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Acute cardiopulmonary toxicity of inhaled aldehydes: role of TRPA1

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Abstract

Inhalation of high-level volatile aldehydes, as present in smoke from wildfires and in tobacco smoke, is associated with both acute and chronic cardiopulmonary morbidity and mortality, but the underlying mechanisms are unclear. The transient receptor potential ankyrin 1 (TRPA1) protein forms a cation channel (irritant receptor) that mediates tobacco smoke–induced airway and lung injury, yet the role of TRPA1 in the cardiovascular toxicity of aldehyde exposure is unclear. Physiologically, airway-located TRPA1 activation triggers an irritant response (e.g., coughing and “respiratory braking”) that alters the rate and depth of breathing to reduce exposure. Acrolein (2-propenal), a volatile, unsaturated aldehyde, activates TRPA1. Acrolein was used as a chemical weapon in World War I and is present at high levels in wildfires and tobacco smoke. Acrolein is thought to contribute to pulmonary and cardiovascular injury caused by tobacco smoke exposure, although the role of TRPA1 in cardiovascular toxicity is unclear. This mini-review addresses this gap in our knowledge by exploring literature and recent data indicating a connection between TRPA1 and cardiovascular as well as pulmonary injury due to inhaled aldehydes.

Keywords

acrolein; cardiac dysfunction; irritant receptors; pulmonary injury

Introduction

Exposure to extremely high levels of aldehydes may occur during cataclysmic combustion events, such as terrorist bombings and resultant structural and fuel-related conflagrations, as well as during wildfires. Aldehydes are common products of incomplete combustion and include acrolein and crotonaldehyde, which are volatile, unsaturated aldehydes and prototypical electrophilic toxicants. Acrolein (2-propenal) was used as a gas weapon in World War I, and is a combustion product present at high levels in tobacco smoke and wildfires. Because of high chemical reactivity, acrolein and crotonaldehyde are thought to contribute to the pulmonary and cardiovascular injury caused by tobacco smoke exposure;

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Conflicts of interest

The author declares no conflicts of interest

however, the specific role the transient receptor potential ankyrin 1 (TRPA1) receptor plays in the cardiovascular toxicity of tobacco smoke is unclear.

TRPA1 is a cation channel/receptor present on somatosensory neuron terminals of largely unmyelinated C-fiber afferents in the lungs and in the periphery. This channel/receptor encodes information regarding noxious chemicals, mechanosensation (pressure), and temperature, although the latter function is less well supported. In the airways, TRPA1 activation by acrolein, for example, leads to well-known irritant responses that include coughing and “respiratory braking” effects that can invoke apnea and rapid, shallow breathing, presumably to reduce exposure.^{1,2}

In addition to TRPA1, there are many other TRP gene family members that encode specific sensory information and have selective environmental agonists. For example, TRPV1 is a vanilloid cation channel receptor present in the upper airways and oral cavity that is sensitive to capsaicin and cyclohexanone and colocalizes with TRPA1 to nerve endings. There is evidence that cross talk/sensitization occurs between TRPV1 and TRPA1. Another TRP member is TRPM8 (M = melanostatin), which is sensitive to menthol and eucalyptol. Agonism of TRPM8 produces a soothing and cooling sensation associated with intake of mint (e.g., wintergreen, spearmint), and, interestingly, the activation of TRPM8 leads to inhibition of TRPA1. Thus, TRPM8 agonists, such as menthol and eucalyptol, are referred to as “counterirritants,” and in addition to their soothing effect, these agonists would be expected to block the generally protective respiratory braking response, leading to greater overall exposure and potential toxicity, as well as an increased addiction in the case of inhaled nicotine.³ Notably, acrolein is a potent agonist of TRPA1 that leads to respiratory braking, and, thus, the inhibition of TRPA1 (e.g., menthol via TRPM8) could lead to more acrolein exposure and perhaps more cardiopulmonary injury. In the current mini-review, I assess the gaps in our knowledge about TRPA1 and high-level aldehyde exposure are assessed and address the potential for targeting TRPA1 to protect against the cardiovascular toxicity associated with aldehyde exposures (e.g., tobacco smoke).

Inhalation exposures to unsaturated aldehydes

High-level acute exposures

Because of their high reactivity, high-level exposure (even briefly) to unsaturated aldehydes will result in severe injury. Acrolein is a volatile, unsaturated aldehyde with a long history of acute toxicity.⁴ Large quantities of acrolein are synthesized annually (500,000 tons) for industrial use as an herbicide/biocide (Slimicide®, Magnacide®) to manage biological growth in waterways and oil wells and as a main precursor in acrylic acid synthesis.⁵ Moreover, in addition to being used as a chemical weapon in World War I, an industrial chemical of high toxicity and a toxic combustion product,⁶ acrolein is also generated endogenously during lipid peroxidation and inflammation.⁷ It is also present at high levels in tobacco smoke (50–60 ppm) and in enclosed fires (up to 500 ppm).^{5,8}

Brief accidental exposure to high levels of acrolein (i.e., packaged as Magnacide®, 95% acrolein) has resulted in recorded human fatalities that occurred days after exposure despite early clinical treatment.⁹ It is also known that firefighters have a 10- to 100-fold higher risk

of dying due to heart disease–related events during fire suppression than dying of heart disease during any other activity.^{10,11} Despite these observations, the mechanism of lethality remains unknown, yet a potential and plausible mechanism involving TRPA1 is addressed below. In animal studies, brief exposure (30 min) to acrolein at levels found in enclosed and structural fires (> 100 ppm) is lethal.¹² For example, the lethal concentration (LC₅₀) of acrolein inducing 50% mortality at 24 h after a brief exposure was 175 ppm (10-min exposure) in mice.¹² Likewise, the acrolein LC₅₀ at 24 h is 150 ppm following a 30-min exposure in dogs.¹² These data illustrate the relatively high toxicity of inhaled acrolein across different species. Recently, Leikauf *et al.* demonstrated that continuous exposure to 10 ppm acrolein (a lacrymation level¹³) resulted in 100% lethality in C57BL/6J mice within 16 h,¹⁴ so longer exposures at lower acrolein levels also pose a serious threat to health, yet the mechanism of acrolein-induced lethality is not well defined and the role of TRPA1 has not been investigated.

Tobacco smoke and environmental air pollution exposure

Tobacco smoke is a well-known source of a variety of saturated (e.g., acetaldehyde, formaldehyde) and unsaturated (acrolein, crotonaldehyde) aldehydes.^{15,16} Acrolein has been measured in cigarette smoke by a variety of methods and estimated to be present at approximately 50–60 ppm, although this level depends on many factors and is highest during the non-puffing phase of burning (i.e., incomplete combustion).¹³ Cigarette and secondhand smokers inhale enough acrolein that the major acrolein metabolite, 3-hydroxypropyl mercapturic acid (3-HPMA), can be detected in the urine.^{17,18} The 3-HPMA level in cigarette smokers is substantially decreased by abstaining from smoking, indicating that tobacco smoke is the likely source of the resultant urinary 3-HPMA.¹⁹ Other than tobacco smoke and fires, environmental levels of acrolein, even in traffic-laden cities and at tollbooths, are only slightly above ambient and barely measureable.^{20,21} Yet despite this, organisms are finely tuned to respond to inhaled unsaturated aldehydes, even at near ambient levels, as described below.

Pulmonary pathophysiology of inhaled aldehydes and TRPA1

Pulmonary irritant effects and TRPA1

A prominent, well-described, inhaled irritant–evoked response is a neurally mediated (trigeminal) reflexive apnea and rapid respiratory rate with shallow depth termed “respiratory braking.” Alarie *et al.* quantified respiratory responses to numerous different inhaled irritants, including acrolein, in rats using plethysmography.^{22,23} The estimated acrolein level reducing the respiratory rate by 50% (RD₅₀) in rat is approximately 1.68 ppm—a level much lower than that inducing lethality.²⁴ These data indicate a sensitive and conserved reflex in mammals that likely protects the airways from unnecessary toxic exposure. Lee *et al.* characterized the mechanism of high-level acrolein–induced braking as vagus nerve mediated and capsaicin and cold sensitive.²⁵ They concluded that acrolein (350 ppm) stimulated airway C-fibers and rapidly adapting irritant receptors but that the reflexive apnea (and bradypnea) was mediated by C-fibers.²⁵ However, Morris *et al.* found that the response was intact at 1 ppm acrolein in *TRPV1*-null mice, suggesting that the TRPV1 receptor, which is sensitive to capsaicin, was not mediating this response at the much lower

level of acrolein.²⁶ Neurally mediated pulmonary reflexes, including coughing and the braking response, are coordinated by inputs from multiple types of neural afferents, including rapidly adapting receptors (RAR), slowly adapting receptors (SAR), and C-fibers. These different receptor pathways vary in distribution in the airways, alveoli, and lung parenchyma, as well as in conduction velocity (size and myelination), types of expressed nerve terminal receptors, and peptides released from terminals.²⁷ TRPA1 receptors are most associated with C-fibers (unmyelinated, slow conduction velocity fibers, and release of substance P (SubP) and CGRP), especially in the nasal epithelium and upper airways. Because of the complexity of these overlapping pathways, assigning a specific TRPA1-mediated pulmonary effect to a single select neural pathway can be challenging.

Inhalation toxicological studies (nose only or whole body) of high-level unsaturated aldehyde exposures in rodents have limitations for relating injury to humans. First, rodents are obligate nose breathers, so the upper nasal airways (largely innervated by trigeminal sensory afferents) get the full complement of exposure. After high-level toxicant exposure, nasal airway injury, inflammation, congestion, and obstruction can occur. Obligate nose breathers with nasal airway obstruction struggle to breathe, and thus it necessitates a switch to oral breathing and gasping (leading to aspiration of air into the gastrointestinal tract), which confounds assessment of morbidity and mortality after extreme nasal congestion. Second, there is a need to develop a postexposure intervention as a practical tool for treating mass casualty situations in the field (e.g., the September 11, 2001 attacks), but, when using a model wherein the primary injury is severe nasal epithelial damage, inflammation, and obstruction, the resultant data may be less relevant to high-level exposures in humans who can breathe nasally and orally equally well.

TRPA1 (formerly ANKTM1) is widely distributed in the pulmonary system, including the trigeminal (upper airways) and vagal sensory ganglia (upper and lower airways) and the periphery. Its activation by direct chemical stimulation or tissue injury contributes to the local, coordinated inflammatory response, which includes increased blood flow, increased vascular permeability (edema), increased leukocyte binding and extravasation, and sensation of pain. Because of this latter effect, these receptors are integral to neurally mediated detection (sensation) and perception of pain (nociception). When activated, TRPA1 opens its cation channel, and calcium entry triggers release of vesicles containing both SubP and calcitonin gene-related peptide (CGRP). SubP and CGRP are well-known stimulators of increased vascular blood flow, as well as flow to the epithelium and endothelium layers and associated edema.²⁸ These are mediators of the local effects of TRPA1 activation. As a consequence, TRPA1 responses are highly localized and dependent on where the TRPA1 receptors are located. In the airways, TRPA1 activation leads to irritant responses that include coughing and respiratory braking.

Pulmonary injury and TRPA1

Acrolein (and the related crotonaldehyde) is a strong electrophile, and as such it readily forms stable covalent adducts with biological nucleophiles, such as glutathione (GSH), and cysteine-rich proteins. Because of this proclivity, acrolein and crotonaldehyde are potent agonists of TRPA1.²⁹ Acrolein binds TRPA1 intracellular cysteines²⁹ and likely triggers the

opening of the cation channel, allowing calcium entry, neuronal activation, and secretion of the tachykinin peptides SubP and CGRP. These peptides enhance pain signaling (in dorsal root ganglia) and increase local tissue inflammation, blood flow, vascular permeability, and edema.³⁰ Thus, activation of the TRPA1 channel by acrolein is linked with both pain and inflammation, which could contribute to acute tobacco smoke– or acrolein-induced injury in the airways^{1,31–33} and at peripheral sites³⁴ in the cardiovascular system (see below).³⁵

Acrolein has long been considered one of the most injurious compounds present in tobacco smoke,³⁶ and it has been estimated that acrolein alone contributes about 88% of the noncancer (pulmonary and cardiovascular) risk of smoking.^{37,38} There is a large amount of literature supporting the premise wherein acrolein exposure alone accounts for many of the deleterious pulmonary effects of tobacco smoke exposure, including the respiratory braking and airway hyperreactivity responses.^{39,40} Recently, it was found that some of these effects are dependent on TRPA1 activation.^{31,33} As TRPA1 is a cation channel that permits calcium entry, acrolein-induced bronchial smooth muscle hypercontractility and edema are likely TRPA1-dependent events.^{41–44} Crotonaldehyde, also found in tobacco smoke, appears to trigger TRPA1-dependent responses in much the same manner as acrolein.^{8,31,45,46} It remains to be tested, however, whether all effects of unsaturated aldehyde exposure in the lungs or lung cells are strictly dependent on TRPA1, such as effects on pulmonary inflammation and immune defenses^{47–54} and MMP/MuC5/mucin activation and production.^{51,55–57} Thus, it is unclear whether inhaled, acute, high-level acrolein-induced nasal and upper airway epithelial necrosis and sloughing and inflammatory cell infiltration would be altered by the presence or absence of the TRPA1 protein or by TRPA1 antagonism in a mouse model of acrolein inhalation exposure. Future studies in animals with genetic deletion or TRPA1 antagonism will likely reveal whether these events are primarily dependent on TRPA1. Moreover, the benefits of preventing TRPA1 activation in either acute or chronic states of pulmonary irritation associated with asthma, chronic cough, bronchitis and smoking remain to be discerned. By analogy, counterirritants like menthol appear to block pulmonary TRPA1, which can lead to increased exposure to harmful or potentially harmful constituents (HPHC) in tobacco smoke.³ So it remains to be seen whether TRPA1 inhibition would ultimately be a benefit or promote harm (e.g., addiction, cardiovascular injury) under any given specific inhalation conditions.

Cardiovascular pathophysiology of inhaled aldehydes and TRPA1

TRPA1 is widely distributed in the pulmonary system and in the periphery, and its activation by direct chemical stimulation or tissue injury contributes to a local, coordinated inflammatory response that includes increased blood flow, increased vascular permeability (edema), increased leukocyte binding and extravasation, and sensation of pain. Because of the latter effect, these receptors are part of the neural detection (sensation) and perception of pain (nociception). As described above, when activated TRPA1 opens its cation channel, calcium entry triggers release of nerve terminal vesicles containing SubP and CGRP—peptides well known to stimulate vascular blood flow and epithelium and endothelium permeability. The release of these compounds promotes local tissue edema.⁵⁸ These effects are thought to be the result of local TRPA1 activation, but it is unclear if these responses are solely due to neurally mediated responses or involve direct activation of TRPA1 receptors

expressed on cardiovascular cells (of course, these possibilities are not mutually exclusive). Nonetheless, TRPA1 responses are dependent on where the TRPA1 receptors are located, and there is growing evidence that these receptors are expressed in cardiovascular organs and contribute to cardiovascular pathophysiology.⁵⁹

It is interesting to note that a strong irritant response in the airways that leads to airway hyperreactivity and the respiratory braking response is associated with systemic hypotension, suggesting that reflex-dependent vagal output (parasympathetic) likely triggers systemic cardiovascular depression.^{25,27} However, it is unclear if the majority of cardiovascular responses to inhaled aldehydes are neurally mediated specifically via stimulation of pulmonary-located TRPA1 receptors. For instance, several studies have demonstrated that inhaled acrolein (at relatively low levels < 10 ppm) affects arterial blood gases,⁶⁰ baroreceptor sensitivity,⁶¹ platelet activation,⁶² global heart performance,⁶³ and circulating endothelial progenitor cells (EPCs),⁶⁴ but whether any of these effects are dependent on TRPA1 is unknown. The evidence for specific TRPA1-dependent cardiac and vascular effects of inhaled high-level aldehydes is reviewed below.

Cardiac effects

Little evidence exists for a cardiac-specific role of TRPA1 in high-level acrolein exposure in humans. Although firefighters would be expected to have higher potential exposures to acrolein, the higher rates of cardiovascular mortality that occur on the job appear to be strongly related to the current cardiovascular health status of firefighters, suggesting that susceptibility condition is a key component of acrolein-induced morbidity and mortality outcomes.^{65,66} Numerous acrolein-inhalation studies using hypertensive or heart failure-prone animal models appear to support this idea.^{60,61,67} TRPA1 appears necessary for changes in heart rate variability (HRV) in rats exposed to diesel engine exhaust.⁶⁸ The evidence indicates a role for pulmonary TRPA1 in mediating vagal outflow to the heart, although TRPA1 antagonist efficacy may affect TRPA1 in the lungs, as well as systemically. These data provide evidence that cardiovascular effects of acrolein (and other pollutant) exposure may result from pulmonary TRPA1 activation and vagal outflow.³⁵ As indicated above, TRPA1 antagonists prevent acrolein-induced edema and inflammation.^{29,31–33,59} Perhaps TRPA1 antagonists may likewise prevent the cardiotoxicity of other electrophilic chemicals such as formaldehyde, phosgene, and 1,3-butadiene.⁶⁹

Vascular effects

Tobacco smoke (as representative of unsaturated aldehyde exposure) has long been associated with endothelium dysfunction (i.e., loss of the normal vasodilation function of endothelium—the innermost lining of blood vessels), even in naive nonsmokers.^{70, 1} Although such exposures are rarely life-threatening in healthy adults, Winniford *et al.* showed that active smoking induces coronary artery vasospasm that could stimulate ischemia and heart attack.⁷² Whether this effect of active smoking is dependent on acrolein and TRPA1 remains to be demonstrated. Several animal studies have shown that acute cigarette smoke exposure (or smoke extract) can induce endothelium dysfunction.^{73,74} We showed that relatively low-level acrolein exposure (1 ppm 6 h/day, 3 days) recapitulated the effects of

tobacco smoke exposure on endothelium dysfunction in a mouse model of compromised acrolein metabolism (i.e., GSTP-deficient mice).⁷⁵

In contrast to vasospasm, several unsaturated aldehydes (and known TRPA1 agonists), including acrolein, cinnamaldehyde, and 4-hydroxy-*trans*-2-nonenal (4HNE), stimulate vasorelaxation at relatively low levels in isolated or perfused blood vessels.^{76–79} There is also evidence that some of these relaxations are endothelium and TRPA1 dependent, although the evidence is incomplete in the majority of cases.^{35,76} Moreover, TRPA1 may be indirectly activated by aldehydes, as described for nitroxyl-mediated (HNO) release of CGRP from trigeminal afferents to regulate meningeal blood flow,⁸⁰ and perhaps cold-induced cutaneous vasodilation⁸¹ and gout-induced edema/inflammation⁸² as well. Most of these studies address systemic blood vessels, but TRPA1 in the gas-exchanging pulmonary vasculature (e.g., nerve endings or endothelial/epithelial cell) localization could wreak havoc on pulmonary blood flow, gas exchange, permeability, and extravasation/edema. It also remains unclear how inhaled aldehydes such as acrolein (even at high levels present in cigarette smoke) induce systemic endothelium dysfunction,^{70,75} given that rapid biochemical transformations (e.g., glutathiolation, reduction, oxidation) take place well before reaching the blood space (e.g., protein adducts; metabolized to glutathione conjugates).^{21,83} Despite this important consideration and regardless of the mechanism, either vasospasm in coronary arteries or peripheral blood vessel vasodilatation could trigger ischemia and heart attack or hypotension and syncope, respectively, that potentially could induce morbidity and lethality.

TRPA1: a target for antagonism after aldehyde inhalation exposure?

TRPA1 is a promiscuous sensory receptor, as it is activated by a variety of environmental and endogenous noxious compounds, including α,β -unsaturated aldehydes such as acrolein (propenal), crotonaldehyde (butenal; derived from 1,3-butadiene), and 4-hydroxy-*trans*-2-nonenal (4HNE).⁸⁴ The presence of TRPA1 in the pulmonary airways and its role in the protective physiological maneuver termed respiratory braking elicited by inhaled toxins indicates a primary physiological function of TRPA1 to limit pulmonary (and systemic) exposure to airborne toxins. Recently, Ha *et al.* showed that exposure to menthol, present in tobacco smoke and electronic cigarette aerosol, activates a TRPM8-mediated inhibition of TRPA1, leading to greater exposure to nicotine (and perhaps acrolein and more injury) owing to a presumed loss of respiratory braking.³ Collectively, these findings point to a role for TRPA1-mediated respiratory braking in protection against acrolein inhalation. Capsaicin-sensitive fibers containing both TRPA1 and TRPV1 are known to mediate respiratory braking in rodents in response to high- and low-level acrolein exposure.^{25,85} The specific contribution of TRPA1-mediated respiratory braking in pulmonary protection will need to be elucidated in subsequent studies. Because TRPA1 is also widely distributed in the periphery, its activation following inhalation exposure and tissue injury likely contributes to local, coordinated, and complex inflammatory and pain responses. As indicated above, this includes increased blood flow, increased vascular permeability, increased leukocyte extravasation, and induced pain (nociception).

The inflammatory process (similarly to respiratory braking) is generally regarded as protective because it is necessary for healing in that it recruits and augments migration of

inflammatory cells and nutrient flow and immobilizes an injured site, as well as provides spatial information regarding site of injury via central pain neurotransmission. This latter benefit of sensory information is clear when this crucial information is lost, as in leprosy (when peripheral pain signaling is limited), because small injuries/lesions become larger, more open, and infected sores due in part to a lack of spatial recognition.⁸⁶ However, chronic activation of TRPA1, as in arthritis or diabetes (diabetic neuropathy), has a deleterious role.⁸⁷ In this situation, chronic TRPA1 activity contributes to nerve degeneration and insensitivity to subsequent noxious stimuli, leading to injuries (e.g., bed sores) and infection (e.g., gangrene) contributing to morbidity (e.g., amputation).^{87–89} In diabetes, formation of the dialdehyde methylglyoxal (MG) and 4HNE is increased, and MG or 4HNE stimulates TRPA1, leading to enhanced inflammation and pain.⁸⁸ So, in one case, loss of TRPA1 is problematic, but in the other case, chronic activation of TRPA1 is deleterious. So is it possible to give a TRPA1 antagonist after acrolein exposure and still achieve a beneficial effect? It is clear that the TRPA1 antagonist HC-030031, administered in combination with TRPV1 antagonist to wild-type mice with pancreatic cancer, protects against pain and inflammation,⁹⁰ which indicates that endogenous aldehydes are likely involved in this condition as well as other inflammatory conditions (arthritis, diabetic neuropathy). But if TRPA1 antagonism prevents the respiratory braking response (or prevents spatial nociception), then the effects may be equally deleterious, especially with acute inhalation of acrolein. Nonetheless, evaluating TRPA1 antagonist efficacy against inhaled acrolein-induced toxicity may thus be useful in developing postinhalation exposure treatments for victims of a wide range of chemical exposures.

A variety of attributes may influence how effective TRPA1 antagonists may be under acute, high-level acrolein exposure scenarios. This could include sex, age, and ethnicity. For example, female mice have a greater sensitivity to pain-inducing stimuli versus males.⁹¹ This sex-dependent sensitivity is under the control of prolactin and the prolactin receptor, which regulate TRPA1, TRPV1, and TRPM8 in sensory fibers.⁹² By extension, if female mice with more TRPA1 in pulmonary sensory fibers trigger more complete respiratory braking or another maneuver to reduce acrolein exposure, this may be a mechanism that protects females. Whether sex-, age-, obesity- or ethnicity-dependent sensitivity to acrolein occur in humans will need to be explored further. Genetic polymorphisms of the acrolein-metabolizing enzyme GSTP are described to influence sensitivity to environmental exposures. We also observed a significant (rightward shift of LD₅₀) protection against oral acrolein exposure in *Gstp*-null females than in *Gstp*-null males but not in wild-type mice, indicating that route of exposure to acrolein also may be important in sex-dependent protection.⁹³ The potential benefits of TRPA1 antagonism under these conditions is not clear and will be probed in future studies.

Conclusions and future directions

Because of the real threat of terrorist attacks and ensuing explosions/burning of structures, it can be expected that large numbers of civilians will be acutely exposed to high levels of combustion-derived aldehydes, such as acrolein. In addition, there are threats of accidental and occupational exposures (e.g., fire fighters and wildfires), and thus there is a real need to prepare for these potential catastrophic exposure scenarios. Understanding the determinants

of morbidity and mortality is a first step in developing rational interventions that reduce harm following these inevitable and chaotic exposures. For this, determinants of inhaled acrolein-induced morbidity and mortality will need to be better identified, because these bear on developing appropriate postexposure interventions and may be more widely applicable because one of their primary targets is the promiscuous TRPA1 receptor. Our preliminary review supports a role for TRPA1 as an important pre- and postexposure, sex-dependent determinant of acrolein-induced morbidity and mortality. Yet much more needs to be done to assess how best to utilize TRPA1 antagonism to save lives after high-level chemical (e.g., unsaturated aldehyde) exposures.

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