The role and importance of transient receptor potential (TRP) channels in this group of Ca2+ channel regulators have become clearer. The 28 members of this family of cation channels according to sequence homology are separated into six groups: TRP canonical (TRPC), TRP vanilloid (TRPV), TRP melastatin (TRPM), TRP polycystin (TRPP), TRP mucolipin (TRPML) and TRP ankyrin (TRPA). Between the parts containing the sixth and the sixth of the six putative transmembrane domains constituting all TRP proteins is a pore.

The stimuli that can trigger TRP channels are highly diverse, comprising osmotic stress, pressure, temperature fluctuations, exogenous and endogenous substances, such as endogenous inflammatory products, which is in accordance with their role as polymodal triggers. The ability of these channels to combine the activity of a number of the TRPA1 stimuli, signals of cell damage can be used to stimulate stronger reactions.

It seems that there are two contributions in this channel. TRPA1 can contribute to abuse of inflammatory states in the case of abnormal regulation; conversely, it can also act as an alarm of cellular stress, tissue injury, and external harmful stimuli leading to defense mechanisms as shown in fig.7 (Robbe Naert et al 2021).

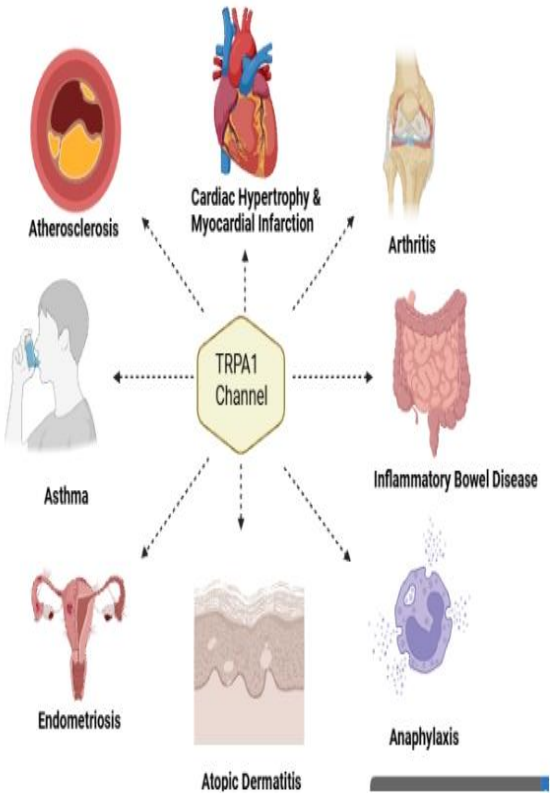


Figure 7: Pathophysiological conditions linked to TRPA1 channel expression in immune cells

The pathophysiological conditions linked to TRPA1 channel expression are depicted in the diagram,

emphasizing the channel's role in a number of inflammatory and disease processes. TRPA1 is associated with respiratory conditions like asthma as well as cardiovascular conditions like atherosclerosis, ventricular hypertrophy, and myocardial infarction. Additionally, it contributes to immunological and inflammatory diseases such anaphylaxis, inflammatory bowel disease, and arthritis. Furthermore, TRPA1 is linked to reproductive problems including endometriosis and skin conditions like atopic dermatitis. Overall, the figure highlights how TRPA1 plays a wide range of roles in the development of disease, especially in relation to inflammation, immunologicsal activation, and sensory signalling.

TRPA1 is primarily expressed in sensory neurons and in a diversity of non-neuronal cells, including dendritic cells, T-lymphocytes, neutrophil granulocytes, and mast cells. Moreover, it was also observed that TRPA1 was immune positive in the human ectopic endometrial tissue infiltrated by macrophages. Its expression was confirmed in murine peritoneal and cutaneous macrophages and its expression of mRNA and protein was reported in human and mouse colon, human oral submucosa, nasal polyps of chronic rhinosinusitis and in primary monocytes. TRPA1 triggers protective reflexes, including apnea, bradycardia, coughing, sneezing, and mucus, and is expressed and functional on peptidergic sensory neurons that innervate the entire respiratory tract.<|human|>TRPA 1 activates protective reflexes, including apnea, bradycardia, coughing-sneezing and mucus, and is expressed (Anita Steib et al 2025)

9.4 Oxidative Stress & Endogenous Toxicants: Due to the fact that TRPA1 is susceptible to reactive oxygen and carbonyl species, it could cause some diseases such as diabetic neuropathy, or the occurrence of peripheral neuropathy following chemotherapy. Also, TRPA1 is an ideal target of inflammatory diseases of the airways because it has a long list of agonists many of which are ingested by eating food or inhaled by breathing polluted air respectively. TRPA1 has been shown to contribute to the itching of patients. There are two types of itch-generating processes, histamine-dependent and histamine-independent. Antihistamines are effective in the treatment of histamine dependent itch and neither antihistamines nor other treatment interventions can reduce histamine independent itch which is often chronic. This histamine-independent itch can be mediated by mas-related G protein coupled receptors (MRGPRs), also known as itch receptors and in the case of chloroquine, a malaria treatment, it is provoked by this antimalarial drug. Histamine-independent, MRGPR-mediated itching has been reported to be dependent on TRPA1. TRPA1 seems to be a component of a number of signalling pathways, including TGR5-induced itching or IL-13-induced itching. The TRPA1 agonist, trans-cinnamaldehyde, is even capable of making people itch. Ultimately, the implication of TRPA1 in itching can be found in both diseases such as chronic atopic dermatitis and contact dermatitis; as well as experimental models. It is noted that TRPA1 responds to unwanted cold temperatures with a critical point of approximately 17 o C (Story et al. 2003). Nonetheless, later studies have elicited a controversial debate about the role of TRPA1 to sense cold (Jannis E. Meents et al 2018)

9.5 TRPA1 as a Target in Organophosphate and Pesticide Toxicity: Organophosphates (OPs) are the active ingredients in many insecticides, herbicides, and nerve gases, also commonly used as plasticizers, solvents and additives in industry. An estimated nearly three million people are exposed to OPs annually. Acute poisoning with OPs in the late stages or chronic exposures to Ops will progress to organophosphate-induced delayed neuropathy (OPIDN) that commonly causes paresthesias, ataxia, and paralysis.

- They show that TRPA1 (Transient receptor potential cation channel, member A1) plays a pivotal role in OPIDN
- Organophosphates directly activate TRPA1
- TRPA1 activation causes Ca^{2+} overload and neuronal hyperexcitability
- TRPA1 is essential for OPIDN development in vivo

Repeated OP exposure causes pain behaviours, nerve fiber injury, ataxia, and paralysis in mice and hens. 2These pathological effects were:

- Strongly reduced by TRPA1 antagonists (HC-030031)
- Almost completely abolished in TRPA1 knockout animals
- Mechanism of OPIDN is independent of AChE inhibition

Even OPs like TOCP that do not inhibit AChE still cause delayed neuropathy through TRPA1 activation.

This explains why standard antidotes (atropine, oximes) fail to prevent OPIDN.

- TRPA1 is a promising therapeutic target

Pharmacological inhibition of TRPA1 protects peripheral and central nerves.

FDA-approved drugs with TRPA1-inhibitory activity (duloxetine and ketotifen) showed significant neuroprotection, suggesting immediate clinical repurposing potential (Qiang Ding et al 2017) channel is involved in the toxic actions of organophosphates, particularly cyclosarin, and put forth Lead Compound as a novel means of inhibition, as studies shows that the Lead Compound, strongly bind to the TRPA1 channel and particularly to serine 1039, blocking its activation, inhibits calcium influx and subsequent neurotoxicity. The ability of Lead Compound to block TRPA1 channel pore (diameter about 10 Å) suggests a strong inhibitory approach to halt adverse physiological responses to organophosphate exposure.

Additionally, Lead Compound exhibits ideal ADMET properties and good stability, so has the potential to be a safe and efficient drug.

This discovery is a significant step toward finding a treatment for neurotoxic effects caused by exposure to organophosphates and will facilitate the creation of selective TRPA1 inhibitors such as Lead Compound for therapeutic purposes, despite requiring more experimental support (Shreya Satyanarayan Bhat et al 2026)

Exposure to pesticides, herbicides, and nerve agents can result in organophosphate (OP) poisoning, a dangerous and potentially fatal illness. These substances cause acetylcholine to build up and overstimulate muscarinic and nicotinic receptors by permanently inhibiting acetylcholinesterase. Several organ systems may be impacted, even though the nervous system is the main one. Although acute kidney damage (AKI) is regarded as a rare and secondary consequence, renal involvement in OP poisoning is acknowledged. According to cohort research, the probability of having AKI was 6.17 times higher for those exposed to OP poisoning than for a control group. Direct tubular toxicity, oxidative stress-induced cellular damage, hypoperfusion from volume loss, and downstream systemic consequences such rhabdomyolysis and metabolic disorders are some of the ways that OP poisoning impairs the kidneys (Gudisa Bereda 2026).

Future Prospects:

Chronic pain is a major health problem which decreases the quality of life in many countries. Efforts are underway to minimise the use of opiates and identify alternatives. Multicellular expression and pleiotropic signalling are characteristics of the molecule encoded by TRPA1, making it a promising target in several human diseases. Pain can be treated with TRPA1 agonists and antagonists, based on the compelling preclinical evidence collected in the last 20 years. Schwann cell TRPA1 and oxidative stress in peripheral nerve fibres, as part of a feed-forward cycle, have been shown to be critical for the maintenance of mechanical allodynia, according to recent evidence. This novel research offers new possibilities for pain control (Daniel Souza Monteiro de Araujo et al 2020).

The unique mechanism of activation and the divergent binding properties of TRPA1 within the TRP family and the ion channel superfamily, in general, are remarkable. TRPA1 is one of the few ion channels that has been identified by human genetics to be involved in pain. The therapeutic effects of TRPA1 antagonists for pain, respiratory disease, itching and other conditions have been proven. What's more, so far, there don't seem to be any major safety concerns for TRPA1 antagonists. Consequently, TRPA1 is now a hot target for new drugs to treat pain, rather than TRPV1 (Jun Chen & David H. Hackos 2015).

The rapid developments in the investigation of TRPs have resulted in a number of papers demonstrating TRPs as important intracellular channels and dysfunction of TRPs as pathogenic drivers in diseases. In this article, all the TRP types are presented and their role in numerous biological processes described. This article also provide an account of TRPs' history, including the strengths and therapeutic modality, and limitations. Some of the negative effects that need to be refined in this research include fever, pain, vomiting and even a lack of effectiveness in some studies' clinical trials. TRP channels are ubiquitous, and can cause systemic effects when they are modulated, which may contribute to these side effects. Moreover, there needs to be an increase in the selectivity of available drugs for TRP channels. Low dose, localised administration and targeted drug delivery are strategies that can be used to help overcome some of these issues (Miao Zhang et al 2023).

The transient receptor potential ankyrin 1 (TRPA1) channel has been extensively studied as a potential therapeutic target for analgesic treatment in a range of pain conditions as it has superior efficacy and safety profiles than current medications. It might be possible to achieve more therapeutic benefits with selective TRPA1 antagonists as this channel has multiple pathogenic roles in humans as shown in fig.8 (alentina Albanese et al 2025).

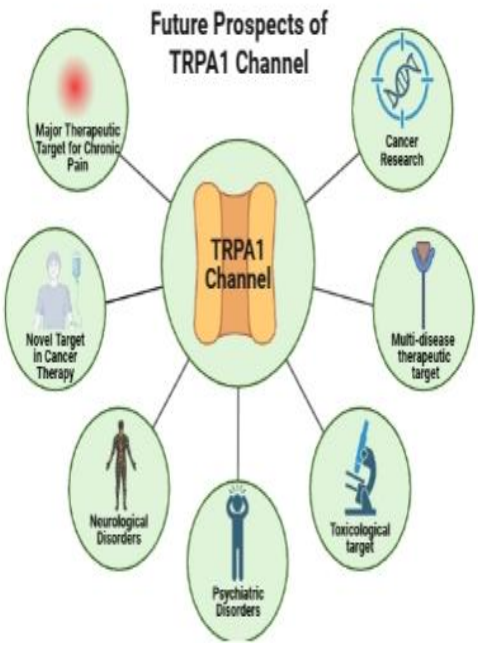


Figure 8: Future Prospects of TRPA1 Channel

The TRPA1 channel's potential as a therapeutic target in a variety of domains is shown in the diagram. TRPA1 is regarded as a key target for the treatment of chronic pain and has promise in cancer research and treatment, both as a novel target and in tumour-related pathways. Given its participation in a variety of physiological and pathological

processes, it may also function as a therapeutic target for multiple diseases. Furthermore, TRPA1 is being investigated in toxicological research to comprehend reactions to damaging stimuli as well as neurological and psychiatric diseases. All things considered, the figure highlights the wide and growing therapeutic significance of TRPA1 in upcoming biological studies and medication development.

TRP channels' function in neuronal physiology and their significance in neurodegenerative, psychiatric, and cognitive problems. TRP channels play a role in vision, cognitive processes, emotions, behaviour, and the sensory transduction of external stimuli such as temperature, pressure, or chemicals.14, 15 Neurological and behavioural problems have been associated with dysregulation of TRP channel activity (lOlesia F. Moroz et al 2025).

Demonstration of the NRF2 led promotion of TRPA1 which aids cancer cells in their tolerance to oxidative stress. Such findings, together with the known importance of NRF2 in the activation of ROS-neutralizing genes, indicate that tumour cells use multiple strategies to cope with extreme oxidative stress conditions, including both canonical (ROS-neutralizing) as well as non-canonical (TRPA1-mediated) oxidative-stress responses. It’s now clear that tumour cells are vulnerable to oxidative-stress defence. So, it's tempting to develop new treatments that will improve the susceptibility of tumour cells to current therapies. But due to the negative consequences of enhanced oxidative stress in healthy tissues, targeting conventional mechanisms of antioxidant defence is challenging. In contrast, TRPA1 inhibitors have yet to show any indication of central nervous system or other side effects and are currently being trialled in clinical practice for treatments of pain and respiratory problems. Thus, these findings highlight the therapeutic value of compromising antioxidant defence processes in many cancers, although methods of improving the pharmacokinetics of TRPA1 drugs and delivery routes are needed for their utility as drugs (Nobuaki Takahashi et al 2018).

The importance of Transient Receptor Potential Ankyrin 1 (TRPA1) channels relies on the fact that they are polymodal sensors that respond to various chemical, thermal and mechanical cues. This research has delineated the molecular mechanisms underlying TRPA1 activation, its widespread distribution in tissues and its involvement in important physiological processes including pain transmission, inflammation, blood vessels and the lungs. Considerable progress has been made in recent years towards understanding TRPA1 signaling pathways and its ligand interactions. Crucially, given TRPA1 is activated by several industrial chemicals, environmental pollutants and reactive electrophiles that are toxic and can cause neurotoxicity, respiratory irritation, and inflammatory conditions, its role in toxicity is increasingly being acknowledged. The improved understanding of TRPA1-mediated signaling may prove useful in developing therapeutic approaches and better risk assessment of chemicals. Future research is warranted examining the toxicological consequences and possible prolonged effects of TRPA1 activation and specific TRPA1 modulators, and the potential use of TRPA1 as an indicator of exposure to environmental and occupational hazards. For the protection of the most vulnerable population (infant and elderly individuals) against lethality and long-term morbidity, the more recent data on speedy termination of SE, absence of recurrent seizures and complete neuroprotection with administration of LY293558 plus caramiphen should be taken into account. Because of higher levels of NMDA receptor activity in younger animals, it is more likely that caramiphen's NMDA receptor antagonistic properties will be further crucial for complete neuroprotection in young animals. Caramiphen is no new drug. It was first approved by the FDA in 1973 as over-the-counter antitussive for children over the age on two. But poor efficacy as an antitussive (not safety) resulted in FDA withdrawal of approval poor 1984. However, before the LY293558 + CRM combination drug can be used in humans, dose and dose regimen dependent efficacy and safety studies are undoubtedly necessary (Vassiliki Aroniadou-Anderjskaa et al 2020).

It is evident from the pathophysiology of TRPA1 concerned with variety of disorders, still the research on this channel's impact on some diseases is still in its early stages and that the study of its function is bit difficult and complex, but the researchers have made some progress. It was revealed that there are certain similarities between the TRPA1 and various diseases. One important reason for the emergence and progression of several disorders is the involvement of the TRPA1 channel (Jiajing Li rt al 2023).

Due to its role as a chemical sensor for irritation and cell damage, as well as its connection to a number of disorders, it has received a great deal of clinical interest. For example, a rise in Ca2+ concentration caused by TRPA1-activated in trigeminal ganglion neurons causes hydrogen sulfide-mediated vasodilation. Shu-ichiro Sasakia et al 2025 as per latest observation made by TRPA1 is of crucial toxicological significance for the future treatment guideline.

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Ethics statement:

This paper, "Molecular Determinants, Distribution, Physiology, and Toxicological Significance of TRPA1 Channels", involves no experimental research, human subjects, or animal studies that need ethical approval. For academic openness and integrity, all acknowledged sources were appropriately referenced. It has been tried to provide an objective, accurate, and thorough literature review and the data interpretation. The development of this paper did not involve any instances of scientific misconduct, data manipulation, or plagiarism.

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