BIOMOLECULES & THERAPEUTICS

Review
Biomol Ther 32(2), 192-204 (2024)

Inhaled Volatile Molecules-Responsive TRP Channels as Non-Olfactory Receptors

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Abstract

Generally, odorant molecules are detected by olfactory receptors, which are specialized chemoreceptors expressed in olfactory neurons. Besides odorant molecules, certain volatile molecules can be inhaled through the respiratory tract, often leading to pathophysiological changes in the body. These inhaled molecules mediate cellular signaling through the activation of the Ca^{2+}-permeable transient receptor potential (TRP) channels in peripheral tissues. This review provides a comprehensive overview of TRP channels that are involved in the detection and response to volatile molecules, including hazardous substances, anesthetics, plant-derived compounds, and pheromones. The review aims to shed light on the biological mechanisms underlying the sensing of inhaled volatile molecules. Therefore, this review will contribute to a better understanding of the roles of TRP channels in the response to inhaled molecules, providing insights into their implications for human health and disease.

Key Words: Transient receptor potential channel, TRPV1, TRPA1, Volatile organic compound, Non-olfactory receptors

INTRODUCTION

There are various volatile molecules present in the surrounding air that pass through the respiratory tract, which is connected from the nasal cavity to the lungs. Among those, odorant molecules transmit scent information to the brain by activating the olfactory receptors of olfactory nerve cells within the olfactory epithelium. These volatile compounds can originate from various sources, including industrial processes, vehicle emissions, and consumer products. As harmful substances, it is important to note that when inhaled, they can pose a substantial risk to human health (Lee *et al*., 2023). Extensive studies have supported that these inhaled molecules play a role in mediating cellular signaling by activating the Ca^{2+}-permeable transient receptor potential (TRP) channels in peripheral tissues. For instance, it has been established that unsaturated aldehydes such as crotonaldehyde, which is present in tobacco smoke, can activate the TRPA1 channel (Facchinetti *et al*., 2007; Andrè *et al*., 2008). This channel is involved in essential protective mechanisms in the body, such as coughing or respiratory suppression. Interestingly, inhalation anesthetics have been reported to stimulate several TRP channels as a side effect, despite their primary purpose of inducing and maintaining anesthesia (Bahnasi *et al*., 2008; Cornett *et al*., 2008; Eilers *et al*., 2010; Kichko *et al*., 2015b).

This review focuses on the biological functions of TRP channels that respond to volatile molecules including hazardous, anesthetic, and plant-derived compounds as well as pheromones (Fig. 1). The review aims to discuss the potential implications of these compounds in human health. Moreover, we will delve into the mechanisms through which TRP channels can be targeted to control pain, regulate respiratory and immune system function, and prevent adverse responses to harmful volatile molecules.

TRP CHANNELS

Transient receptor potential channels are non-selective cation channels that primarily facilitate the influx of Ca^{2+} into the cell. Thus, TRP channels play a crucial role in intracellular calcium signaling pathways, which regulate a wide range of cellular processes, including neurotransmitter release, proliferation, differentiation, gene transcription, cell death, and

Open Access https://doi.org/10.4062/biomolther.2023.118

Received Jun 20, 2023 **Revised** Jul 8, 2023 **Accepted** Jul 12, 2023
Published Online Aug 8, 2023

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inflammation (Jang *et al*., 2012). Based on their sequence homology and functional properties, TRP channels are largely classified into six distinct subfamilies, namely TRPV (TRPV1–TRPV6), TRPA (TRPA1), TRPM (TRPM1–TRPM7), TRPC (TRPC1–TRPC7), TRPP (TRPP1–TRPP3), and TRPML (TRPML1–TRPML3) (Nilius and Owsianik, 2011). TRP channels exhibit responsiveness to a diverse array of stimuli, including chemical substances, temperature changes, and mechanical stress. This unique characteristic highlights their potential as sensors capable of detecting and responding to various environmental changes that surround our bodies. As a representative example, distinct physiological temperatures are regulated by thermo-sensitive TRP channels including TRPA1 (<17°C), TRPM8 (<23°C), TRPV4 (>27°C) TRPV3 (>32°C) TRPV1 (>42°C), and TRPV2 (>52°C) (Patapoutian *et al*., 2003). These channels play a crucial role in sensing and responding to temperature changes in the body, contributing to the maintenance of thermal homeostasis (Wang and Siemens, 2015). In addition, several TRP channels are activated by pungent chemicals such as capsaicin (TRPV1), allicin (TRPA1), allyl isothiocyanate (TRPA1), and menthol (TRPM8) in sensory neurons (Caterina *et al*., 1997; Peier *et al*., 2002; Bandell *et al*., 2004; Macpherson *et al*., 2005). These TRP channels play a key role in detecting and responding to the sensation of pungency, which is the characteristic sharp, tingling, or spicy sensation caused by certain chemicals.

Interestingly, TRP channels are expressed in various cell types within the olfactory and respiratory system, including airway epithelial cells, smooth muscle, and nociceptive C-fibers that innervate this region (Nassenstein *et al*., 2008; Caceres *et al*., 2009; Lin *et al*., 2021). TRP channels are involved in the detection of inhaled irritants such as hazardous molecules, anesthetics, and ozone. The encounter of volatile molecules with TRP channels leads to the influx of ions into the cells, triggering a cascade of events that modulate physiological processes such as pain, inflammation, airway smooth muscle tone, and mucus secretion (Fig. 2).

HAZARDOUS COMPOUNDS

Volatile compounds with aldehyde functional group

Aldehydes are organic compounds in which a carbon atom shares a double bond with an oxygen atom (C=O-R-H). Majority of aldehyde-containing compounds are likely to exist as vapors in the surrounding air owing to their low boiling point. Aldehyde-containing volatile organic compounds (VOCs) are commonly generated in the ambient air through incomplete combustion processes from various sources like motor vehicles and chemical industrial plants. Additionally, they can also be formed through photochemical reactions involving precursor molecules and ozone. Aldehydes are recognized for their higher toxicity and reactivity compared to other VOCs because of the presence of a carbonyl group, which enables them to engage in various chemical reactions. Chronic exposure to aldehydes is associated with the development of serious diseases, including asthma, chronic obstructive pulmonary disease (COPD), lung cancer, and sick building syndrome (Win-Shwe *et al*., 2013). Studies have reported that a wide range of aldehydes can activate TRP channels (Table 1). Understanding the mechanism of activation is necessary to better predict the potential risks associated with hazardous compounds.

Acrolein, a toxic aldehyde utilized in various industries and generated through incomplete combustion, exhibits toxicity and acts as an irritant to the respiratory and sensory systems upon exposure (Achanta and Jordt, 2017). A majority of studies have primarily focused on the TRP channels present in somatosensory nerve endings, which play an important role in generating pain and irritation responses. The involvement of TRP channels became evident when the administration of a non-selective TRP channel blocker, ruthenium red, was found to inhibit the acrolein-induced calcium influx. This observation highlights the role of TRP channels in mediating the cellular response to acrolein exposure (Inoue and Bryant, 2005). Notably, identifying TRPA1 as an ion channel expressed in C-fibers has established it as the primary sensor responsible for

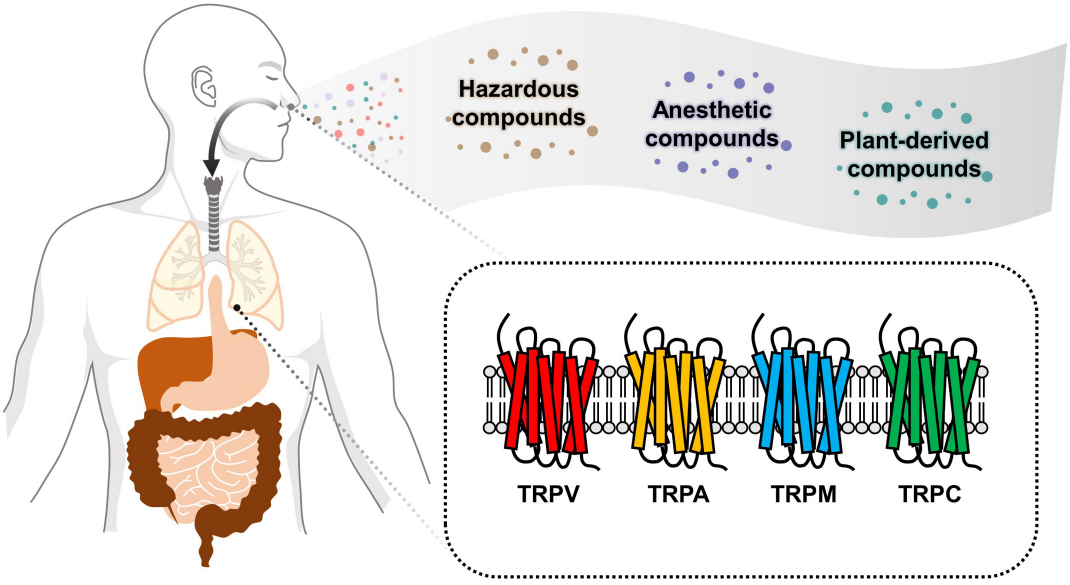


Fig. 1. A schematic overview of the inhaled volatile compounds and the TRP channels that respond within the body.

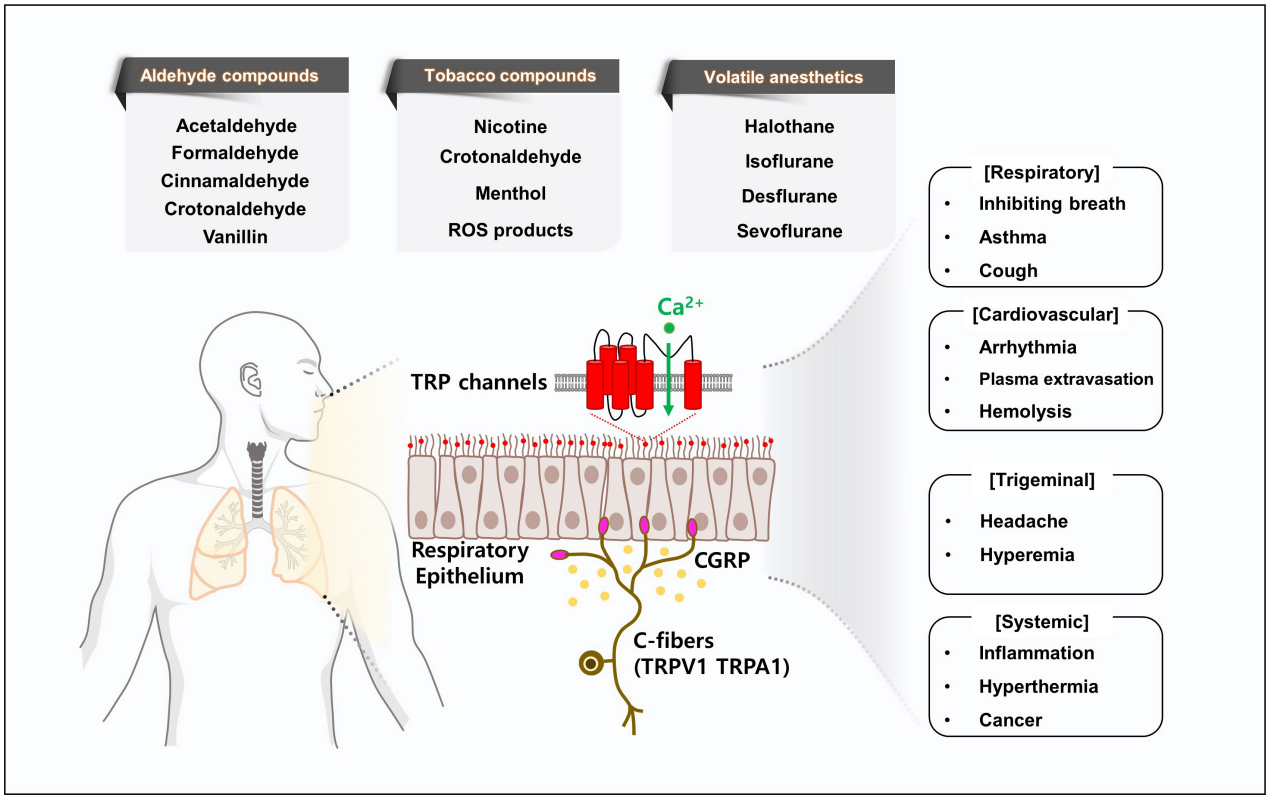
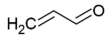
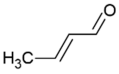
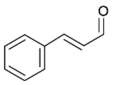
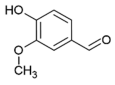


Fig. 2. An overview of the types of molecules that elicit activation of TRP channels and the associated symptoms.

Table 1. Summary of aldehydes modulating TRP channels

Aldehydes		TRPA1	TRPV1	TRPV3	TRPM8
		Effects: inflammation, arrhythmia, hyperemia, headache, respiratory inhibition, adrenaline secretion			
Acrolein		Activation	Enhancement		
Formaldehyde		Activation			Synergistic Effect
Acetaldehyde		Activation			
Crotonaldehyde		Activation			
Cinnamaldehyde		Activation			
Vanillin		Activation	Activation	Activation	

detecting acrolein (Bautista *et al*., 2006). The calcium influx elicited by acrolein in sensory neurons was absent in mice lacking the *TRPA1* gene (Macpherson *et al*., 2007). Furthermore, it was observed that TRPA1 mediates acrolein-induced neurogenic inflammation by triggering the release of pro-inflammatory neuropeptides in sensory nerve endings located in the lungs, trachea, and larynx (Andrè *et al*., 2008). Additionally, the inhibition of TRPA1 significantly alleviates inflammation in animal models of asthma, thus highlighting the important role of TRPA1 in the development and progression of this respira-

tory condition (Caceres *et al*., 2009). The inhalation of acrolein vapor by normal mice has been observed to cause immediate and transient inhibition of breathing, whereas TRPA1-null mice exhibited increased acrolein-induced mortality (Conklin *et al*., 2017). Moreover, when mice were treated with a TRPA1 inhibitor called HC-030031, they showed higher respiratory rates upon exposure to acrolein, leading to improved survival rates. Recent studies have reported an association between cough and single-nucleotide polymorphisms (SNPs) in TRPA1 and TRPV1. These SNPs in the genetic sequence of TRPA1 and TRPV1 have been found to be linked to the occurrence or severity of cough symptoms (Yoon *et al*., 2022). These findings highlight the role of TRPA1 in the inflammatory response associated with acrolein exposure in these respiratory tissues. In addition to respiratory problems, exposure to acrolein is also associated with cardiac arrhythmia and cardiovascular distress, thereby increasing the risk of heart failure or stroke. The involvement of TRPA1 in this process is indicated by the abolition of acrolein-induced arrhythmia through genetic deletion of TRPA1 (Perez *et al*., 2015; Kurhanewicz *et al*., 2017). Further, acrolein-induced TRPA1 activation is implicated in the heightened meningeal blood flow response, which can result in headaches (Kunkler *et al*., 2014).

Another volatile aldehyde, formaldehyde, is widely used in various industries and poses health risks to humans. Short-term exposure to formaldehyde can lead to eye and respiratory tract irritation, causing symptoms such as coughing, wheezing, chest pain, and bronchitis. Additionally, formaldehyde has been linked to the development of various cancers, including myeloid leukemia and brain, nasopharyngeal, sinonasal, and lymphohematopoietic cancers (Soffritti *et al*., 2002). The inhalation of formalin has also been associated with toxicity in the bone marrow and impairments in learning and memory processes in the brain (Lu *et al*., 2008; Yu *et al*., 2014). The activation of TRPA1 by formaldehyde has been demonstrated through the induction of acute pain using formalin injection, which is frequently employed in animal pain models (McNamara *et al*., 2007). In addition, formaldehyde exposure activates TRPA1 receptors located in the endothelium of blood vessels, thereby causing postprandial hyperemia owing to the relaxation of the superior mesenteric artery (Jin *et al*., 2019). The observed synergistic effect between formaldehyde and cold temperature activation of human TRPA1 channels is of particular interest. Co-exposure to temperatures below 16°C and inhalation of formaldehyde induce increased mucus hypersecretion and inflammation in the lungs, thereby exacerbating the symptoms of allergic asthma (Wu *et al*., 2020). In this regard, the administration of antagonists targeting both TRPM8 and TRPA1 channels has resulted in a significant reduction in inflammatory factors. Consequently, these ion channels represent potential therapeutic targets for managing asthma (Wu *et al*., 2020).

Acetaldehyde is characterized by a fruity odor and is classified as an extremely very volatile organic compound (VVOC) that is easily absorbed into the body through various pathways such as the respiratory tract, gastrointestinal tract, and dermal routes (Fouw, 1995; Salthammer, 2016). Acetaldehyde is produced from burning sources such as woodstoves, fireplaces, coffee roasting, tobacco burning, and vehicle exhaust. It is also formed as a metabolite of ethanol in the human body. Acute nociceptive behaviors are evoked in mouse footpads upon intradermal administration of acetaldehyde, and these behaviors are effectively abolished by the TRPA1 inhibitor camphor (Bang *et al*., 2007).

Crotonaldehyde, also referred to as crotonal, is an unsaturated aldehyde, which is produced during the combustion of fuels and in tobacco smoke. It exerts several detrimental effects on human health. Exposure to crotonaldehyde can lead to mutagenic and cytotoxic effects and trigger inflammatory responses and cell death. This compound has been implicated in causing damage to the genetic material, adversely affecting cellular function, and promoting inflammation and cell death. Within the human body, crotonaldehyde activates TRPA1 receptors located in airway epithelial cells and vasculature. This activation triggers a cascade of events that can result in injury to the airway tissues and the initiation of an inflammatory response. The interaction between crotonaldehyde and TRPA1 receptors contributes to the pathogenesis of airway tissue damage and inflammation (Andrè *et al*., 2008; Lin *et al*., 2021).

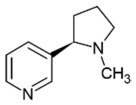
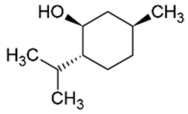
Cinnamaldehyde, derived from the *Cinnamomum* genus, is commonly utilized as a flavoring agent because of its characteristic aroma and taste. It is also utilized as a fragrance in various products and has applications as a fungicide, filtering agent, and corrosion inhibitor in different industries (Cocchiara *et al*., 2005). A remarkable study has demonstrated that cinnamaldehyde can induce nociceptive behavior in mice by activating the TRPA1 channel. This activation of TRPA1 leads to the perception of pain or discomfort in response to cinnamaldehyde exposure (Bandell *et al*., 2004). Intravenous injection of cinnamaldehyde stimulates the secretion of adrenaline by activating TRPA1 in sensory and adrenal sympathetic nerves (Iwasaki *et al*., 2008). These findings highlight the role of TRPA1 as a molecular sensor for cinnamaldehyde and in the nociceptive response and adrenaline secretion.

Vanillin, a flavor compound primarily extracted from vanilla seeds, is commonly used in a variety of food products because of its pleasant aroma. However, excessive consumption of vanillin has been linked to potential liver and kidney damage. It is important to note that high levels of vanillin intake may have adverse effects on these organs. Nevertheless, several reports have indicated the potential therapeutic applications of vanillin in promoting liver regeneration and regressing liver fibrosis (Ni *et al*., 2005; Fouad and Al-Melhim, 2018; Ghanim *et al*., 2021). Further research is needed to elucidate the effects of vanillin on liver health and its potential benefits in liver fibrosis treatment. Although vanillin activates several receptors, such as TRPV1, TRPV3, and TRPA1, in trigeminal neurons, the precise physiological functions of vanillin remain unclear (Xu *et al*., 2006; Lübbert *et al*., 2013). Extensive research is required to unravel the complete picture of how vanillin affects the body and to uncover its potential implications in various physiological functions.

Tobacco smoke

Tobacco smoke has been widely recognized as a leading cause of irritation in the tracheal and bronchial mucosa. Extensive research has been conducted to elucidate the mechanisms through which cigarette smoke exerts its irritant effects on the respiratory tract (Table 2). In 1983, Lundberg *et al*. demonstrated that pretreatment with capsaicin, an activator of TRPV1, inhibited airway mucosa sensitization to cigarette smoke (CS), suggesting that TRPV1 plays a crucial role in detecting CS (Lundberg and Saria, 1983). Upon inhalation, CS activates capsaicin-sensitive neurons expressing

Table 2. Summary of the components of tobacco smoke modulating TRP channels

Tobacco smoke		TRPA1	TRPV1	TRPM8
		Effects: inflammation plasma extravasation, lung cancer		Effects: mucin secretion, inflammation, ROS production
Smoke aldehydes		Activation		
Nicotine		Activation		
Menthol				Activation
ROS by smoking		Activation	Activation	

TRPV1, leading to the triggering of neurogenic inflammation. This activation results in the release of neuropeptides such as substance P and neurokinin A (Lundberg and Saria, 1983; Delay-Goyet and Lundberg, 1991). However, it was observed that the selective TRPV1 receptor antagonist, capsazepine, failed to prevent CS-induced plasma extravasation (Geppetti *et al*., 1993). Although TRPV1-expressed sensory nerves are involved in CS irritation, TRPV1 itself does not mediate the neuronal activation. In contrast, the non-specific TRP channel blocker ruthenium red inhibits CS-induced extravasation, indicating the potential involvement of other TRP channels in CS reactions (Geppetti *et al*., 1993). Afterwards, the observation of TRPA1 expression in the lung nerves of mice suggested its potential involvement as a novel channel activated by CS (Bautista *et al*., 2006; Nassenstein *et al*., 2008).

Cigarette smoke contains a complex mixture of chemicals, including acrolein, acetaldehyde, and various unsaturated aldehydes (Huber *et al*., 1991; Facchinetti *et al*., 2007; Kim *et al*., 2023). Several experiments have provided evidence that specific components in CS collectively activate the TRPA1 channel. First, a study demonstrated that CS extract induces an elevation in intracellular calcium levels in cells expressing TRPA1 heterogeneously (Andrè *et al*., 2008). Additionally, certain aldehydes present in CS, such as crotonaldehyde and methacrolein, have been identified as TRPA1 agonists (Andrè *et al*., 2008; Escalera *et al*., 2008). CS has been found to stimulate the trachea by activating TRPA1. This is evidenced by the increased tracheal plasma extravasation, which is predominantly inhibited by TRPA1 blockers or genetic ablation of TRPA1 (Andrè *et al*., 2008). Moreover, TRPA1 knockout mice exhibit an 80% decrease in CS-induced release of CGRP from the superfused trachea, whereas TRPV1 knockout mice show no considerable reduction (Kichko *et al*., 2015b). Notably, TRPA1 has been implicated in the development of small cell lung cancer (SCLC) associated with smoking. It is upregulated in cancer cells, leading to the elevation of intracellular calcium levels and suppression of apoptosis, which potentially promote the progression of SCLC (Schaefer *et al*., 2013).

Nicotine, a highly addictive component of cigarettes, has the ability to vaporize in its unprotonated form and enter the gaseous phase. Although nicotine primarily acts on nicotinic acetylcholine receptors to induce stimulation, it has been observed that its activation pathway is not involved in the irritation caused by nicotine. In fact, the acetylcholine receptor antagonist mecamylamine failed to completely inhibit the release of CGRP (Kichko *et al*., 2015a). Subsequently, Kichko *et al*. (2015a) showed that TRPA1 knockout mice had a substantial decrease in CS-induced CGRP levels in the trachea and larynx. Another study has demonstrated that nicotine facilitates airway constriction in animal models through the activation of TRPA1 (Talavera *et al*., 2009).

Reactive oxidative stress (ROS) generated from smoking activates lung vagal C-fiber effects (LVCAs), which can be effectively suppressed by antioxidants (Lin *et al*., 2010). In this regard, TRPV1 and TRPA1 have been proposed as potential targets for activation by ROS (Weng *et al*., 2013). Subsequent studies have reported that TRPV1 and TRPA1 can be activated through treatment with H_2O_2, as confirmed using patch clamp and calcium imaging techniques (Sawada *et al*., 2008; DelloStritto *et al*., 2016). In the context of oxidation sensing by TRP channels, cysteine oxidation has been regarded as the principal mechanism. Takahashi *et al*. (2011) identified Cys421 and Cys621 of human TRPA1 to be responsible for TRPA1 activation. Similarly, Ogawa *et al*. (2016) proposed that Cys-258 and Cys-742 of human TRPV1 are crucial sites for activation. These findings highlight the potential role of oxidative stress in modulating TRPV1 and TRPA1 activity, suggesting their involvement in cellular responses to oxidative damage and inflammation induced by cigarette smoking.

Menthol, a widely used compound added to cigarettes, is known for its cooling effect, which is achieved through its binding to the TRPM8 (Peier *et al*., 2002). Tobacco smoke has the potential to exacerbate inflammation through the activation of the TRPM8 pathway, which is expressed in the lungs and nasal mucosa (Liu *et al*., 2015, 2018; Nair *et al*., 2020). Indeed, inhibition of TRPM8 has been presented to alleviate airway inflammation in asthma model mice treated with cold air stimulus The combined exposure to cold air and CS has been found to induce excessive mucus secretion through the activation of TRPM8 (Li *et al*., 2012). It has been observed that TRPM8 is involved in the generation of reactive oxygen species (ROS) subsequent to menthol binding (Nair *et al*., 2020).

Other hazardous compounds

Inhalation of ozone poses a substantial health risk, particularly in industrialized nations, because of its detrimental effects on respiratory function. Ozone stimulates nociceptive bronchopulmonary nerves and elicits action potentials by activating TRPA1 channels. When TRPA1 is heterologously expressed in HEK293T cells, it leads to calcium influx upon ozone treatment. Notably, TRPA1 knockout mice do not exhibit activation of bronchopulmonary nerves in response to ozone exposure (Taylor-Clark and Undem, 2010). Furthermore, current evidence links ozone exposure with an increased risk of developing allergic asthma and exacerbating existing asthma conditions. According to a previous study, TRPV1 is indirectly involved in ozone-induced respiratory diseases. The inhibition of TRPV1 by melatonin has been proposed as a prospective therapeutic target for ozone-induced asthma exacerbation (Li *et al*., 2019; Chen *et al*., 2021). Recently, Li *et al*. (2022) demonstrated the efficacy of both TRPA1 and TRPV1 antagonists in preventing airway inflammation induced by ozone exposure. These findings highlight the potential of TRPA1 and TRPV1 as therapeutic targets for ozone-induced respiratory diseases.

Additionally, there are numerous hazardous compounds associated with resin additives that have the ability to cause irritation by affecting TRP channels. Specifically, TRPA1 has been investigated for its potential activation by certain alcohols, such as 2-ethyl-1-hexanol (2-EH), 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (Texanol) (Mori *et al*., 2023). Trigeminal nociceptive fibers present in the nasal organs express a diverse range of ion channels that respond to various irritants. Among these channels, TRPV1 expressed in trigeminal ganglion neurons is associated with aversive responses to irritants such as benzaldehyde, cyclohexanol, eugenol, and toluene. However, *in vitro* studies have revealed that benzaldehyde and toluene do not activate the TRPV1 ion channel (Silver *et al*., 2006; Saunders *et al*., 2013). Moreover, chemosensory cells in the nasal cavities that express TRPM5 respond to a wide range of odorous irritants (Lin *et al*., 2008).

ANESTHETIC COMPOUNDS

Volatile general anesthetics (VGAs) comprise a diverse group of volatile and gaseous substances used as anesthetics, which share the common ability to suppress the central nervous system (Franks, 2008). VGAs induce symptoms such as hypnosis (unconsciousness), amnesia (memory loss), and muscle relaxation (Miller *et al*., 2002). These effects are desired during surgical procedures to ensure patient comfort and facilitate medical interventions. General anesthetics target numerous ion channels to inhibit the central nervous system. VGAs activate $GABA_A$ receptors, which are inhibitory receptors in the brain, and potassium (K^+) channels, which help regulate neuronal activity. They simultaneously inhibit glutamate (excitatory) receptors and inhibit the release of neurotransmitters from presynaptic terminals (Franks and Lieb, 1988; Wakamori *et al*., 1991; van Swinderen *et al*., 1999; Yamakura and Harris, 2000). These actions contribute to the overall depressant effects of general anesthetics on the CNS. However, the exact mechanisms underlying the complete anesthetic effect are not fully understood and may involve additional factors.

VGAs stimulate peripheral neurons to cause side effects such as coughing, laryngeal spasms, irritation of the airway mucosa, and secretion, which may result in part from stimulation of laryngeal C-fibers (Mutoh *et al*., 1998; Mutoh and Tsubone, 2003). The expression of TRPV1 in afferent nerves sensitive to capsaicin, which triggers pulmonary defense responses such as apnea, cough, and cardiovascular effects, has been reported in numerous animal studies (Coleridge and Coleridge, 1984; Tsubone *et al*., 1991; Coleridge and Coleridge, 1994; Mutoh *et al*., 1998). There are various inhalation anesthetics, including halothane, isoflurane, desflurane, and sevoflurane, which are used to induce and maintain general anesthesia. Each of these anesthetics exhibits different reactivity towards several TRP channels, and accumulated studies have demonstrated that these VGAs can modulate the activation of TRP channels.

In previous studies, it was discovered that isoflurane alone did not activate TRPV1. Further investigations have revealed that VGAs potentiate the TRPV1 currents evoked by capsaicin, heat, or protons, which are mediated by protein kinase C in a dependent manner (Cornett *et al*., 2008). The interaction between emulsified isoflurane and TRPV1 can enhance nociceptive inhibition by QX-314, a blocker of voltage-activated sodium channels (Zhou *et al*., 2014). In contrast, a recent study has suggested that TRPV1 is directly activated by both isoflurane and halothane, which was inhibited by capsazepine (Vanden Abeele *et al*., 2019). VGA-induced TRPV1 activation is associated with the development of malignant hyperthermia, a pharmacogenetic disorder characterized by uncontrolled calcium release in the muscles triggered by inhalational anesthetics. Notably, among patients with malignant hyperthermia, those with identified TRPV1 variants exhibited higher sensitivity to VGAs compared to that of patients without TRPV1 variants (Vanden Abeele *et al*., 2019).

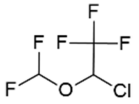
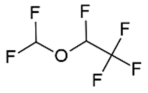
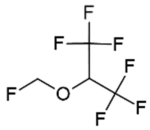
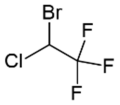
In addition, TRPA1 can be directly activated by isoflurane and desflurane in a concentration-dependent manner. Halothane and sevoflurane failed to generate TRPA1-induced currents (Matta *et al*., 2008). Exposure to desflurane resulted in an elevation of laryngeal C-fiber activity in the respiratory tract, which was effectively suppressed by a selective blocker of TRPA1 but not by an inhibitor of TRPV1. This finding highlights the substantial involvement of TRPA1 in mediating neuronal activation induced by VGAs (Mutoh *et al*., 2013).

A recent study (2020) has discovered that although VGAs have the ability to activate TRPA1, they also inhibit the activation of TRPA1 currents in response to specific ligands such as allyl isothiocyanate (AITC) (Ton *et al*., 2020). Thus, the bimodal control of TRPA1 by volatile VGAs was suggested as a potential important feature for modulating nociceptive signaling and ischemia. As TRPA1 is a molecular sensor of hypoxia (Takahashi *et al*., 2011), this TRPA1 inhibition by VGA may contribute to the vasodilation of cerebral arteries during ischemia (Pires and Earley, 2018).

Accumulated studies have demonstrated that VGA-induced TRP channel activation is involved in pain transmission and inflammation. The activation of TRPV1 by desflurane and isoflurane leads to an increase in the release of CGRP in the trachea, which was reduced by approximately 75% in mice that lacked TRPV1 (Kichko *et al*., 2015b).

Remarkably, desflurane-induced CGRP release was completely inhibited in TRPA1-deficient mice (Kichko *et al*., 2015b). The stronger activation of TRPA1 by isoflurane leads to a greater extent of neuroinflammation compared to that induced by sevoflurane (Matta *et al*., 2008). Moreover, Eilers *et*

Table 3. Summary of the volatile general anesthetics modulating TRP channels

VGAs		TRPA1	TRPV1	TRPM3	TRPM8	TRPC5
		Effects: CGRP release, respiratory inhibition	Effects: CGRP release, hyperthermia		Effects: Hypothermia respiratory inhibition	
Isoflurane		Activation	Enhancement		Activation (Inhibition by prolonged exposure)	
Desflurane		Activation	Enhancement		Activation (Inhibition by prolonged exposure)	
Sevoflurane			Enhancement	Inhibition	Activation (Inhibition by prolonged exposure)	
Halothane			Activation	Inhibition	Activation (Inhibition by prolonged exposure)	Inhibition
Chloroform				Inhibition		Inhibition

al. (2010) reported that isoflurane induces mechanical hyperalgesia through a TRPA1-dependent mechanism. Additionally, isoflurane was shown to elicit TRPA1-dependent constriction of isolated bronchi (Eilers *et al*., 2010).

Furthermore, Li *et al*. (2015) investigated the physiological implications of VGAs on TRPV1 and TRPA1 channels using TRPA1 and TRPV1 knockout mice. Consequently, TRPA1-deficient mice exhibited a shortened induction latency during isoflurane anesthesia, but not sevoflurane anesthesia, compared to wild-type mice (Li *et al*., 2015). In contrast, the response of TRPV1-deficient mice to both isoflurane and sevoflurane was similar to that of wild-type mice. Based on these results, the increased sensitivity to isoflurane anesthesia in TRPA1-deficient mice suggests that TRPA1 channels may play a role in altering respiration patterns during isoflurane anesthesia. In contrast, the absence of TRPV1 genes did not considerably affect the response of mice to anesthesia.

Other TRP channels, such as TRPC and TRPM, have also been implicated in the effects of VGAs. In the peripheral nervous system, TRPC5-mediated calcium entry is inhibited by halothane and chloroform (Bahnasi *et al*., 2008). Also, TRPM8 is activated by halothane, isoflurane, desflurane, and sevoflurane, resulting in immediate calcium influx (Vanden Abeele *et al*., 2013). However, prolonged exposure eventually leads to continuous inhibition of TRPM8 (Vanden Abeele *et al*., 2013). This sustained inhibition of TRPM8 may contribute to the occurrence of hypothermia. Notably, TRPM8 deficient mice displayed a partial reduction in both hypothermia and the inhibition of respiratory drive induced by VGAs (Vanden Abeele *et al*., 2013).

On the contrary, halothane, chloroform, isoflurane, and sevoflurane exert an inhibitory effect on the activation of TRPM3 in both heterologously expressed cells and neurons in a concentration-dependent manner (Kelemen *et al*., 2020).

The modulations of TRP channels by VGAs and their physiological effects are summarized in Table 3.

PLANT-DERIVED COMPOUNDS

Volatile compounds derived from a variety of foods or aromatic plants have been used historically for their medicinal properties in the treatment of various ailments, including diarrhea, coughing, and ulcers. These volatile compounds have applications in therapeutics, perfume, and food industries. Moreover, they have been the subject of preclinical studies exploring their potential as antitumor, anti-inflammatory, antioxidants, and antibacterial agents (Bakkali *et al*., 2008; Edris, 2007; Saviuc *et al*., 2015; Korinek *et al*., 2021). The effects of volatile compounds on modulating TRP channels, whether by activating or suppressing them, are of particular interest, as understanding the precise mechanisms is promising for the development of novel therapeutic interventions (Jang *et al*., 2015; Soares *et al*., 2021).

Numerous studies have documented the effects of volatile ingredients found in food on TRP channels in various pathophysiological conditions. For instance, allyl isothiocyanate found in wasabi, allicin and diallyl disulfide derived from garlic, and cinnamon aldehyde present in cinnamon have been identified as substances that interact with TRPA1 channels. Among those, gallic-derived sulfide components have also been found to activate TRPV1 channels (Macpherson *et al*., 2005). In particular, allicin exhibits a wide range of biological activities, including antimicrobial effects. Allicin vapor has been reported to exhibit antimicrobial properties against lung pathogenic bacteria, including multi-drug resistant strains, from the genera *Pseudomonas*, *Streptococcus*, and *Staphylococcus*, which suggests its potential as a treatment for pulmonary mycoses (Reiter *et al*., 2017). Given the absence of volatile antibiotics

for pulmonary infections, the inclusion of allicin, particularly at sublethal doses in conjunction with oral antibiotics, could serve as a valuable adjunct to the existing treatment options.

Menthol, derived from mint plants, is commonly used as a flavor additive in a wide range of consumer and medicinal products. The TRPM8 channel, expressed in whole lung tissue and human bronchial epithelial cells, plays a role in the mechanism of menthol-induced cough suppression (Li *et al*., 2011). Indeed, the activation of TRPM8 by menthol has long been employed as a means to suppress cough (Laude *et al*., 1994; Grace *et al*., 2014). Furthermore, genome-wide association studies have identified a connection between TRPM8 and conditions such as migraine and allodynia, indicating the potential of menthol for use in targeted approach for personalized migraine treatment (Dussor and Cao, 2016; Ling *et al*., 2019). The activation of meningeal TRPM8 by external agonists can have controversial effects, both inducing and alleviating headache behaviors, which highlight the intricate involvement of TRPM8 in the pathology of migraine (Borhani Haghighi *et al*., 2010; Dussor and Cao, 2016).

Inhalation of certain plant ingredients has been associated with the onset of headaches. For example, *Umbellularia californica*, commonly referred to as the 'headache tree,' is known to induce severe headache when its vapors are inhaled. The leaves of this plant contain umbellulone, which is a monoterpene ketone known for its irritant properties. Activation of TRPA1 has been proposed as a potential mechanism underlying headache, as it can lead to the release of CGRP in trigeminal neurons (Nassini *et al*., 2012). Further electrophysiological analysis has determined that umbellulone acts as a bimodal activator of TRPA1 and a weak activator of TRPM8 (Zhong *et al*., 2011).

In addition, various volatile compounds derived from herbal plants have been identified as agonists for TRP channels, indicating their potential role in modulating TRP channel activity. In more detail, eugenol, a compound found in basil and clove, exhibits anti-inflammatory properties by inhibiting the cyclooxygenase enzyme. Additionally, eugenol has been shown to activate TRPV1 and TRPV3 channels (Xu *et al*., 2006). Given that several inhibitors of TRPV1 and V3 have also been reported to exert anti-pruritic and anti-inflammatory effects, further research is needed to elucidate the conflicting mechanisms associated with TRPV3 activation (Bujak *et al*., 2019; Han *et al*., 2021). Similarly, thymol, obtained from thyme (*Thymus vulgaris*), activates the TRPV3 channel and has been documented as an anti-inflammatory and wound healing agent (Xu *et al*., 2006). Linalool, commonly present in the Lamiaceae family, activates both TRPA1 and TRPV1 (Wang *et al*., 2022). Intriguingly, although linalool can independently activate TRPA1, it also exhibits inhibitory properties against the activation of TRPA1 by other agonists, such as AITC (Hashimoto *et al*., 2023). Consequently, this inhibition leads to a reduction in TRPA1-mediated nociceptive behaviors (Hashimoto *et al*., 2023). Vanillin, extracted from *Vanilla planifolia*, elicits mild effects on the central nervous system. The anti-inflammatory effect of vanillin has gained attention, prompting further research into its relationship with the activation of TRPV channels (Ghanim *et al*., 2021; Ciciliato *et al*., 2022). Taken together, the investigation of volatile compounds derived from plants and their interactions with TRP channels has garnered considerable interest in the quest for potential novel therapeutic drugs. The identification of these compounds as agonists or modulators of TRP channels provides insights into their potential pharmacological effects and opens up possibilities for developing targeted therapies in various fields, including pain management, inflammation, respiratory disorders, and neurological conditions. Further research in this area may unveil new avenues for drug discovery and lead to the development of innovative treatments.

PHEROMONES

Pheromones are chemical signals known as semiochemicals that carry information within a particular species (Jones and Parker, 2005). These chemical compounds are produced and released by individuals, influencing the behavior or physiology of other members of the same species. Pheromones play a crucial role in various biological processes, including communication, mate selection, territorial marking, alarm signaling, and social organization (Fan and Ting, 2014). They are detected by specialized sensory receptors in organisms, triggering specific physiological or behavioral responses.

Pheromones exhibit varying volatility based on their chemical structure (Jones and Parker, 2005). The volatility of a pheromone is influenced by its chemical structure. Generally, volatile pheromones are composed of small molecules that have low molecular weight and high vapor pressure. These properties allow them to easily evaporate and disperse in the surrounding environment, enabling efficient transmission and detection by potential receivers (Zhou and Rui, 2010). Alternately, non-volatile pheromones are typically larger molecules with higher molecular weight and lower vapor pressure. These molecules are less likely to evaporate and disperse into the air, making them better suited for close-range communication or direct contact with conspecifics (Cardé and Millar, 2009). This differentiation significantly impacts the transmission and detection of pheromones by conspecifics.

In plants, certain volatile compounds function as pheromone-like signals. They attract pollinators and seed dispersers, while also serving as a defense mechanism against pests and pathogens. These volatile compounds play a crucial role in plant reproduction and protection (Bouwmeester *et al*., 2019). Additionally, in *C. elegans*, the TRPV family member OSM-9 is involved in sensing attractant odorants such as diacetyl and pyrazine (Colbert *et al*., 1997). TRPC channels have been reported to be essential for detecting chemicals, such as nicotine, that regulate behavior of *C.elegans* (Feng *et al*., 2006). Similarly, certain volatiles in insects function as pheromones, guiding social behavior and serving as cues for locating hosts or prey. For instance, *Drosophila melanogaster* TRPA1 is essential for the avoidance response to citronellal, a widely used insect repellent (Kwon *et al*., 2010). In this regard, citronella indirectly activates *Drosophila* TRPA1 through a G protein/PLC signaling cascade, whereas it directly activates the TRPA1 channel in African mosquitoes (Kwon *et al*., 2010). A recent study has challenged previous findings and proposed that citronellal acts as a direct agonist for TRPA1 in *Drosophila*, human, and African mosquito species (Du *et al*., 2015).

In rodents, pheromones convey information such as animal location, food or threat presence, sexual attraction, courtship, and dam-pup interactions. The TRPC2 channel is specifically found in neurons of the vomeronasal organ (VNO) in rodents, primarily in the sensory microvilli of VNO neurons. Pheromones binding to V1 and V2 receptors in the vomeronasal organ activate the phospholipase C (PLC) pathway through G

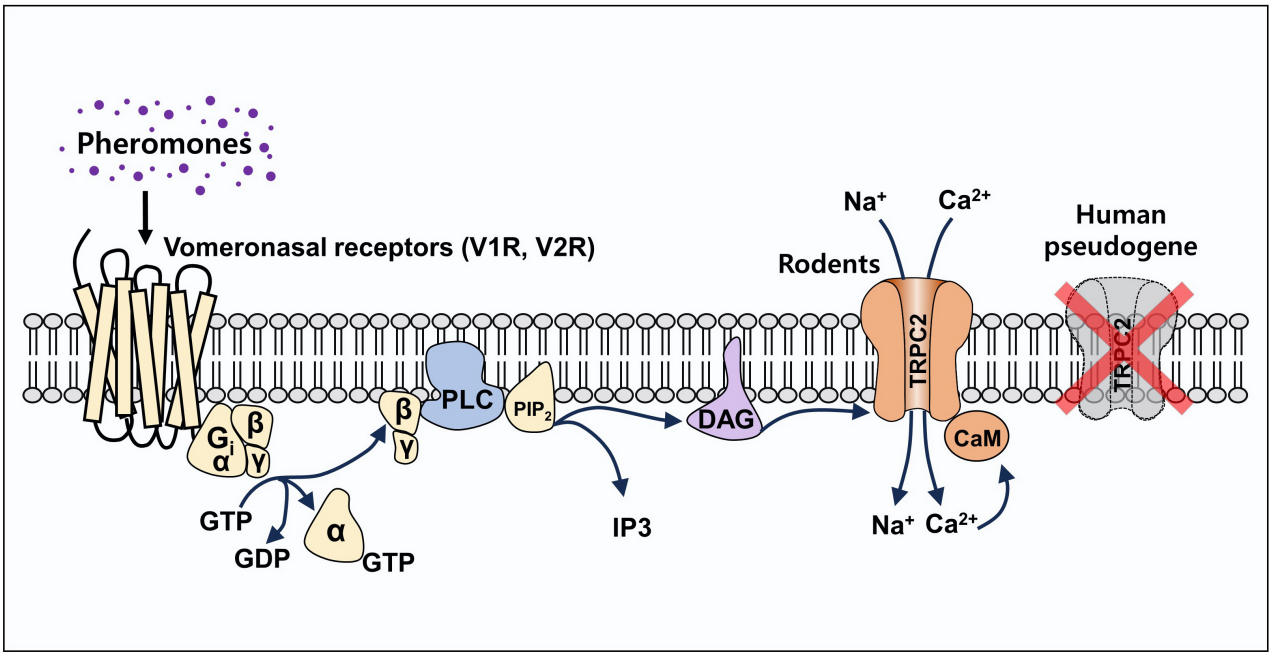


Fig. 3. The pheromone sensing mechanism by the TRPC2 channel. In the vomeronasal organ, the pheromone signal transduction pathway begins at vomeronasal receptors. Upon pheromones binding, the V1R/V2R activates G-proteins. The activated G-proteins stimulate the cleavage of PIP2 into IP3 and DAG via PLC. DAG activates TRPC2 channel, leading to influx of cationic ions. Ca^{2+}/calmodulin directly inhibits the activity of TRPC2. The human TRPC2 gene is a pseudogene that generates premature stop codons, resulting in a severely truncated protein. DAG, diacylglycerol; GDP, guanosine diphosphate; GTP, guanosine triphosphate; Ins(1,4,5)P3, inositol 1,4,5-trisphosphate; PIP, phosphatidylinositol-4,5-bisphosphate; PLC, phospholipase C; CaM, calmodulin.

protein signaling (Matsunami and Buck, 1997). DAG (diacylglycerol), which is produced as a result of the activation of the PLC pathway, stimulates TRPC2 channels. This stimulation leads to a depolarizing influx of Na^+ and Ca^{2+} in VNO neurons, resulting in an increase in the firing rate of these neurons (Zhang *et al*., 2010) (Fig. 3). Unlike other mammals, including rodents, humans have non-functional TRPC2 owing to genetic mutations (Vannier *et al*., 1999). These mutations lead to the formation of premature stop codons in the TRPC2 gene, resulting in the production of a severely truncated protein. As a result, humans are believed to have lost the functionality of TRPC2 in pheromone detection and signaling, making us less reliant on these chemical cues for social and reproductive behaviors compared to other species.

CONCLUSIONS AND PERSPECTIVES

From air, various volatile molecules can be inhaled through the respiratory tract, which can subsequently induce pathophysiological changes in humans. Peripheral nerves located in the nose, mouth, and throat play a crucial role in protecting the body against chemical hazards by initiating perceptions and reflexes. These sensory nerves serve as the first line of defense, detecting and responding to potentially harmful chemicals in the environment. Sensory irritation caused by chemical stimuli can induce a concentration-dependent decrease in respiratory rate, a phenomenon referred to as "respiratory braking." This mechanism serves as a protective response to prevent the inhalation of toxic substances. When the sensory nerves in the respiratory system detect irritants, they transmit signals to the brain, triggering a reflexive decrease in respiratory rate.

In humans, TRP channel-mediated calcium influx plays a critical role as a signaling mechanism to maintain physiological homeostasis and detect potential threats. This review comprehensively explored the biological functions of TRP channels in response to volatile molecules. It highlighted the role of TRP channels as molecular sensors in detecting and responding to environmental cues, and discussed their involvement in various physiological processes and pathological conditions related to the inhalation of volatile substances. Certainly, unraveling the mechanisms of TRP channel activation is crucial for assessing the potential risks associated with hazardous compounds and identifying potential therapeutic targets. By gaining insights into the specific molecular interactions and signaling pathways involved in TRP channel activation, we can better understand how these channels contribute to the physiological responses and pathological effects induced by volatile molecules. Such knowledge can aid in the development of strategies for risk assessment, prevention, and treatment of conditions associated with exposure to these substances.

CONFLICT OF 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.

ACKNOWLEDGMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI22C1973000022).

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