Review

The role of TRPA1 channels in thermosensation

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A R T I C L E   I N F O

A B S T R A C T

Transient receptor potential ankyrin 1 (TRPA1) is a polymodal nonselective cation channel sensitive to different physical and chemical stimuli. TRPA1 is associated with many important physiological functions in different species and thus is involved in different degrees of evolution. TRPA1 acts as a polymodal receptor for the perceiving of irritating chemicals, cold, heat, and mechanical sensations in various animal species. Numerous studies have supported many functions of TRPA1, but its temperature-sensing function remains controversial. Although TRPA1 is widely distributed in both invertebrates and vertebrates, and plays a crucial role in tempreture sensing, the role of TRPA1 thermosensation and molecular temperature sensitivity are species-specific. In this review, we summarize the temperature-sensing role of TRPA1 orthologues in terms of molecular, cellular, and behavioural levels.

1. Introduction

TRPA1 (also known as ankyrin-like with transmembrane domains protein 1 (ANKTM1) or the wasabi receptor) derives its name from numerous (14–18, depending on species) ankyrin repeat domains (ARs) at the N-terminus (Jaquemar et al., 1999; Mosavi et al., 2002; Story et al., 2003). The *trpa1* gene was first cloned from human fibroblasts in 1999 and is located on human chromosome 8 in band 8q13 (Jaquemar et al., 1999). TRPA1 is a homotetrameric nonselective cation channel, where each monomer contains six transmembrane domains(S1–S6) with cytoplasmic N- and C-termini and the pore loop is between S5 and S6 (Zygmunt and Hogestatt, 2014). TRPA1 is widely distributed in many tissues and organs and is expressed in neuronal cells such as dorsal root ganglion (DRG) neurons, trigeminal ganglia (TG) neurons, and nodose ganglia neurons (Story et al., 2003; Jordt et al., 2004; Nagata et al., 2005; Fajardo et al., 2008), as well as in non-neuronal cells such as astrocytes, hair cells, ventricular cardiomyocytes, pulmonary epithelial cells, and multiple immune cells (Clarke and Attwell, 2011; Nagata et al., 2005; Andrei et al., 2017; Buch et al., 2013; Naert et al., 2021). TRPA1 is involved in a variety of physiological and pathological processes (Talavera et al., 2020), such as neuropathic pain (Nativi et al., 2013), oxygen sensing (Takahashi et al., 2011), inflammation (Bandell et al., 2004; Bautista et al., 2006), obesity (Mahajan et al., 2021), itching (Wilson et al., 2013), mechanical allodynia and thermal hyperalgesia in drug treatment (Nassini et al., 2011), respiratory disease (Mukhopadhyay et al., 2016) and cardiovascular diseases (Gao et al., 2020). In addition, animals employ TRPA1 as an important chemoreceptor for detecting different chemicals *in vivo* and *in vitro*. TRPA1 can be activated by electrophilic reagents like allyl isothiocyanate (AITC) (Jordt et al., 2004) and non-electrophilic reagents like menthol (Karashima et al., 2007). The detection role of TRPA1 for compounds is conserved in animals, especially for harmful chemicals. TRPA1 can be activated by electrophilic reagents in almost all animals, from worms, and insects to mammals (Arenas et al., 2017; Chen et al., 2009; Bianchi et al., 2012; Jordt et al., 2004; Laursen et al., 2015).

The activities of all biomolecules, including RNA, DNA, proteins, and lipids, change with temperature. Thus, the sense of fluctuating external temperature is crucial for the survival of animals, and TRPA1, a member of temperature-sensitive ion channels, is deeply involved in the evolutionary adaptation of different species. However, since the discovery of the TRPA1 ion channel, its temperature sensitivity has always been fascinating and confusing. The temperature-sensing properties of TRPA1 are strongly enormously and species-specific (Laursen et al., 2015; Sinica and Vlachova, 2021) (see Table 1). Therefore, this review briefly demonstrates and describes the temperature-sensitive properties and thermal sensing roles of TRPA1 in different species.

2. Thermosensation of TRPA1 in mammals

2.1. Temperature sensitivity of mammalian TRPA1

In the initial report, Patapoutian's group found that noxious cold temperatures of approximately 17 °C could activate mouse TRPA1 (Story et al., 2003). Later research, however, ignited a contentious argument about the TRPA1 as a cold-activated channel. Following the first publication of TRPA1 as a cold-sensitive channel, several studies demonstrated that human (Jordt et al., 2004; Chen et al., 2013), mice (Nagata et al., 2005), rhesus monkey (Chen et al., 2013), squirrel (Matos-Cruz et al., 2017) TRPA1 orthologues expressed in HEK293 or *Xenopus* oocytes heterologous systems were not activated by cold. A study identified an alternative splice variant of the mouse *Trpa1* gene, TRPA1b, which can increase the expression of TRPA1a (full-length). However, they found that neither TRPA1a, TRPA1b alone nor TRPA1a + TRPA1b co-expressed was activated by cold stimulation down to 10 °C in the absence or presence of intracellular calcium (Zhou et al., 2013).

In addition to the controversy around whether or not heterologously expressed TRPA1 could be activated by cold, there is currently no definitive data regarding the cold sensitivity of TRPA1 in cultured or acutely isolated neuronal cells. Acute noxious cold (10 °C) does not activate rat DRG neurons (del Camino et al., 2010). Not only the ratio of cold-sensitive neurons in the trigeminal ganglion (TG) of TRPA1 knockout mice was not significantly changed compared to WT (wild type) mice (Bautista et al., 2006; Knowlton et al., 2010), but also TRPM8 (transient receptor potential melastatin 8, a cold sensor (Bautista et al., 2007) knockout mice were unchanged compared to TRPM8$^{-/-}$/TRPA1$^{-/-}$ double knockout mice (Knowlton et al., 2010).

Following these negative results, several published studies support the initial conclusion that TRPA1 acts as a cold-sensitive channel. These studies included heterologous expression of mouse and human TRPA1 and TRPA1-positive neurons from mice and rats (Moparthi et al., 2014; Karashima et al., 2009; Fajardo et al., 2008; Sawada et al., 2007; Bandell et al., 2004).

Over the past 20 years, numerous reports have shown that mammalian TRPA1 is a cold-activated channel. With the decrease in temperature, the single channel conductance of TRPA1 decreased, while open probability (Po) increased significantly (Sawada et al., 2007; Karashima et al., 2009). Ca^{2+} increased the cold activation activity of TRPA1 channels even though cold-activated TRPA1 was not dependent on intracellular Ca^{2+} release (Karashima et al., 2009). Moreover, the cold activation gating thermodynamics of TRPA1, such as entropy and enthalpy changes, were negative, consistent with the known cold activation channel TRPM8 (Karashima et al., 2009). We hypothesize that the degree of increase in channel Po and decrease in single-channel conductance during cooling may play a role in determining whether macroscopic currents can be detected with TRPA1 cold activation. According to a study, human TRPA1 shares the same cold sensitivity as TRPM8 in terms of its intrinsic features (Moparthi et al., 2014; Zakharian et al., 2010). Human TRPA1 that had been purified and placed into planar lipid bilayers demonstrated cold sensitivity independent of the N-terminal ARs (Moparthi et al., 2014).

Despite experimental evidence from several types of research does

not support that TRPA1 is the molecular basis of cold sensitivity in DRG and TG neurons (Jordt et al., 2004; Babes et al., 2004; Bautista et al., 2006; Knowlton et al., 2010). However, some studies have detected cold activation of TRPA1 expressed neurons not only in the TG and DRG but also in other neurons in response to cold temperature (Karashima et al., 2009; Sawada et al., 2007; Fajardo et al., 2008). A study demonstrated that mTRPA1 and TRPA1-expressing TG neurons might be triggered by cold, albeit the rate of cold activation was slow; hence, they hypothesized that this could partially explain why some studies failed to identify cold responses in TRPA1-positive neurons (Jordt et al., 2004; Bautista et al., 2006).

The pharmacological (TRPA1 antagonists) and genetic (TRPA1 knock-out mice) evidence suggests that TRPA1 is the essential molecular basis of cold sensing in mice vagal sensory neurons (Fajardo et al., 2008). Nodose ganglion neurons' cold-evoked responses are blocked by TRPA1 antagonists and reduced in TRPA1 knock-out mice (Fajardo et al., 2008).

2.2. Temperature detection by TRPA1

2.2.1. Cold sensation

TRPA1 is thought to have important roles in pain, chemoreception, and inflammation, but its role in cold sensation remains debated. For mammalian cold receptors, TRPM8 is recognized to play an important role in cold/cool sensation (McKemy et al., 2002; Peier et al., 2002; Madrid et al., 2006; Bautista et al., 2007; Dhaka et al., 2007), and TRPM8 knockout mice exhibit severely diminished neuronal and behavior were clearly shown to be severely attenuated by cold sensation (Bautista et al., 2007; Dhaka et al., 2007). Unfortunately, TRPA1 knockout mice failed to resolve the controversy of whether TRPA1 is a cold receptor or not.

Whether cold sensation is altered in TRPA1 knockout mice has emerged as an opposite conclusion in different studies. Two early research published in the same year yielded opposite results on whether TRPA1 is involved in mammalian cold sensation (Bautista et al., 2006; Du and Kang, 2020).

TRPA1-deficient mice show normal cold sensitivity, suggesting that the channel is not required for acute noxious cold sensing (Bautista et al., 2006; Knowlton et al., 2010). Evidence suggests that a fraction of cold-sensitive neurons does not rely on TRPA1 to produce cold responses (Jordt et al., 2004; Bautista et al., 2006; Knowlton et al., 2010).

Interestingly, previous findings indicated that a robust cold sensitivity emerges in the early stages of animal development well before the emergence of TRPA1 and TRPM8, indicating the possibility of alternative cold transduction pathways in early development (Hjerling-Leffler et al., 2007). Accordingly, a study conducted employing a pharmacological TRPA1 antagonist and knockout mice showed that TRPA1 receptors have no effect on the deep body and skin temperature, indicating that they are not involved in autonomic thermoregulatory responses (de Oliveira et al., 2014). As a result, TRPA1 as well as TRPM8 aren't the only exclusive ion channels that induce cold perception, and additional mechanisms.

However, several studies have shown that the proportion of cold-sensitive neurons in TRPA1-deficient mice is reduced (Sawada et al., 2007; Karashima et al., 2009; Fajardo et al., 2008). Moreover, subsequent investigations demonstrate that subcutaneous injection of TRPA1 agonists induces cold hypersensitivity in WT mice, but not in TRPA1 knockout mice, indicating that TRPA1 is implicated in cold-induced nociceptive behavior in mice under pathological settings (Andersson et al., 2009; del Camino et al., 2010; Andersson et al., 2012; Gentry et al., 2010). A study observed significant differences between TRPM8$^{-/-}$/TRPA1$^{-/-}$ double knockout mice and TRPM8-deficient mice by analyzing the cold avoidance behavior of mice in the thermal ring track assay (30 and 5 °C) (Winter et al., 2017).

Similarly, there were no significant differences in the latency of the first behavioral response to cold in WT and TRPA1$^{-/-}$ two genotype mice after placement on a cold plate at 0 °C (Bautista et al., 2006; Karashima et al., 2009). But TRPA1$^{-/-}$ mice in the cold plate test showed a significantly lower total number of jumps and a considerably longer latency for

Table 1
Temperature sensitivity data for TRPA1 orthologues from different animal species.

Species	Heat/cold	Threshold (°C)	Expression system	References
Human (*Homo sapiens*)	cold sensitive	≤17	DRG neurons	Story et al. (2003)
	cold sensitive	About 17-20	HEK 293	Moparthi et al. (2014)
	cold sensitive	About 16-18	Oocytes	Bandell et al. (2004)
	heat sensitive	N.D.	HEK293	Hynkova et al. (2016)
	bidirectional	N.D.	HEK293; F11 neuroblastoma cells	Sinica et al. (2019)
	bidirectional	N.D. (heat); N.D. (cold)	Planar lipid bilayers; HEK293	Moparthi et al. (2016)
	cold insensitive	–	HEK293	Chen et al. (2013)
	cold insensitive	–	HEK293	Miyake et al. (2016)
Rhesus monkey (*Macaca mulatta*)	cold insensitive	–	HEK293	Chen et al. (2013)
Mouse (Mus musculus)	cold sensitive	17.5 ± 3.5(CHO)	CHO; HEK293; Oocytes	Story et al. (2003)
	cold sensitive	N.D.	CHO; HEK293	Jabba et al. (2014)
	cold sensitive	About 16	Oocytes	Viswanath et al. (2003)
	cold sensitive	About 15–16 (Oocytes)	CHO; Oocytes	Bandell et al. (2004)
	cold sensitive	16(CHO); 18.9 ± 0.4(TG neurons)	CHO; TG neurons	Karashima et al. (2009)
	cold sensitive	<15.5 ± 0.52(DRG neurons); 17.2 ± 1.2 (HEK293, whole-cell); 16.5 ± 2.7 (HEK293, inside-out)	HEK293; DRG neurons	Sawada et al. (2007)
	cold sensitive	16	HEK293	Chen et al. (2013)
	cold sensitive	N.D.	HEK293; DRG neurons	Miyake et al. (2016)
	cold sensitive	About 17-20	CHO	Startek and Talavera (2020)
	bidirectional	N.D.	HEK293; F11 neuroblastoma cells	Sinica et al. (2019)
	cold insensitive	–	HEK293	Nagata et al. (2005)
Rat (*rattus norvegicus*)	cold sensitive	21.9 ± 1.2	Nodose ganglion neurons	Fajardo et al. (2008)
	cold sensitive	About 18	HEK293	Chen et al. (2013)
	cold sensitive	N.D.	CHO	de Oliveira et al. (2014)
	cold sensitive	N.D.	HEK293	21068322 (del Camino et al., 2010)
	cold insensitive	–	DRG neurons	Babes et al. (2004)
	cold insensitive	–	DRG neurons	del Camino et al. (2010)
Thirteen-lined ground squirrel (*Citellus tridecemlineatus*)	cold insensitive	–	Oocytes	Matos-Cruz et al. (2017)
Chicken (*Gallus gallus*)	heat sensitive	39.4 ± 1.1(Oocytes)	Oocytes; HEK293; DRG neurons	Saito et al. (2014)
Rattlesnake	heat sensitive	26.3/23.3	Oocytes	Kang (2016)
Rattlesnake (*Crotalus atrox*)	heat sensitive	27.6 ± 0.9(HEK293)	HEK293; Oocytes; TG neurons	Gracheva et al. (2010)
	heat sensitive	N.D.	Oocytes	Cordero-Morales et al. (2011)
	heat sensitive	N.D.	Oocytes	Du and Kang (2020)
Boas (*Boa constrictor*)	heat sensitive	N.D.	Oocytes; TG neurons	Du and Kang (2020)
	heat sensitive	29.6 ± 0.7(Oocytes)	HEK293; Oocytes; TG neurons	Gracheva et al. (2010)
Python (*Python bivittatus*)	heat sensitive	32.7 ± 1.3(Oocytes)	Oocytes; TG neurons	Gracheva et al. (2010)
Rat snake (*Elaphe obsolete lindheimerii*)	heat sensitive	37.2 ± 0.7(Oocytes)	HEK293; oocytes; TG neurons	Gracheva et al. (2010)
Chinese three-keeled pond turtle (*Mauremys reevesii*)	heat sensitive	28.0 ± 0.2(SF9 cells)	SF9 cells; DRG neurons	Ye et al. (2021)
Anolis lizards (*Anolis allogus*)	heat sensitive	33.5 ± 0.69	Oocytes	Akashi et al. (2018)
Anolis lizards (*Anolis homolechis*)	heat sensitive	36.4 ± 0.79	Oocytes	Akashi et al. (2018)
Anolis lizards (*Anolis sagrei*)	heat sensitive	36.1 ± 0.78	Oocytes	Akashi et al. (2018)
Green anole lizards (*Anolis carolinensis*)	heat sensitive	35.8	HEK293	Kurganov et al. (2014)
	heat sensitive	33.9 ± 0.8(Oocytes)	Oocytes; HEK293; DRG neurons	Saito et al. (2012)
African clawed frog (*Xenopus laevis*)	heat sensitive	TRPA1a: 37.8 ± 0.6; TRPA1b: 36.4(Oocytes)	Oocytes; HeLa cells	Saito et al. (2016)
Western clawed frog (*Xenopus tropicalis*)	heat sensitive	39.7 ± 0.7(Oocytes)	Oocytes, HEK293; DRG neurons	Saito et al. (2012)
	heat sensitive	39.9 ± 0.5	Oocytes	Saito et al. (2016)
Zebrafish (*Danio rerio*)	bidirectional (zTRPA1b); heat insensitive(zTRPA1a)	cold: < 10; heat: > 25	Oocytes	Oda et al. (2016)
Medaka (*Oryzias latipes*)	heat sensitive	unclear	Oocytes	Oda et al. (2017)
Pufferfish (*Takifugu rubripes*)	bidirectional	>25(heat); 7.9 ± 0.5 (cold)	Oocytes	Oda et al. (2018)
Honey bee (*Apis mellifera*)	heat sensitive	33.9 ± 0.6	HEK293	Kohno et al. (2010)
Mosquito (*Anopheles gambiae*)	heat sensitive	N.D.	Oocytes	Wang et al. (2009)
	heat sensitive	28.5 ± 0.7	HEK293	Li et al. (2019)
	heat sensitive	N.D.	Oocytes	Hamada et al. (2008)
Mosquito (*Aedes aegypti*)	heat sensitive	32 ± 0.8	HEK293	Nguyen et al. (2022)
Mosquito (*Culex pipiens pallens*)	heat sensitive	21.8 ± 0.7	HEK293	Nguyen et al. (2022)
Mosquito (*Aedes aegypti*)	heat sensitive	32 ± 0.8	HEK293	Li et al. (2019)

Table 1 (*continued*)

Species	Heat/cold	Threshold (°C)	Expression system	References
Mosquito (*Culex pipiens pallens*)	heat sensitive	21.8 ± 0.7	HEK293	Li et al. (2019)
Mosquito (*Anopheles stephensi*)	heat sensitive	30.3 ± 0.9	HEK293	Li et al. (2019)
Fruitfly (*Drosophila*)	heat sensitive	N.D.	*Drosophila* S2 Cells	Wang et al. (2013)
	heat sensitive	30(dTRPA1-A); 30(dTRPA1-B); 34(dTRPA1-C); 31(dTRPA1-D)	*Drosophila* S2 Cells	Gu et al. (2019)
	heat sensitive	N.D. (dTRPA1-A); N.D. (dTRPA1-D)	Oocytes	Luo et al. (2017)
Fruitfly (*Drosophila melanogaster*)	heat sensitive	29.7 ± 0.3(dTRPA1-A); 27.8 ± 0.4(dTRPA1-B)	Oocytes	Kang et al. (2011)
	heat sensitive	24-29(Oocytes); 27(CHO)	Oocytes; CHO	Viswanath et al. (2003)
	heat sensitive	N.D.	Oocytes	Hamada et al. (2008)
	heat sensitive	33.7 ± 1.0	Oocytes	Gracheva et al. (2010)
Starfish (*Patiria pectinifera*)	heat sensitive	34.8 ± 0.5	Oocytes	Saito et al. (2017)
Mites (*Tropilaelaps mercedesae*)	heat sensitive	N.D.	HEK293	Peng et al. (2016)
Mites (*Varroa destructor*)	heat sensitive	N.D.	HEK293	Peng et al. (2016)
Nematode worm *Caenorhabditis elegans*	cold sensitive	N.D.	PVD neurons; FLP neurons; HEK293	Chatzigeorgiou et al. (2010)
	cold sensitive	N.D.	Intestine cell	Xiao et al. (2013)

N.D., Not Defined.

the first jump compared to WT mice (Karashima et al., 2009). In addition, TRPA1$^{-/-}$ mice showed significantly longer tail-flick latency in the cold tail-flick test (Karashima et al., 2009). This suggests that some of the conflicting research results may be due to inconsistent experimental design or analytical approaches. In conclusion, the role of TRPA1 in sensing noxious cold temperatures has not been established and it is not yet possible to answer whether TRPA1 is a cold receptor *in vivo*.

Although there are still conflicting opinions on whether TRPA1 is a cold sensor in mammals, TRPA1 contributes to cold hypersensitivity is supported by many studies (del Camino et al., 2010; Ji et al., 2008; da Costa et al., 2010; Gentry et al., 2010; Yamamoto et al., 2015).

2.2.2. Heat sensation

In addition to reports of cold perception in mammals, it has been shown that TRPA1 also plays a vital role in noxious heat stimuli. A previous study seems to support that TRPA1 mediates a critical physiological role in noxious heat sensing in rodents (Hoffmann et al., 2013). A recent study demonstrates that TRPA1 is tightly linked to heat perception and that there is redundancy in noxious heat transduction in mice. They found extensive co-expression of transient receptor potential vanilloid 1 (TRPV1), transient receptor potential melastatin-3 (TRPM3), and TRPA1 in wild-type heat-sensitive TG neurons; when they combined elimination of TRPA1, TRPV1, and TRPM3 they obtained heat-insensitive mice, and TRPV1$^{-/-}$/TRPM3$^{-/-}$/TRPA1$^{-/-}$ triple knockout (TKO) showed a complete loss of perception of acute noxious heat stimuli; whereas mTRPA1 expressed in CHO cells treated with hydrogen peroxide was able to detect heat-activated currents, while hydrogen peroxide treatment did make TRPA1 more sensitive to heat, allowing heat to excite TRPA1-expressing neurons (Vandewauw et al., 2018). This is in line with previous studies showing that the heat sensitivity of mTRPA1 depends on the channel or cellular redox state (Moparthi et al., 2016). However, the physiological mechanism of how TRPA1 is oxidized *in vivo* to contribute to heat sensing remains unknown.

3. Thermosensation of TRPA1 in non-mammals

TRPA1 temperature sensitivity has been documented more frequently in organisms other than mammals, and there are species-specific variations in TRPA1 temperature sensitivity. In addition to shared chemosensitivity, TRPA1 is also used as a sensor of warm or noxious temperatures in other animals (Talavera et al., 2020; Hoffstaetter et al., 2018; Saito and Tominaga, 2017). Different species use TRPA1 to perform different physiological functions by adapting its temperature-sensing properties, for example, some snakes use TRPA1 for infrared radiation detection (Gracheva et al., 2010), worms, flies, and clawed frogs use TRPA1 as a cold or heat sensor to detect noxious temperature (Chatzigeorgiou et al., 2010; Tracey et al., 2003; Saito et al.,

2012), and turtle embryos use TRPA1 to sense warm temperature for behavioral thermoregulation and to maintain their optimal body temperature (Ye et al., 2021).

3.1. TRPA1 acts as a thermosensor in invertebrates

A result obtained on *Caenorhabditis elegans* suggests that cold sensitivity of TRPA1 appears to be conserved in worms and mice, TRPA1 is responsible for cold sensation in *C. elegans* posterior ventral dorsal (PVD) neurons and intestinal cells (Chatzigeorgiou et al., 2010; Xiao et al., 2013). Expressing *C. elegans* and mouse TRPA1 cDNA in PVD neurons rescues the cold-insensitive phenotype of *trpa1* deletion mutants (Chatzigeorgiou et al., 2010). Similarly, wild-type TRPA1 expression in the intestine is sufficient to rescue the cold response defect in *trpa1* mutant worm intestinal cells (Xiao et al., 2013). Furthermore, heterologous expression of TRPA1 in *C. elegans* FLP neurons and CHO cells confers cold sensitivity to both (Chatzigeorgiou et al., 2010).

Unlike *C. elegans* TRPA1 is cold-sensitive, planarian worm, mites, flies, mosquitoes and honeybees TRPA1 orthologues are heat-activated (Arenas et al., 2017; Tracey et al., 2003; Gu et al., 2019; Kohno et al., 2010). *Tropilaelaps mercedesae* (TmTRPA1) and *Varroa destructor* (VdTRPA1) showed conserved chemosensitivity, while all isoforms of TmTRPA1 and VdTRPA1L isoform were potential heat sensors (Dong et al., 2016; Peng et al., 2016). *Drosophila melanogaster* TRPA1 (dTRPA1) acts as a temperature-sensitive channel involved in a variety of temperature-related behaviors like thermosensation (Zhong et al., 2012; Kwon et al., 2008; Kang et al., 2011), temperature-dependent rhythmic activity (Das et al., 2016; Roessingh and Stanewsky, 2017) and thermotaxis (Rosenzweig et al., 2005; Hamada et al., 2008; Kwon et al., 2008) in *Drosophila*.

The dTRPA1 channel has five isoforms (dTRPA1-A, B, C, D and E), which are used to detect electrophilic compounds and temperatures (Gu et al., 2019; Zhong et al., 2012; Kang et al., 2010, 2011; Hamada et al., 2008). All dTRPA1 isoforms were activated by heat except for dTRPA1-E, dTRPA1-C mediates ultraviolet and electrophilic reagent detection, while dTRPA1-D (temperature coefficients, Q_{10} around 50) is essential for the detection of noxious thermal stimuli (Gu et al., 2019).

Mosquitoes, like *Drosophila*, adapt the properties of their TRPA1 isoforms to meet their different needs (Kang et al., 2011). Different species of mosquitoes adapt to diverse thermal ecological niches by changing the TRPA1 temperature activation thresholds (Li et al., 2019; Nguyen et al., 2022). The thermal activation threshold (33.9 ± 0.6 °C, Q_{10} = 17.2) of honeybee (*Apis mellifera*) TRPA1 is well consistent with the thermal preference of honeybees (~35 °C) and may help bees detect elevated brood nest temperatures and maintenance of normal brood nest temperatures (Kohno et al., 2010).

3.2. TRPA1 channels are involved in thermosensation in non-mammalian vertebrates

In addition to invertebrates, vertebrates achieve different temperature sensing functions by altering TRPA1 properties.

Similar to mammals, TRPA1 and TRPV1 are highly overlapping in the DRG neurons of chickens (Saito et al., 2014). However, the threshold of heat activation of chicken TRPA1 is 39.4 °C, slightly below body temperature (41–42 °C) (Saito et al., 2014), indicating that chicken TRPA1 may not be a noxious heat receptor and that its physiological role is unclear.

Several vertebrate families possess sensory organs dedicated to infrared radiation detection: vipers, pythons, boas, and vampire bats, while snakes use a similar molecular strategy to sense infrared radiation, evolutionarily selecting TRPA1 as a specific and highly sensitive thermosensor in pit organ (Gracheva et al., 2010). *Boidae*, *Pythonidae,* and *Crotalinae* have a special pit organ, a sensory system that detects infrared radiation innervated by nerve fibers of the TG (Gracheva et al., 2010). By comparing transcriptomic data of TG and DRG in pit-bearing snakes, researchers found that TRPA1 is highly enriched in TG innervating the pit bearing and exhibits strong thermal sensitivity; rattlesnakes, boas, and pythons, with buccal fossa had thermal activation thresholds of 27.6 °C ($Q_{10} = 13.7$), 29.6 °C, and 32.7 °C, respectively, while rat snake (*Elaphe obsoleta lindheimeri*) (non-pit) TRPA1 has a higher thermal activation threshold of 37.2 °C ($Q_{10} = 8.8$) (Gracheva et al., 2010).

Among the two TRPA1 paralogs in zebrafish, zebrafish TRPA1a is chemosensitive while zebrafish TRPA1b ($Q_{10} = 8.2$) is temperature-sensitive (Oda et al., 2016). zebrafish TRPA1b and pufferfish TRPA1 expressed in oocytes exhibit bimodal temperature properties, which were activated by both temperatures above 25 °C (but without a clear threshold) and below 10 °C (Oda et al., 2016, 2018). In contrast, TRPA1 in medaka (*Oryzias latipes*) cannot be activated by cold and is heat activated (Oda et al., 2017).

The thermal activation threshold of 39.7 °C ($Q_{10} = 59.2$) for western clawed frog (*Xenopus tropicalis*) TRPA1 matches the temperature preference of this species (Saito et al., 2012). Besides the thermal tolerance, the diversity of thermal sensations affects species' preferred temperature ecological niche. *Xenopus laevis* and *X. tropicalis* adapted to different temperature environments depending on the heat-induced activity and sensitivity of TRPA1 and heat desensitization or heat sensitization of TRPV1 channels (Saito et al., 2016). Further studies found that the activity of TRPA1 to heat showed a significant correlation with warm and cool adaptations in four clawed frog species. Xbo-TRPA1a (*Xenopus borealis*) and Xla-TRPA1a (*X. laevis*) exhibit higher heat-induced activity than Xmu-TRPA1a (*Xenopus muelleri*) and Xtr-TRPA1 (*X. tropicalis*), which is consistent with their thermal ecological niches, that *X. borealis* and *X. laevis* are adapted to cooler environments than *X. muelleri* and *X. tropicalis* (Saito et al., 2019). These findings suggest that changes in the heat-activated activity of TRPA1 rather than in sensitivity largely contribute to the evolutionary shift in heat perception during the thermal adaptation.

The thermal activation threshold of TRPA1 achieves the adaptation of lizards to different temperature environments. Anole lizards (*Anolis allogus, Anolis homolechis,* and *Anolis sagrei*), although distributed in the same location in Cuba, selected different thermal microhabitats separately (Cádiz et al., 2013; Ruibal, 1961). Further study demonstrated that sun-dwelling species, *A. homoelchis* and *A. sagrei*, were more tolerant to heat stimuli than shade-dwelling species, *A. allogus*. Consistent with this result, the heat-evoked threshold of TRPA1 was also higher in *A. homoelchis* and *A. sagrei* than in *A. allogus* (Akashi et al., 2018). This suggests that TRPA1 was involved in the selection of these lizard species' thermal microhabitats as a critical thermosensor.

TRPA1 functions as a thermosensor not just in adults but also in starfish larvae, silkworm larvae, fly larvae, and turtle embryos (Saito et al., 2017; Sato et al., 2014; Rosenzweig et al., 2005, 2008; Luo et al., 2017; Kwon et al., 2008; Ye et al., 2021). Studies using RNA interference

and classical gene mutagenesis revealed that TRPA1 is essential for warming avoidance in *Drosophila* larvae (Rosenzweig et al., 2005, 2008). The heat activation threshold for *Patiria pectinifera* TRPA1 was 34.8 ± 0.5 °C and *P. pectinifera* TRPA1 was expressed in larvae and functioned as thermosensors for positive thermotaxis (Saito et al., 2017). In silkworms, embryonic *Bombyx mori* TRPA1 was activated above 21 °C ($Q_{10} = 20.5$) and was involved in diapause induction (Sato et al., 2014). By using pharmacological evidence, a recent study demonstrated that TRPA1 and TRPV1 form the molecular basis of embryonic behavioral thermoregulation in *Mauremys reevesii* embryos (Ye et al., 2021). Since behavioural thermoregulation is widespread in the embryos of reptiles and birds (Li et al., 2014), these species likely use a similar molecular basis of temperature sensing during (and even after) the hatching period.

4. Molecular basis of thermal activation of TRPA1

The theory of Clapham and Miller and the study of Chowdhury et al. suggested that according to the laws of thermodynamics, all temperature-sensitive channels should be cold- and heat-sensitive (Clapham and Miller, 2011; Chowdhury et al., 2014). Two studies reported that TRPA1 in mice and human has bimodal thermal properties and is activated by cold and heat (Moparthi et al., 2016; Sinica et al., 2019). Similarly, This U-shaped thermosensitivity of TRPA1 was also observed in zebrafish (*Danio rerio*) and pufferfish (*Takifugu rubripes*) (Oda et al., 2016, 2018).

Both the N-terminal and pore domains are important for the temperature sensitivity of temperature-sensitive transient receptor potential channels (thermo-TRPs) such as TRPA1, TRPV1, and TRPM8 (Wang et al., 2013; Cordero-Morales et al., 2011; Laursen et al., 2016; Yang et al., 2010, 2020; Lu et al., 2022). Interestingly, the N-terminal MHR1-3(melastatin homology regions 1 to 3) of TRPM8 confers its cold activation function (Lu et al., 2022), and the hydrophobicity of the pore region amino acids regulates the cold activation efficiency (Yang et al., 2020), while purified human TRPA1 lacking the N-terminal ARD (ankyrin repeat domain) (Δ1–688 hTRPA1) can still be cold activated (Moparthi et al., 2014). Replacement of the human TRPA1 ARD with the heat-sensitive rattlesnake TRPA1 or dTRPA1 ARD confers heat sensitivity to human TRPA1 (Cordero-Morales et al., 2011), while a recent study found that two single point mutations in the N-terminal ARD of mosquito TRPA1 altered its heat activation threshold (Nguyen et al., 2022), suggesting that the N terminal has a critical role in TRPA1 heat-sensitivity.

The directionality of TRPA1 temperature activation has also been linked to its N-terminal ARD and pore regions. In mouse TRPA1, three single point mutations (S250N, M258L and D261G) in ankyrin repeat six caused it to be heat-sensitive (Jabba et al., 2014), while in dTRPA1, a single amino acid mutation (R1073Q) in pore region changed its heat sensitivity to cold sensitivity (Wang et al., 2013). Using Clapham and Miller's theory (Clapham and Miller, 2011), it is possible that differences in amino acid residues in TRPA1 homologs result in a shift in the detectable minimum temperature of channel opening, causing TRPA1 temperature activation to appear to reverse its directionality (Laursen et al., 2015). This may explain the differences in TRPA1 temperature sensitivity across species.

The interaction network formed by the interaction between ARD and helix-turn-helix motifs allows ARD to transmit information to the pore (Paulsen et al., 2015). In temperature-sensitive channels, the hydrophobicity of amino acid residues is partially responsible for their temperature sensitivity (Yang et al., 2020; Sosa-Pagan et al., 2017). Thus, the studies on the hydrophobicity of amino acid residues near the pore region and N terminus of TRPA1 may enhance the understanding of the mechanism of TRPA1 temperature activation.

5. Brief overview of the physiological and pathological roles of TRPA1

Besides thermosensation, TRPA1 channels are widely involved in nociceptive, pathological, and inflammatory pain processes, such as

mechanical and thermal hypersensitivity (Obata et al., 2005; Nassini et al., 2011; del Camino et al., 2010; Staff et al., 2017), cancer pain (Antoniazzi et al., 2019), chemical-induced pain (Kwan et al., 2006; Bandell et al., 2004), visceral pain (Yang et al., 2008; Kondo et al., 2009; Balemans et al., 2017), migraine (Benemei et al., 2014; Nassini et al., 2014). Meanwhile, a gain-of-function mutation (N855S) in human TRPA1 causes a rare channelopathy pain syndrome which is named familial episodic pain syndrome (FEPS) (Kremeyer et al., 2010). Moreover, several human TRPA1 gene polymorphisms have been linked to cramp-fasciculation syndrome (CFS), crisis pain in sickle cell disease, and childhood asthma (Nirenberg et al., 2018; Jhun et al., 2018; Gallo et al., 2017).

Besides nociceptive neurons, TRPA1 is widely expressed in immune cells and is associated with various pathophysiologies, including inflammation (Naert et al., 2021). TRPA1 in immune cells is associated with anaphylaxis (Matsuda et al., 2020), chronic itch in atopic dermatitis (Oh et al., 2013), arthritis (Horvath et al., 2016; Batai et al., 2019), atherosclerosis (Zhao et al., 2016; Wang et al., 2020), colitis (Bertin et al., 2017), cardiac hypertrophy and fibrosis (Wang et al., 2018), kidney injury (Ma et al., 2019; Wu et al., 2021; Ma and Wang, 2021), and inflammatory bowel disease (Cseko et al., 2019). TRPA1 also mediates vascular physiology and cardiovascular diseases including arrhythmia, heart failure, and myocardial fibrosis in addition to atherosclerosis (Gao et al., 2020). Activating the TRPA1 channel causes vasodilation, which regulates blood flow and blood pressure (Gao et al., 2020).

The variety of physiological and pathological processes such as urogenital function, itch, ischemia, cancer, gastrointestinal tract diseases, respiratory disease, obesity, diabetes, and pancreatitis involving TRPA1 makes this channel an important therapeutic target (Talavera et al., 2020). Both agonists and antagonists of TRPA1 are used in clinical and pre-clinical trials for various diseases (Talavera et al., 2020, Souza Monteiro de Araujo et al., 2020; Chen and Hackos, 2015; Heber and Fischer, 2019; Koivisto et al., 2018; Chen and Terrett, 2020).

6. Conclusions

In contrast to other thermo-TRPs, such as TRPV1 and TRPM8, which play similar roles in temperature sensing across species (Hoffstaetter et al., 2018), TRPA1 is a distinct temperature receptor in diverse invertebrates and vertebrates. The role of TRPA1 in temperature sensing varies by species (Laursen et al., 2015; Sinica and Vlachova, 2021). TRPA1 is a very intriguing channel with a high degree of functional plasticity involved in the evolution of temperature-environment adaptations in different animals to suit their physiological needs. TRPA1 has been reported in some species (e.g., zebrafish (Oda et al., 2016), pufferfish (Oda et al., 2018), human, and mouse (Sinica et al., 2019)) to be activated by heat and cold, and this bimodal thermal property gives it the potential to act as both heat and cold sensors.

In contrast to the well-defined temperature sensitivity of non-mammalian TRPA1, the temperature sensitivity of mammalian TRPA1 is highly ambiguous, and its temperature response is modified *in vivo* by several variables, including H_2O_2, reactive oxygen species, and Ca^{2+} (Vandewauw et al., 2018; Moparthi et al., 2016; Miyake et al., 2016, 2017; Karashima et al., 2009). In the meantime, the residues important for perceiving hypoxia and hyperoxia are preserved in mammals (Mori et al., 2017). These studies suggest that oxidative stress products created by noxious heat and cold stimuli may be a precondition for the temperature sensitivity of TRPA1 channels (Vandewauw et al., 2018). TRPA1 is more likely to be a downstream mediator than a primary sensor, even if it is implicated in mammalian temperature sensing. Therefore, further research is required into the function of TRPA1 in mammalian thermosensation.

Author contributions

All authors contributed in the preparation of this manuscript. H.Z. and R.L. contributed to preparing the draft version. C.W., K.Z., P.M.K., A.L. and L.T. critically reviewed and revised the manuscript. All authors read and approved the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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