



Transient receptor potential Ankyrin 1: structure, function and ligands

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Abstract

Introduction: Transient receptor potential ankyrin 1 (TRPA₁) is a protein expressed in many living organisms. During the study of TRPA₁, its unique biological role as a universal and polymodal sensor of various altering agents was found. The aim of this study is to search and generalize information about structural features and molecular determinants, mechanisms of activation, action and modulation of TRPA₁ as a universal pain and inflammation sensor, as well as the nature of activators and antagonists of this target and their therapeutic potential.

Materials and methods: This article presents an overview of the results of scientific research of TRPA₁, its modulators, as well as an overview of their pharmacological potential over the period from the discovery of these channels to the present, with an emphasis on the last decade.

Results and discussion: The main collected data on expression, structural features and molecular determinants, mechanisms of activation and action of TRPA₁ indicate its role as a universal and labile element of the primary response of the body to adverse exogenous and endogenous factors. Regardless of the nature of the stimulus, hyperstimulation of TRPA₁ channels can lead to such phenomena as pain, inflammation, itching, edema and other manifestations of alteration, and therefore TRPA₁ blockade can be used in the treatment of various diseases accompanied by these pathological conditions. Currently, TRPA₁ antagonists are being actively searched for and studied, as evidenced by a high patent activity over the past 14 years; however, the molecular mechanisms of action and pharmacological properties of TRPA₁ blockers remain understudied.

Conclusion: Acquire of new information about TRPA₁ will help in the development of its modulators, which can become promising analgesics, anti-inflammatory drugs, bronchodilators, and agents for the treatment of cardiovascular diseases of new generations.

Keywords

TRPA₁, transient receptor potential ankyrin, structure, activation of TRPA₁.

Introduction

Transient receptor potential ankyrin 1 (TRPA₁) belongs to an extensive and diverse group of relatively non-selective cation channels permeable to such ions as **potassium**, **sodium**,

magnesium, and **calcium** and called transient receptor potential (TRP) channels (Samanta et al. 2018). TRP channels got their name from the *trp* gene of *Drosophila*, first described by Cosens and Manning (1969). Deletion of this gene caused a transient abnormal response of photoreceptors to

light on an electroretinogram, when mutant flies, exposed to permanent exposure of bright light, stopped making a phototactic choice in a T-shaped maze, and restored their light sensitivity only some time later in dim ambient light (Cossens and Manning 1969). The slow recovery of the mutant eye and the temporary blindness of the mutants led to the name of *trp* as a protein gene responsible for the “temporary (transient) receptor potential”. The TRP family of channels is currently represented by eleven subfamilies, united on the basis of sequence homology into two groups, and each subfamily includes several members (Himmel and Cox 2020). The ankyrin subfamily, which currently includes 7 members, is widely represented in the organic world. At the same time, proteins of this subfamily can be both specific to a certain group of organisms, for example, HsTRPA, expressed only in hymenoptera, and widely represented in various taxa, for example, TRPA₁ found in vertebrates, arthropods, mollusks, nematodes, and other organisms (Peng et al. 2015). In some cases, the corresponding proteins of various species are somewhat different in the quantitative and qualitative composition of amino acids (for example, rat TRPA₁ contains 1125, and mouse – 1115 amino acid residues), which causes the species-specific action of some biologically active compounds (thioamines, caffeine) (Chen et al. 2008; Talavera et al. 2020). As a result of studying the activity of TRPA₁, it became possible to determine its role as a universal and polymodal sensor of various adverse factors: physical (high and low temperatures, mechanical stimuli, radiation), chemical (irritants and toxins), and biological (metabolites, toxic bacterial products) (Viana 2016). The presented review is aimed at highlighting the basic data on the structure, activation mechanisms and molecular determinants associated with the human TRPA₁ and their relationship with the therapeutic potential of TRPA₁ blockers.

Materials and methods

The article presents an overview of the literature data and the results of research studies on the structure, function of the channel and their connection with the performed physiological functions, as well as the structure of activators and antagonists of TRPA₁ obtained from available and open sources for the period from 1998 to the present, with an emphasis on the last 10 years. Information was collected in such electronic resources as: PubMed, PubChem, Elibrary, Scopus, Web of Science, WIPO for the main search queries: “TRPA₁”, “TRPA₁ structure”, “TRPA₁ functions”, “activation of TRPA₁”, and “TRPA₁ antagonists”.

Results and discussion

TRPA₁ gene and expression

In humans, the TRPA₁ gene is located in chromosome 8, band 8q21.11, and consists of 73635 bases and 29 exons, and an open mRNA reading frame of the gene encodes

a polypeptide consisting of 1119 amino acids with a molecular weight of 127.5 kDa (Talavera et al. 2020). The expression of the gene varies depending on the age of the organism and the type of cells. Although TRPA₁ was initially isolated from SV40 transformed/immortalized human fibroblasts, it is mainly expressed in C- or A-fibers of small-diameter sensory ganglia, including posterior horns of a spinal cord, trigeminal and nodular ganglia (Beskhemelnitsyna et al. 2016; Meents et al. 2019). TRPA₁ channel co-expresses with such nociceptive markers as tachykinins, substance P, neurokinin A and calcitonin gene-related peptide, for which their participation in neurogenic inflammatory reactions was determined (Choi and Nardo 2018). In the central nervous system, TRPA₁ is expressed in hippocampal neurons, where it is apparently associated with the cannabinoid receptor CB1 in astrocytes, where it is involved in maintaining intracellular Ca²⁺ levels and regulation of inhibitory synapses (Araújo et al. 2017; Jiang et al. 2019). TRPA₁ expression was also shown in Schwann cells, colon cells and enterochromaffin cells, in all respiratory tract, keratinocytes, melanocytes, vascular endothelial cells, tooth pulp fibroblasts, and other cells (Souza et al. 2020). Thus, TRPA₁ channels are mainly located either in nociceptors or in tissues exposed to the external environment or exogenous factors. This is mainly due to the fact that TRPA₁ acts as a universal sensor to diverse stimuli that adversely affect the vital activity of the organism.

Structure and molecular determinants of TRPA₁

Like most other representatives of transient receptor potential channels, TRPA₁ has four levels of protein organization. The quaternary structure of ankyrin TRP channels is a homo- or heterotetramer formed by the integration of subunits consisting of 6 transmembrane domains (S1 – S6). According to Oakes and Domene (2019), subunits may belong to one or more subfamilies of TRP channels, for example, Cheng (2010) shows the functionally active integration of four TRPA₁ subunits or two TRPA₁ and two TRPV₁ (TRPV is a vanilloid TRP channel, which is a structurally similar cation channel characterized by the presence of 6 ankyrin repeats, and for which the participation in thermo- and nociception was found). In the center of the quaternary protein structure, there is a negatively charged pore (P) capable of passing cations through, usually Ca²⁺ and Mg²⁺ (Fig. 1).

Each TRPA₁ subunit, which is a tertiary organization of the protein structure, consists of 6 transmembrane domains containing α -helices. The fifth and sixth α -helices form reentrant pore loop consisting of the pore helix 1, 2 and intracellular N- and C-terminals, which are totally 78% of the polypeptide weight. At the same time, only 14% is the C-terminal, and the remaining 64% of the protein mass is the N-terminal containing 16 ankyrin repeats, the presence of significant number of which caused this protein to be named “ankyrin-like with transmembrane domains protein 1: (ANKTM1) and to be renamed as the “ankyrin channel transient receptor potential 1” after it was found to be

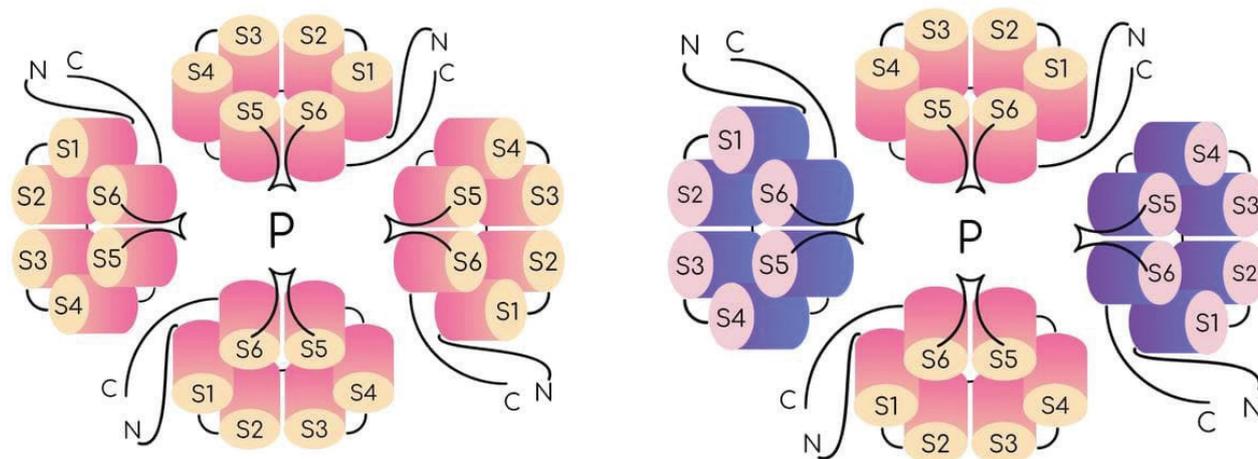


Figure 1. Scheme of the quaternary structure of homotetrameric (left) and heterotetrameric (right) TRPA₁ channel (top view). Note: P is the pore of the channel, S1–S6 are transmembrane domains.

related to the TRP channel family (Suo et al. 2020). It is noteworthy that later a new subfamily of the TRP channels called “non-mechanoreceptor” (TRPN) was discovered, the genes of which are widely expressed in animals, but are a pseudogene in amniotes, in particular, in humans, and contain about 28–29 ankyrin repeats in their structure (Schüler et al. 2015). Ankyrin (from Greek. ἄγκυρα – anchor) repeats are an example of a protein motif consisting of 33 amino acid residues, forming α -helices connected by loops, which supposedly participate in protein-protein interactions and/or provide protein embedding in the phospholipid bilayer (Li et al. 2006).

The most detailed data on the TRPA₁ structure was obtained due to the electron cryomicroscopy, and mutational studies and studies of TRPA₁ chimeras made it possible to isolate clinically and pharmacologically significant elements of the protein. So, in the article of Paulsen et al. (2015) presented the results of a study of the structural features of a full-length human TRPA₁, using electron cryomicroscopy of single particles with a resolution of 4 Å in the presence of various ligands. With the greatest accuracy, a three-dimensional structure was obtained for the Lys446–Thr1078 protein chain segment, without a detailed understanding of the structure of distal cytoplasmic fragments – up to 12 ankyrin repeats (AR1–12) from the N-terminal and after the coiled-coil domain of the C-terminal, as well as the region containing Cys665, linkers S1 – S2, S2 – S3, S3 – S4 and the connection between the third β -strand, which is part of the β -sheet and the coiled-coil domain (dotted line in Fig. 2).

Structural modeling of the ankyrin repeats showed that a quaternary protein structure is formed due to the interaction of the coiled-coil domain of the C-terminals of four subunits which placed in the center of the channel, below the ion-permeable pore, while the distal N-terminals are located outside, thereby participating in the formation of a structure similar to an anchor displayed in electronic photos in the form of a crescent. Myo-inositol hexaphosphate molecules also participate in maintaining the quaternary structure of the protein, acting as a stabilizing cofactor between the coiled-coil

domains of the C-terminals, due to the formation of ionic bonds with Leu1046 and Lys1050 of one and Leu1048 and Leu1052 of the other subunits (Paulsen et al. 2015).

Ankyrin repeats include several sites responsible for the specific sensitivity of the channel. So according to Zayats et al. (2013), the EF-hand domain (Gly479 – Leu486 as part of 12th ankyrin repeat) is one of the sites responsible for the sensitivity of the channel to intracellular calcium concentration (according to Christensen et al. (2016), others include, for example, Asp915), Ser250, deletion of which reverses the thermal sensitivity of the channel from cold to heat, and to Glu179, involved in temperature perception and identified in the study of chimeric TRPA₁ of humans and rattlesnakes (Naziroglu and Braidy 2017). TRPA₁ sensitivity sites to the oxygen level in the cell are also located at the N-terminal: with normal oxygen saturation, Pro394 is in a hydroxylated state, inhibiting the opening of the channel, which prolinhydroxylase is responsible for. But with hypoxia, the activity of prolinhydroxylase decreases, which leads to an increase in the number of non-hydroxylated Pro394 TRPA₁ channels with increased activity (Miyake et al. 2016). However, hyperoxia leads to reversible oxidation of Cys633 and Cys856, changing the reactivity of the channel (Kannler et al. 2018). The involvement of Cys540 in the sensitivity of the channel to the concentration of active forms of nitrogen in the cell was also shown (Takahashi and Mori 2011).

A pre-S1 region accessible to water molecules is behind the ankyrin repeats and consists of a linker domain and a pre-S1 helix, which includes 4 amino acid residues responsible for the sensitivity of TRPA₁ to electrophilic irritants. These 4 reactive pendant radicals of the amino acids – Cys621, Cys641, Cys665 and Lys710 – form covalent links with various electrophilic agents, acting as toxins, irritants and signaling molecules of inflammation and pain, changing the conformational structure of the protein (Zhao et al. 2020). The TRP-like domain spatially links up with the pre-S1 region and follows the S6 segment. It is responsible for the “transmission” of the conformational signal from the covalently modified amino acid residues

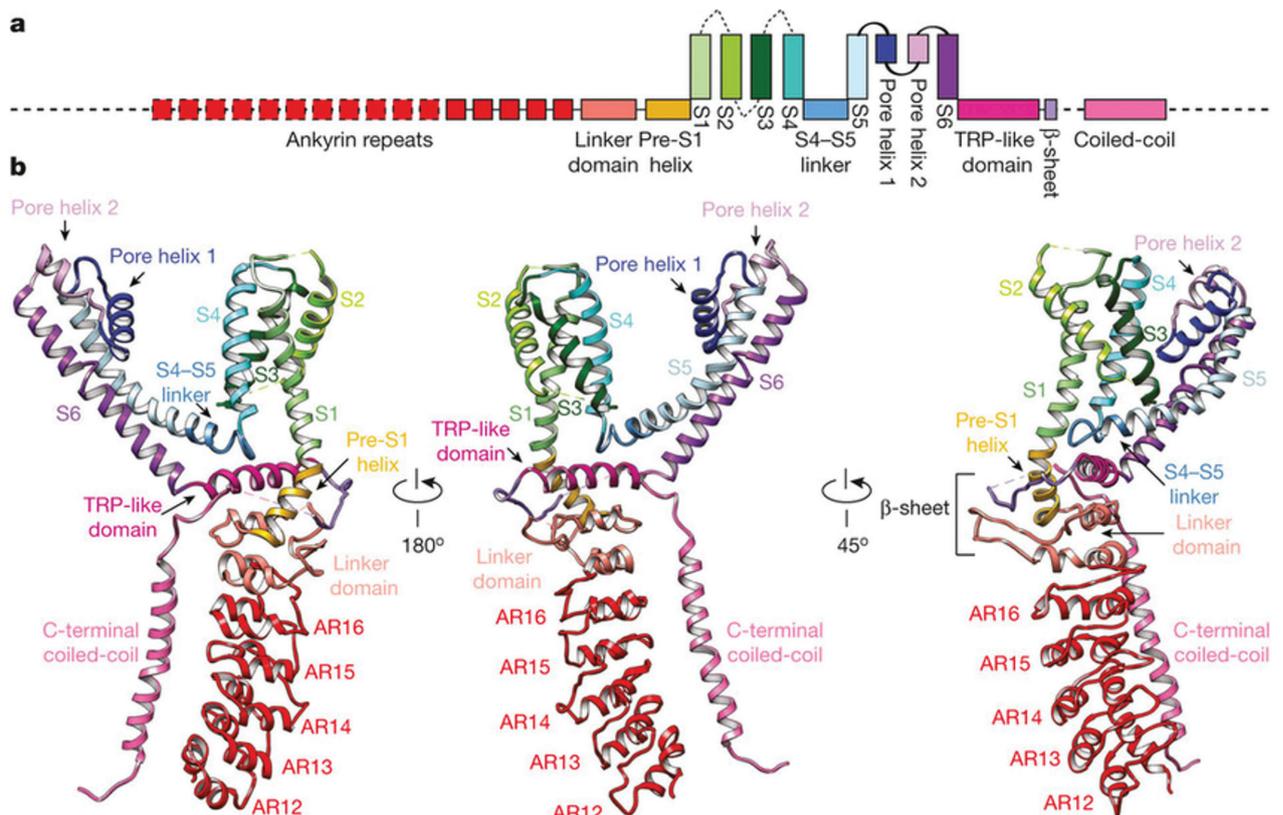


Figure 2. The three-dimensional structure of TRPA₁. **a.** A linear domain structure; **b.** A three-dimensional structure, a three-side view. **Note:** S1 – S6 – transmembrane segments, TRP – transient receptor potential, AR-12 – AR-16 – ankyrin repeats).

to the channel gates, which leads to their opening and intracellular cation influx (Paulsen et al. 2015).

For the intracellular C-terminus, sensitivity to calcium concentration by calmodulin has also been shown. The Leu992 – Asn1008 site binds to calcium-ion-activated calmodulin, resulting in sensitization and subsequent slow desensitization of the receptor (Zimova et al. 2020). It is noteworthy that heavy metal ions (Zn^{2+} , Cu^{2+}) also cause potentiation of TRPA₁, but by interaction with His983 and Cys1021 of the C-terminal (Miura et al. 2013).

As noted earlier, TRPA₁ is based on the four transmembrane subunits, each of which contains 6 transmembrane segments with the fifth and sixth domains connected by the reentrant pore loop consisting of the pore helix 1, 2. The second pore helix contains anionic amino acid residues (Glu920, Glu924, and Glu930) attracting cations and repulsing anions. The channel pore includes two constrictions called channel gates, the upper of which, with a diameter of 7–8 Å, is formed by the residues Asp915 of four subunits, and the lower – by the hydrophobic residues Ile957 and Val961, forming a ring, presumably with a diameter of 6 Å (Paulsen et al. 2015). Thus, the channel gate is wide enough to pass relatively large ions such as barium, calcium and magnesium. At the same time, activation of the channel by agonists causes reversible dilation of the channel pore, which leads to the transmission of even such large cations as the Yo-Pro fluorescent dye and meglum (Chen et al. 2009). And binding to a positively charged non-selective ion channel blocker, ruthenium red,

which forms stable ion bonds in the channel pore and prevents the cations flow, was shown for the anionic upper channel gates (Asp915) and Glu920 of the second pore helix (Wu et al. 2017).

For the selective antagonist A-967079, interaction with Tyr874 of the S5 transmembrane segment and Phe909, which is part of the pore helix 1, as well as presumably with four more surrounding amino acid residues (Ser873, Leu881, Phe944, and Val948), was revealed, which prevents the opening of the channel gate (Paulsen et al. 2015). It is noteworthy that the supposed binding site of such general anesthetics as isoflurane and propofol overlaps with the binding site of antagonist A-967079 (Ton et al. 2020). And mutations in the key amino acids of the binding site of A-967079 do not influence the activity of another selective antagonist, HC-030031, which indicates the presence of other TRPA₁ blocker binding sites, but their search by cryo-electron microscopy was unproductive (Paulsen et al. 2015). Further study of the molecular determinants of TRPA₁ antagonists by chimeric studies and point mutations helped to isolate Asn855, which is part of the loop between the 4th and 5th transmembrane segments, as well as the C-terminal, significantly contributing to the inhibitory effect of HC-030031 (Gupta et al. 2016).

Other binding sites with biologically active compounds have been detected for the transmembrane backbone. It has been shown that TRPA₁ is activated by binding essential oil compounds – menthol, thymol and carvacrol – with Ser873 and Thr874 in the S5 transmembrane segment

(Meents et al. 2016). And the amino acid residues Ser943 and Ile946, which are part of the S6 transmembrane domain, form bonds with **thioamines** that are antagonistic to human TRPA₁, but cause activation of rat TRPA₁ when interacting with Ala946 and Met949 (Chen et al. 2008). The transmembrane part also includes five residues of cysteine and lysine, three of which (Cys727, Lys771, and Cys834) are in a lipophilic medium and, therefore, can be modified by hydrophobic electrophiles, including secondary messengers of inflammation and pain (Paulsen et al. 2015).

Thus, due to the presence of both selective (binding site of **calmodulin**, heavy metals) and non-selective sensory molecular determinants (reactive cysteine and lysine amino acid residues) described above, the ankyrin TRP channel serves a universal and labile sensor of diverse stimuli, whereas the molecular mechanisms of action and binding sites of selective TRPA₁ antagonists require further study.

Activation and post-activation effects of TRPA₁

TRPA₁ can be activated by the various stimuli: physical, chemical and biological. Story et al. (2003) in their initial studies talked about the sensitivity of TRPA₁ to low temperatures (below 17 °C), but not in every instance it was possible to reproduce the activation of the channel by cold, so today the cold sensitivity of TRPA₁ is relatively controversial (Weyer-Menkhoff and Lötsch 2019; Weyer-Menkhoff et al. 2019). It has also been shown that TRPA₁ has mechanosensitivity, manifested only in the oxidized form of protein, which may be a cause of mechanical allodynia in the inflammatory process, when reactive oxygen species accumulate (Moparthi and Zygmunt 2020). In human melanocytes, TRPA₁ is indirectly activated by ultraviolet radiation, which leads to an increase in melanin synthesis and skin pigmentation (Bellono et al. 2013).

Moreover, TRPA₁ is one of the main chemosensors in living organisms. Compounds agonists of TRPA₁ are extremely diverse in nature. They can be divided into selective synthetic compounds discovered and used when studying the nociceptive properties of TRPA₁ (for example, compound PF-4840154, described by Ryckmans et al. (2011), which is a derivative of piperidine-5-carboxamide, EC₅₀=23 nM), nonelectrophilic compounds (**menthol**, **thymol**, **carvacrol**, **nicotine**, **clotrimazole**, **nifedipine**, **diclofenac**, etc.) and the most extensive group of electrophilic compounds forming covalent bonds with TRPA₁ cysteine residues. Among electrophilic agonists, hydrophobic compounds can also be distinguished (**4-oxo-2-nonenal** is a product of lipid peroxidation; **4,5-epoxyeicosatrienoic acid** is an endogenous signaling molecule) and relatively hydrophilic irritants of natural origin, for example, **allicin** contained in **garlic**, **allyl isothiocyanate** formed in mustard and horseradish; **cinnamaldehyde**, etc., as well as anthropogenic: **formaldehyde**, **acrolein**, **crotonaldehyde**, **hydrogen peroxide**, **nitrogen oxides**, heavy metals and endogenous compounds: **methylglyoxal**, reactive oxygen and nitrogen species (Cheng et al. 2010; Mukaiyama et al. 2020).

TRPA₁ can also be activated by transmitting an intracellular signal from other receptors, including G-protein-coupled receptors (GPCR) (Fig. 3).

Thus, it was found that **bradykinin**, a nonapeptide with a known algogenic effect, via the bradykinin B2 receptor activates or sensitizes TRPA₁ by phosphorylation of TRPA₁ by protein kinase A (PKA) or via the phospholipase pathway (PLC – **phospholipase C**, PIP2 – **phosphatidylinositol diphosphate**) via **diacylglycerol** (DAG) (Al-Shamlan and El- Hashim 2019). The phospholipase pathway of TRPA₁ activation is also involved in the transmission of a signal from the protease-activated receptor-2 (PAR2), interacting with **trypsin** and **tryptase** of mast cells, the synthesis of which increases in allergic reactions (Chen et al. 2016). The intracellular signal of prostaglandin E2 (PGE2), a mediator of inflammation, pain and edema interacting with prostaglandin receptors (EP), is also transmitted through the adenylate cyclase system (AC), which leads to the accumulation of cAMP and activation of PKA (Dall'Acqua et al. 2014). Sensitization of the TRPA₁ channel can also occur through its phosphorylation by **protein kinase C** (PKC) activated by the bile acid receptor (TGR5) during its interaction with bile acids, which have shown a pruritogenic (itching) effect (Lieu et al. 2014). Itching can also be caused by an antimalarial drug chloroquine, and a peptide of the adrenal medulla of cattle (BAM8–22), which interact with MAS (derived from the surname Massey)-related GPCRs (MrgprA3 and MrgprC11), leading to the dissociation of G-protein, the disconnected β-subunit of which directly activates TRPA₁ (Wilson et al. 2011). Regulation of the ankyrin TRP is also carried out at the level of its gene. Thus, nerve growth factor (NGF), for which anti-inflammatory effects have been identified, suppresses a transcription of the TRPA₁ gene via phosphorylated mitogen-activated protein kinase p38 (MAPK) activated by the tyrosine kinase receptor A (TrkA) (Diogenes et al. 2007).

It is also known that TRPA₁ can be activated by **lipopolysaccharide** (LPS), a component of the outer membrane of all gram-negative bacteria formed during their death, but the molecular mechanisms of this interaction are uncertain. It is assumed that LPS, embedded in the phospholipid bilayer, changes the tension of the membrane, which leads to the opening of the channel (Startek et al. 2018). Thus, TRPA₁ may be involved in the body's immune response to the bacterial pathogenic factors.

Summarizing the above, TRPA₁ can be activated not only by the direct action of adverse stimuli of physical, chemical and biological nature, but also be regulated indirectly through more specific receptors of pro-inflammatory, algogenic and pruritogenic factors, thereby confirming its role as one of the main integral sensors of pain and inflammation.

Regardless of the factor and the mechanism of TRPA₁ activation, it leads to an intracellular influx of **calcium**, which in nociceptor terminals causes membrane depolarization and propagation of the action potential into

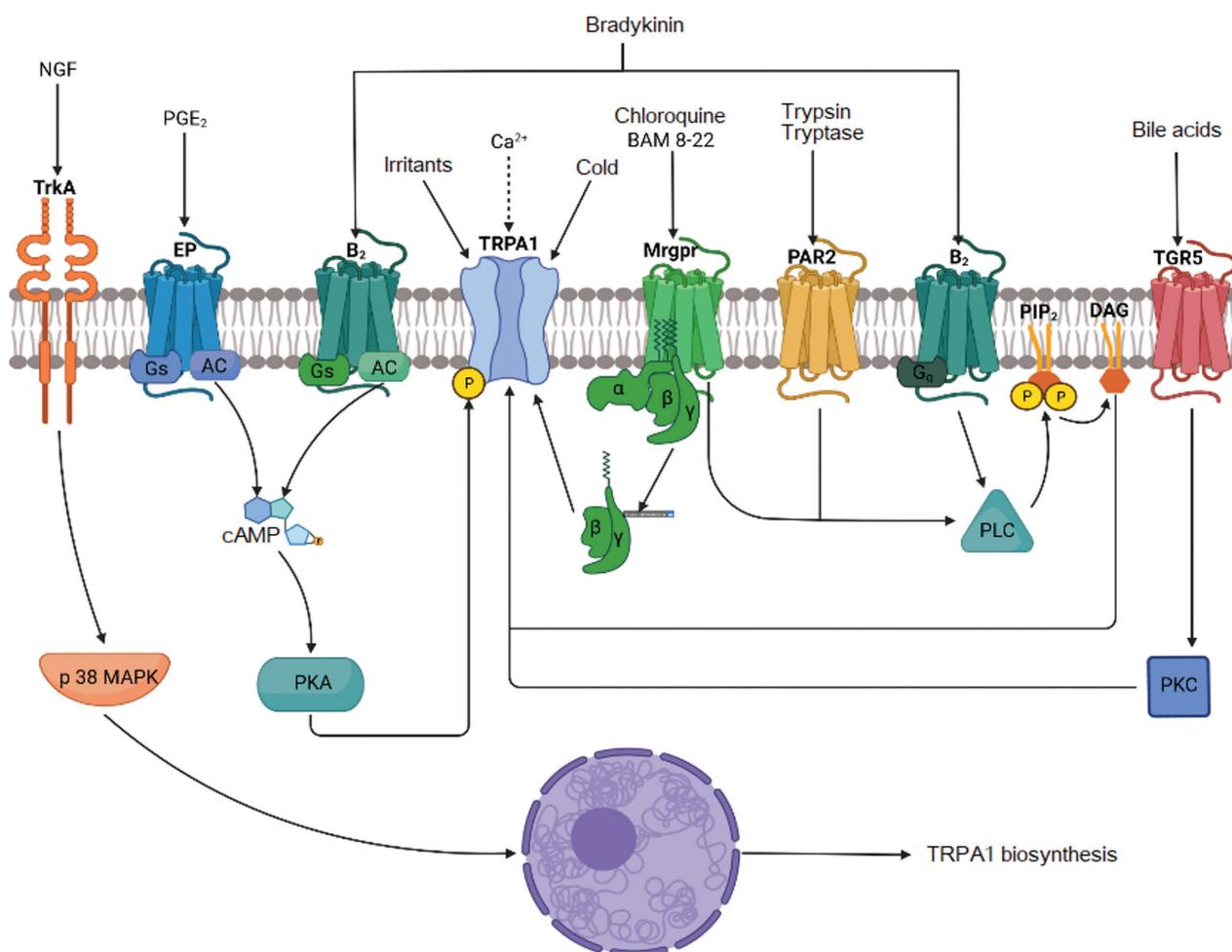


Figure 3. Intracellular regulation of TRPA₁ activity. **Note:** NGF – nerve growth factor, TrkA – tyrosine kinase receptor A, p 38 MAPK – mitogen-activated protein kinase p38, PGE₂ – prostaglandin E₂, EP – prostaglandin receptor, G_s(q) – G-proteins, AC – adenylate cyclase, cAMP – cyclic adenosine monophosphate, PKA – protein kinase A, P – phosphate residue, BAM 8-22 – a peptide of the adrenal medulla of cattle, PAR2 – protease-activated receptor-2, B₂ – a bradykinin receptor, PLC – phospholipase C, PIP₂ – phosphatidylinositol diphosphate, DAG – diacylglycerol, TGR5 – a G protein-coupled bile acid receptor, PKC – protein kinase C.

the central nervous system, causing a sensation of pain. Pain can also be caused by dilation of cerebral vessels when calcium ions entering through the TRPA₁ activate potassium channels. In turn, pain is aimed at avoiding the unfavorable factor that caused it. In barrier cells, intracellular calcium influx releases vasodilators, pro-inflammatory agents and algogens (for example, substance P and a peptide associated with the calcitonin gene), causing local vasodilation, edema, lymphocyte influx, aimed at preventing the spread of harmful agents throughout the body and activation of the body's defense mechanisms (Gouin et al. 2017). Thus, TRPA₁ is the primary link in the signaling mechanism and protection of the body from adverse factors of the internal and external environment.

TRPA₁ antagonists

Hyperstimulation of TRPA₁, caused by a super-strong or a long-acting irritant, can lead to physiological and psychological disorders, manifesting as pain and inflammatory process. Today, there has been an active search for and

study of TRPA₁ activity regulators that could be useful in the treatment of various diseases accompanied by pain and inflammation or caused by an inflammatory process, which is evidenced by a high patent activity (with over 30 patents since 2007) in this area. Analysis of available data on the TRPA₁ antagonists has shown that they can be divided into two large groups: natural antagonists showing weak activity and selectivity, for example: terpenoids and phenols described in Hoag and Salerno patent (2020) and synthetic TRPA₁ blockers, most diverse in their structure.

Historically, the first patented TRPA₁ antagonists were commercially available Cambridge-5861528 and HC030031, which are representatives of an extensive group of fused pyrimidinediones, and AP 18, a representative of the oxime group (Patapoutian and Jegla 2007). These compounds are characterized by inhibitory concentrations in the micromolar range and low solubility, so at the moment they are used only in research. Further search for TRPA₁ blockers was aimed at improving the structure of fused pyrimidinediones and the discovery of new classes of compounds. Thus, replacement of a fused

pyrrole ring with imidazole (WO 2009144548), thiophene (WO 2010109334), isothiazole (WO 2010109328), furan and isoxazole (WO 2011114184) rings and a combination of various pendent groups reduced the inhibitory concentration to the nanomolar range, and appending a hydrophilic substituent in pendent groups with the formation of arylacetylmines (CN 103261201) increased the solubility of the derivatives (Chaudhari et al. 2009; Kumar et al. 2010a, b; Chaudhari et al. 2011; Sukers et al. 2015). In addition to arylacetylmines, phthalimides (WO 2009118596) and quinazolinones (US 20090325987), which together form a subgroup of arylacetamides (Muthuppalniappan 2009a, b), can be referred to compounds similar to pyrimidinedione-fused ones, with TRPA₁ antagonistic activity. This subgroup, together with N-arylsulfonylacetamides, divided into cyclic (for example, WO 2016128529) and acyclic (for example, WO 2014135617), is part of an extensive group – acetamides (Fruttarolo et al. 2014; Estrada et al. 2016). Other groups of TRPA₁ blockers include 4-fluorine (WO 2014053694), carbonic acid derivatives (WO 2014056958), imidazopyridines (WO 2014076021), phenyl pyrazinopyrimidine diones (RU 2014147911), bicyclic oxadiazoles (WO 2018162607) and tetrahydrofuranil oxadiazoles (WO 2019182925), 3-aryloxy-3-arylpropylamines (WO 2020035040) (Arvela et al. 2014; Bachmann et al. 2014; Brotherton-Pleiss et al. 2014; Kochkarov et al. 2016; Chen et al. 2019; Terrett et al. 2019; Wang et al. 2020).

Despite all the structural diversity of compounds with TRPA₁ antagonistic activity in vitro, only a few compounds have been subjected to preclinical tests. This is due not only to the low solubility of most compounds, but also to the heterogeneity of human and rodent TRPA₁ channels. For example, according to Chen et al. (2008) representatives of the AMG group (AMG 2504, AMG5445, AMG9090, etc.) exhibit a partial agonistic activity or do not interact with TRPA₁ of rats.

The possibility of treatment of acute pain with TRPA₁ antagonists was shown in preclinical studies. In the study of Beskhmel'nitsyna et al. (2018; 2019a; 2019b), the compound ZC02-0012 showed analgesic activity superior to that of ketorolac according to hot plate and acetic acid-induced writhing tests, as well as anti-inflammatory activity, comparable to that of **diclofenac sodium**. Intraplantar injection of AR18 reduced mechanical hyperalgesia in wild-type mice and had no effect in mice with TRPA₁ genetic knockout (Petrus et al. 2007). In Wei et al study (2011), intrathecal administration of A-967079 or Chembridge-5861528 reduced secondary mechanosensitivity after injection of capsaicin or formalin. In a number of works by David et al. (2008); Wei et al. (2009); Chen et al. (2011), it has been shown that the systematic administration of HC-030031 and Chembridge-5861528 reduces the response to mechanical stimuli in rats with neuropathy and inflammation. In 2018, Galderma SA patented a number of TRPA₁ antagonists for the treatment of atopic dermatitis (Ouvry et al. 2018). In van

den Berg et al. study (2021), compound BI01305834 reduced bronchospasm in guinea pigs in response to the allergens. The antitussive effect of GRC 17536 was demonstrated in **citric-acid**-induced cough responses in guinea pigs (Mukhopadhyay et al. 2014). Li et al. (2019) showed the possibility of using HC-030031 in the treatment of cardiac dysfunction caused by myocardial infarction in mice. The selective TRPA₁ blocker reduced cardiac fibrosis and apoptosis of cells after myocardial infarction and significantly increased angiogenesis in the border zone of infarction. Intraperitoneal or intrathecal administration of Chembridge-5861528 suppressed neuropathy caused by diabetes in the absence of noticeable side effects during single or long-term administration (Wei et al. 2010).

According to Chen and Terrett (2020), today only 5 compounds (CB-625, GRC 17536, ODM-108, HX-100, and GDC-0334) reached the stage of clinical trials; however, as far as it is known from open sources, the development of all 5 molecules was discontinued mainly due to unsatisfactory pharmacokinetic parameters, and therefore the search for and study of new selective TRPA₁ antagonists, which would be promising for further development of new analgesics, anti-inflammatory drugs, bronchodilators, and agents for the treatment of cardiovascular diseases, is an urgent unsolved problem.

Conclusion

Human TRPA₁ is a recently discovered nonselective cation channel expressed mainly in nociceptor neurons and barrier cells. This channel has four levels of protein structure organization and stands out against the background of other related transmembrane proteins by an impressive intracellular N-terminal containing 16 ankyrin repeats. Accumulated data on the TRPA₁ structure and activity, obtained by electron cryomicroscopy in mutational and chimeric studies, allowed us to select a number of molecular determinants and mechanisms indicating its role as a universal sensor of adverse factors of various (physical, chemical and biological) nature, which are converted into nerve impulses or neurohumoral local responses aimed at protection of the body from the effects of these factors. Despite the protective function of the TRPA₁ channel, an increase in its activity can lead to a number of pathological conditions characterized by pain and inflammation. Currently, there is an active search for and study of the mechanisms of action of TRPA₁ antagonists, which, as shown in preclinical studies, can become effective agents in the treatment of pain, neuropathy, inflammatory processes, atopic dermatitis, cardiovascular diseases, and respiratory pathologies. Since 2007, various classes of compounds with TRPA₁ antagonistic activity in nanomolar concentrations have been synthesized and patented, but none of them is currently used as a drug, and the molecular mechanisms of action and properties of the discovered compounds have not been sufficiently studied.

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Conflict of interests

The authors declare no conflict of interests.

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