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STATE OF THE ART REVIEW

Mucus Transpiration as the Basis for Chronic Cough and Cough Hypersensitivity

David A. Edwards[1,3] · **Kian Fan Chung**[2]

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Abstract

Chronic cough is characterized by a state of cough hypersensitivity. We analyze the process of transpiration, by which water appears to evaporate from laryngeal and tracheal mucus as from the surface of a leaf, as a potential cause of cough hypersensitivity. In this process, osmotic pressure differences form across mucus, pulling water toward the air, and preventing mucus dehydration. Recent research suggests that these osmotic differences grow on encounter with dry and dirty air, amplifying pressure on upper airway epithelia and initiating a cascade of biophysical events that potentially elevate levels of ATP, promote inflammation and acidity, threaten water condensation, and diminish mucus water permeability. Among consequences of this inflammatory cascade is tendency to cough. Studies of isotonic, hypotonic, and hypertonic aerosols targeted to the upper airways give insights to the nature of mucus transpiration and its relationship to a water layer that forms by condensation in the upper airways on exhalation. They also suggest that, while hypertonic NaCl and mannitol may provoke cough and bronchoconstriction, hypertonic salts with permeating anions and non-permeating cations may relieve these same upper respiratory dysfunctions. Understanding of mucus transpiration and its role in cough hypersensitivity can lead to new treatment modalities for chronic cough and other airway dysfunctions promoted by the breathing of dry and dirty air.

Keywords Mucus · Dehydration · Cough · Cough hypersensitivity · Bronchoconstriction · Hypertonic aerosols · Transpiration

Introduction

Chronic cough is a condition that affects around 10% of the adult population worldwide and is associated with various respiratory or non-respiratory conditions, without evident cause, while frequently associated with a state of hypersensitivity to tussive or non-tussive stimuli [1]. This hypersensitivity state may be caused by a neuroinflammatory process that enhances the sensitivity of the cough peripheral vagal sensory neurons in the larynx and upper airways [2]. Recent evidence [3] suggests that high rates of water evaporation from laryngeal and tracheal mucus arising by exposure to dry air [4], cold air [5], mouth breathing [6], or high minute volume [7] can elevate pressure within airway surface liquid (ASL), leading to secretion of ATP [8] for prolonged duration and activation of the cough neural pathways [9]. This review details underlying dehydration processes at the level of the surface epithelial liquid and mucus layer focusing on emerging understanding of the process of mucus transpiration.

Airway Surface Liquid as Mediator of Inhaled Air Humidification

Dehydration of the upper airways exacerbates respiratory illnesses, from asthma [10] and COPD [11] to influenza [12] and COVID-19 [13]. Dehydration further elevates the health dangers of dirty air in chronic ways, by the slowing of inhaled particle clearance [14, 15] and in acute ways, as in the provocation of bronchoconstriction [16] and even

✉ David A. Edwards
dedwards@seas.harvard.edu

[1] John Paulson School of Engineering and Applied Sciences, Harvard University, 29 Oxford St, Pierce Hall, Cambridge, MA 02138, USA

[2] National Heart & Lung Institute, Imperial College London, 227B Guy Scadding Building, Royal Brompton Hospital, London SW7 2AZ, UK

[3] Center for Nanomedicine, Johns Hopkins School of Medicine, 400 N Broadway St, 6th Floor, Baltimore, MD 21231, US

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sleep apnea—dry and dirty air at night prolongs sleep apnea events, while humidified and dirty air do not [17]. Strenuous exercise, which can multiply inhaled air flow by a factor of ten, exacerbates upper airway dehydration and the dangers it poses to the breathing of dirty air, leading to the secretion of inflammatory cytokines [18] and elevated risks of cough and bronchoconstriction [19], among other respiratory disorders [20] such that respiratory distress is the primary non-injury reason for reporting to a sports clinic [20].

Since the thermal mapping study of McFadden and coworkers [21], processes of heating and humidification of inhaled air have been thoroughly explored [22–24]. In these studies, it has generally been assumed that water evaporates from airway surface liquid (ASL) as it does from any body of water exposed to unsaturated air, while recent evidence suggests that, particularly in the vicinity of the larynx and trachea where air flow on inspiration is greatest owing to the laryngeal jet [25], evaporation occurs in tandem with a process commonly known as transpiration [3].

Transpiration is a phenomenon widely observed in nature [26] that occurs when water evaporates over the surface of a hydrogel, leading to an osmotic pressure difference over the thickness of the hydrogel that eventually pulls water up from beneath the hydrogel. Water evaporation over the thin epidermis of a leaf can lead to osmotic pressure differentials as large as 1000 atmospheres [26], pulling water over distances of 10 m or more from moist soil. Evaporation over upper airway mucus, a far thinner hydrogel barrier, leads to pressure elevation that is inevitably more modest, while on the mouth breathing of dry and dirty air can potentially surpass 1000 Pascals, provoking inflammation and dysfunction [3].

Transpiring hydrogels tend to form thin layers of water condensation on contact with the atmosphere [27]. In the upper airways, where exhaled air becomes supersaturated on air entry into the trachea owing to the drop in temperature that occurs as air travels from the central and lower airways into the mouth, these condensation layers are refreshed on every exhalation, with approximately 33% of the water that evaporates on inhalation condensing on exhalation [24]. Condensation layer thickness reflects environmental conditions [28], thickening when evaporation rate is low, and thinning when it is high [3]—a kind of barometer of the osmotic pressure differential that keeps the transpiring hydrogel moist even in dry air conditions.

Inhalation of isotonic, hypotonic, and hypertonic aerosols is a common strategy for modifying the condensation layer and thereby physically modifying ASL structure and function for diagnostic, hygienic, and therapeutic purposes [29–32]. Advances in the understanding of mucus transpiration and the interrelated water condensation layer might serve the utility of these and other medical aerosols for the management of respiratory illnesses worsened by the breathing of dry and dirty air, such as chronic cough [1].

Transpiration

Transpiration from evaporating hydrogels has been studied for over a century since the early experiments by Darwin [33], who observed that coating a leaf's surface with vaseline reduces water evaporation while does not prevent it altogether. Transpiration differs from normal evaporation in that, while the latter leads to no pressure elevation within the evaporating liquid, the former elevates pressure in the following manner. Evaporation over the hydrogel leads to a redistribution of osmolytes across the hydrogel and thus an osmotic pressure gradient, which is equal and opposite in direction to a "water pressure" gradient. This latter pressure, i.e., the pressure that might be directly measured by a manometer inside the water pores of the gel and frequently referred to as the "pervadic" pressure [34], drives water flow toward the evaporating surface. Total hydrostatic pressure in the hydrogel being the sum of osmotic and pervadic pressures, osmotic pressure elevation increases the total hydrostatic pressure within the hydrogel, which is the origin of the hydrostatic head that pulls water up from the roots to the surface of a transpiring leaf. Transpiration accounts for an estimated 4/5th of all water evaporated from the earth's soil and 1/8th of all water evaporated from the earth [35] and is frequently exploited for water filtration systems in engineered hydrogel materials [36].

In recent years, basic transpiration principles have been analyzed in many natural and engineering contexts [37–40]. Etzold et al. [40] notably studied transpiration in polymer hydrogel beads in steady-state evaporative conditions with varying relative humidity, reporting a steady-state redistribution of polymer mesh strands, with polymer strands more concentrated near the evaporating surface of the bead. This redistribution of mass, obeying a cubic dependence of polymer mass fraction on distance from the base of the beads, is indeed the physical origin of the osmotic pressure gradient observed in the study [40]. Overall, mass conservation within the hydrogel leads then to a steady-state shrinkage of the hydrogel beads. The greater the evaporation rate, the greater the stratification of polymer, the greater the shrinkage, and the greater the hydrostatic head. Total pressure increase ΔP grows linearly with evaporation rate q at relatively low evaporation rates, while with q^3 at high evaporation rates. Equivalently, the overall water permeability of the transpiring hydrogel remains unchanged with increasing q at low evaporation rates, while at high evaporation, it diminishes with q^{-2} (owing to compression).

Mucus Transpiration

Humans lose over the course of a day from 200 mL to 1 L of water due to breathing depending on the dryness and coolness of inhaled air and minute volume [41]. This loss of water to the environment reflects a net movement of water from airway epithelia into the ASL. In steady-state breathing conditions, this slow movement of water equals the evaporation rate itself such that ASL volume is conserved. When this evaporative convection is sufficiently strong to retard the ability of molecules or particles within mucus to move independently by diffusion, mass accumulates near the evaporating surface, generating an osmotic pressure gradient and the basic conditions for transpiration. In the human larynx and trachea, such transpiration conditions exist, as can be seen by consideration of the Peclet number (*Pe*), which characterizes the relative rates of convective to diffusive motion. With mucus thickness $h \sim 10^{-5}$ m, mucin strand diffusivity, $D \sim 10^{-12}$ m^2/s, and evaporation rates ranging in conditions of tidal breathing to exercise from $q \sim 10^{-7}$ m/s to 10^{-6} m/s, $Pe = qh/D > 1$.

Edwards and Chung [3] analyzed the consequences of mucus transpiration to evaporative water flow in the human upper airways in conditions ranging from dry (10% relative humidity) to moist (60% relative humidity) air, slow and fast breathing, nasal, and mouth breathing. They determined the overall pressure exerted on the airway epithelium as a function of breathing conditions and compared their results to those of Button et al. [42], who measured ATP secretion from ciliated epithelial cells as a function of mechanical compression of cilia in vitro, and the findings of Fowles et al. [43], who measured the frequency of cough in asthmatic human subjects following topical ATP deposition by aerosol, to deduce a quantitative relationship between breathing conditions and cough propensity in hypersensitive airways.

Their results are summarized in Fig. 1, as relates to the mouth breathing of dry air with relative humidity 10% by asthmatic human subjects. As ventilation rate increases from normal tidal breathing ~ 15 to 30 L/min to minute volumes characteristic of exercise (upward of 100 L/min), osmotic pressure on airway epithelia elevates, easily surpassing 1000 Pa, leading to ATP secretion [42], triggering of P2X3 receptors [9], and cough [43].

The alignment of theory and experiment pictorially represented in Fig. 1, together with similar theoretical/experimental alignment for associated upper airway dysfunctions [3], suggests that the coupling of upper airway dehydration and a mucus transpiration inflammatory (MTI) pathway may contribute to the prevalence of chronic cough. Mechanistically, upper airway mucus appears, as a consequence of the transpiration process, to thicken and thin [similar to the deformation of transpiring synthetic hydrogels observed on changes in environmental conditions [40]] with variation in breathing conditions, stressing underlying airway epithelia as a continual physiological response to the quality of

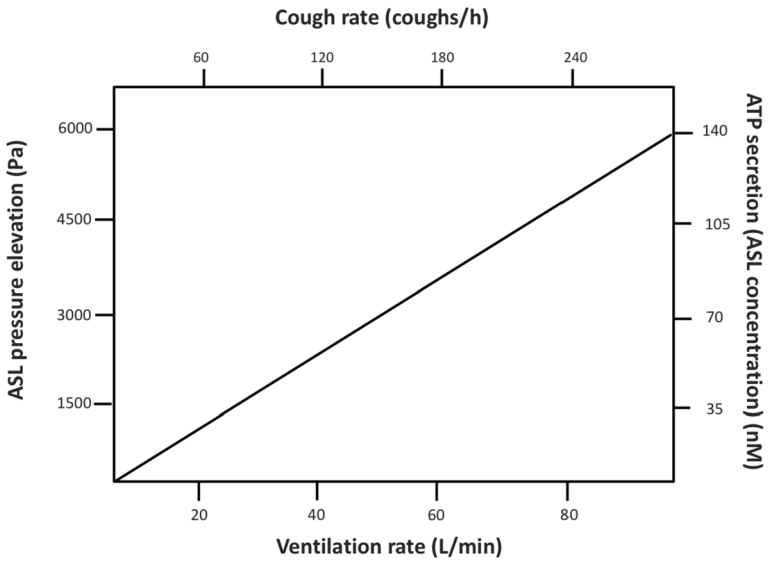

Fig. 1 Cough provocation in hypersensitive airways by the mouth breathing of dry (10% RH) air [3]. Original figurative representation of predicted [3] relationships between cough rate and ventilation rate in asthmatic airways as a function of ASL pressure elevation and ATP secretion. ASL pressure elevation is predicted as a function of ventilation rate without fitted parameters. ATP secretion is predicted by assuming linear pressure-secretion kinetics and determination of the linear coefficient by fitting of the experimental in vitro data of Button et al. [43]. Cough rate is assumed to be linearly dependent on ATP concentration with determination of the linear coefficient by fitting of the experimental human cough data obtained in asthmatics following inhalation of ATP [44]. The illustrated relationship between ventilation rate and cough rate accurately predicts cough rate as observed in asthmatics on exposure of the trachea to cool dry air [4]

inhaled air. Such alterations in upper airway mucus, yet to be observed, may impact mucus barrier function and eventually the response of the upper airways to the breathing of dirty air.

MTI Pathway

Sharp local gradients of osmolarity form in the MTI pathway of the kind that appear in drought conditions across the epidermis of a leaf, pulling water from deeper and deeper into dry soil, and leading to the wilting of the leaf [44]. In the case of laryngeal and tracheal ASL (see Fig. 2), the "wilting of the leaf" phenomenon implies sustained secretion of ATP [43], which elevates likelihood of P2X3 cough receptor activation [9], while also elevates cytosolic calcium [45] and down-regulates CFTR channel activity in the apical membrane of airway epithelia [46]. Inflammatory cytokine secretion recruits mast cells [47] and eosinophils [48]. Reduced bicarbonate secretion into ASL accompanying reduction in CFTR activity can lead to acidity, possibly triggered by secretion of carbonic anhydrase by eosinophils [49], thereby activating TRPV receptors [50] and acid-sensitive ion channels (ASIC) as a parallel route to cough provocation.

Strenuous exercise exacerbates the MTI pathway by accelerating airway dehydration [7, 18–20, 51]. Exercise promotes cough in hypersensitive airways by elevation of ATP concentration in the ASL and activation of P2X3 receptors (as reflected in the ATP cough-dependence shown in Fig. 1), while also by acidification of the ASL and activation of acid-sensitive cough receptors. Thus, while ASL naturally maintains isotonicity in states of health and disease [52], hyperosmolar gradients do arise along the MTI pathway and are especially elevated in states of exercise, offering insight into the interchangeability of exercise-induced and hyperosmolar-aerosol-induced provocations for cough and bronchoconstriction [53, 54].

Measures of exhaled breath condensate pH and chloride concentration may be effective monitors of MTI, both of which have been reported to be suppressed in chronic cough patients [55], while elevated FeNO may reflect a broader (as asthmatic) inflammatory signature and be a less sensitive measure of the MTI pathway itself [56]. Recognition and elucidation of the thin layer of water that condenses over upper airway mucus on exhalation, and appears to persist on transpiring mucus, may provide further insight into the MTI pathway, as reviewed below.

The Condensation Layer

Condensation layers exist on leaves [27, 28] and artificial transpiring hydrogels [57]. They come about in the following way. Water condenses on the hydrogel free of solute. On condensation, solutes in the hydrogel diffuse into the condensed layer to equilibrate concentration differences. Evaporation concentrates these solutes in the condensation layer driving diffusion back into the hydrogel. The hydrogel, with elevated solids concentration near the evaporating surface, reflects diffusing solutes to degrees that vary with solute size and structure, promoting an osmotic pressure in the condensation layer that adds to the osmotic pressure formed by transpiration within the hydrogel itself.

In the upper airways, condensation occurs with every breath. During normal tidal mouth breathing of modestly humid air approximately 3 mg of water evaporate in the human trachea such that on exhalation approximately 1 mg returns to the trachea by condensation of supersaturated air. Given a typical human tracheal surface area of 60 cm^2, this suggests that between ~ 166 nm and ~ 1.66 µm condenses in the trachea with each exhalation in conditions ranging

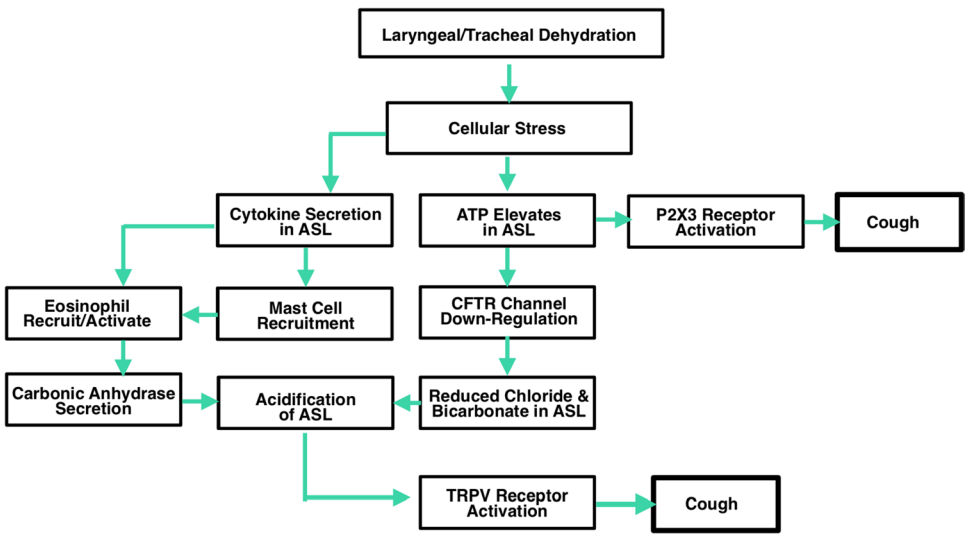

Fig. 2 A conjectural map of the mucus transpiration inflammatory (MTI) pathway for cough provocation. Upper airway dehydration results in airway epithelial cellular stress (Fig. 1), ATP secretion into the ASL [42], and activation of P2X3 receptors, promoting cough [9]. Sustained ATP elevation further leads to CFTR down-regulation in the apical epithelial membrane [47], which reduces bicarbonate flux into the ASL, promoting acidification of the ASL, and cough provocation by parallel activation of TRPV receptors [50]

from normal tidal breathing to strenuous exercise. Edwards and Chung [3] therefore assumed a condensation layer thickness of 1 µm, similar to the characteristic dimension reported for the water layer on leaves [27]. Others [28] have reported condensation layer thickness on a dry leaf varying between ~ 9 µm and ~ 18 µm from very dry (20% RH) to moist (80% RH) conditions.

Condensation layer thickness appears to be reflected in the relative number of respiratory droplets generated during a normal shallow tidal breath [3]. Exhaled breath particles (EBP) associated with normal tidal breathing break off of the condensation layer surface by the shear of inhaled air, which in the larynx and trachea moves with a laryngeal jet [58] speed (~ 3 m/s) similar to that required to generate sea spray [59]. EBP have been observed to increase and decrease in number by a factor of ~ 2 on the movement of human subjects from humid to dry back to humid air conditions [60], the same degree of condensation layer thickness change observed on the surface of a dry leaf in dry and humid air conditions [28]. Doubling the thickness of the condensation layer will halve the concentration of surfactant and diminish propensity for droplet breakup [3] and respiratory droplet generation having been shown to increase dramatically with increased presence of lung surfactant [61]. How this change in condensation layer height comes about is suggested by the theory of mucus transpiration as illustrated in Fig. 3, where fall in the thickness of the condensation layer accompanies diminution of the mucus water permeability in a manner typified by the shrinkage of the transpiring hydrogels studied by Etzold et al. [40].

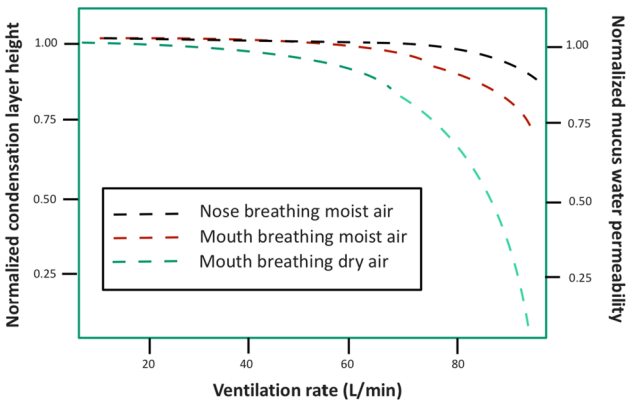

Fig. 3 Mouth and nose breathing impact on condensation layer stability. Original figurative representation of predicted [3] condensation later thickness versus ventilation rate as a function of ventilation rate and normalized mucus water permeability for cases of nose and mouth breathing of moist and dry air. As ventilation rate increases, the mass accumulation of mucus solids near the evaporating surface reduces mucus water permeability. This reduces water permeation into the condensation layer, which then loses height. The ventilation rate dependence of condensation layer height is similar to its dependence on reduction of relative humidity or temperature, as both processes elevate evaporation rate in the upper airways

Condensation layers on upper airway mucus may play a role in airborne pathogen infection and transmission [32, 62, 63], in the deposition and opsonization (surfactant coating) of inhaled particles [64], and possibly in regulating mucosal compressive forces delivered by the inhalation and excessive accumulation of PM 2.5, as observed to date in non-pulmonary mucosa [65].

Hydrating the Airways with Isotonic, Hypotonic, and Hypertonic Aerosols

Replenishing and compositionally altering the condensation layer by the aerosol deposition of isotonic, hypotonic, and hypertonic solutions have a long history of practice in respiratory science and healthcare [29, 31], led by the pioneering research of Anderson [66, 67].

Zuim et al. [68] recently reported results from a double-blinded human clinical study of hypertonic aerosol delivery of the four principal airway chloride salts demonstrating the relative longevity of divalent salt (notably magnesium chloride) laryngeal hydration. They demonstrate by numerical analysis of a generalization of the theoretical model developed by Sandefur, Boucher and Elston [69] that topical deposition in the upper airways of hypertonic salts provides hydration for shorter or longer time periods depending on whether salt cations permeate the apical epithelial membrane (Na^+, K^+) or do not (Ca^{++}, Mg^{++}), with the latter hydrating longest as the divalent cations clear most slowly by a periciliary pathway. They also predict that salts with the principal permeating cation (Na^+) risk transient acidification of ASL by lowering chloride channel CFTR permeation in parallel with rapid ASL hydration. The same phenomenon occurs on the delivery of a hypertonic aerosol lacking the permeating anion (Cl^-), as with mannitol. By avoiding the permeating cation and including the permeating anion, hypertonic divalent salts appear to avoid acidification and the associated provocations that follow from activation of TRPV receptors [50].

Hypertonic divalent salt (HDS) aerosols with slow-clearing non-permeating cations and permeating anions may therefore be useful as non-pharmacological means to deactivate the MTI pathway for prophylaxis and treatment of chronic cough and related dysfunction of upper airway dehydration. Easily delivered to the larynx in the form of a nasal aerosol from a hand-held pump spray with large droplet diameter (8–15 µm), they permit effective laryngeal hydration in a few breaths [68], possibly reducing ATP and acidity triggers of cough (Fig. 2). Such aerosols may yield chronic as well as acute therapeutic benefits if buffered to alkalinity, since deposition of ~ 6 mg of alkaline solution onto the larynx and trachea, where total water volume is ~ 60 mg for

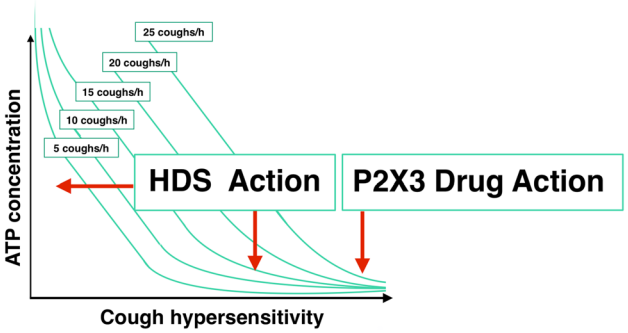

Fig. 4 A conjectural illustration of mechanism of action of HDS aerosols versus P2X3 antagonist drugs for reducing cough incidence as a function of airway fluid ATP concentration and cough hypersensitivity. The immediate action of HDS is to reduce ATP secretion into the ASL, by de-activating the MTI pathway, while with prolonged daily treatment, HDS may reduce airway inflammation and acidity, lowering the conditions for chronic cough hypersensitivity. By reducing the source of ATP in the ASL, HDS potentially complement P2X3 antagonist action, aimed at blocking ATP binding at the site of the cough receptor.

a human adult, potentially elevates ASL pH and accelerates the shutting down of the TRPV cough pathway. Alkaline HDS might further serve as useful adjuvants to P2X3 antagonist and other upper airway receptor-targeting therapeutics.

Figure 4 provides an illustration of how shutdown of the MTI pathway via HDS aerosol delivery ($MgCl_2$ or $CaCl_2$) may complement P2X3 antagonism for the treatment of chronic cough. Predicated on the assumption that environmental provocation of the MTI pathway is a common condition underlying laryngeal hypersensitivity, HDS aerosol treatment (as illustrated in Fig. 4) reduces agonist action at the P2X3 receptor, complementing the function of P2X3 drugs, while also reducing TRPV/ASIC activation and the ASL inflammation that promotes laryngeal hypersensitivity.

Conclusion

Transpiration of water appears to sustain normal lung function notwithstanding the steady loss of water that humidifies the air we breathe. Contemporary conditions, including climate change, aging of the human population, and the rise in rates of obesity, challenge the transpiration process in human upper airways, either by reducing airborne water content (through the increased frequency of breathing air-conditioned air) or whole-body water content (owing to prevalence of dehydration among the elderly and the obese), creating "drought-like" conditions in the upper airways. This promotes inflammation and upper airway dysfunction, such as cough, akin to the wilting of a leaf. It would also appear to promote changes in structure and function of upper airway mucus, of the kind that have been observed in natural and artificial transpiring hydrogels. This may couple laryngeal dehydration with an MTI inflammatory response promoting cough hypersensitivity and ultimately chronic cough.

Clarifying the phenomenology of mucus transpiration and its complex interplay with air quality, inflammation, and disease may advance diagnostic, hygienic, and therapeutic interventions for chronic cough and help to reverse airway dehydration and the accompanying neuroinflammatory events that occurs with breathing dry and dirty air.

Author Contributions DAE led the writing of the manuscript notably as relates to the phenomenon mucus transpiration. KFC led the writing of the manuscript notably as relates to cough. Both discussed, edited, and contributed to the final manuscript.

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Declarations

Competing Interests DAE is the founder of Sensory Cloud Inc, a healthcare company developing a new inhaled treatment for chronic cough.

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