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Trigeminally-mediated health effects of air pollutants: sources of inter-individual variability

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Trigeminal (ocular and nasal) irritation comprises the dominant symptom complex in so-called ‘problem buildings’. Imputed etiologic agents in indoor air include extremes of temperature and humidity, the presence of volatile organic compounds, combustion products (including tobacco smoke), ozone (from office machines), and products of indoor air chemistry. In addition to producing primary irritation, mucosal irritants trigger a variety of secondary reflex symptoms, such as nasal congestion, rhinorrhea, and sinus pressure, and may predispose to infection in the form of sinusitis and otitis media. Marked variability in self-reported sensitivity to

indoor air pollutants has been observed, with females, younger individuals, and people with allergies reporting more symptoms. We report on a series of experiments designed to uncover demographic patterns of ‘nasal irritant sensitivity’, as well as potential mechanism(s) involved in observed chemesthetic variability. *Human & Experimental Toxicology* (2007) 26, 149–157

Key words: air pollution; nasal physiology; sensory irritation; trigeminal nerve

Introduction

‘Sensory irritation’, ie, trigeminally-mediated irritation of the eye, nose, and upper pharynx, is an important component of symptom-reporting in problematic indoor environments.¹ In a variety of field studies of so-called ‘problem buildings’, upper airway and ocular mucous membrane symptoms constitute the predominant symptom complex.^{2–5} Furthermore, symptom-reporting is heterogeneous, with females, younger individuals, and individuals with pre-existing allergic rhinitis being more symptomatic in many surveys (Table 1).^{6–12}

These complex symptom-reporting patterns pose a number of questions: Why is upper airway irritation more prevalent than lower airway irritation? Do the symptom-reporting differences, alluded to above, reflect biological differences among demographic subgroups, or merely sociological differences, as suggested by some authors?^{9,13,14} If there are apparent biological differences, what underlying mechanism(s) are operative?

To address these questions, this paper briefly reviews the anatomy and innervation of the upper airway, as well as methods used to objectively document the irritant effects therein. We then review a descriptive study, examining inter-individual variability in so-called ‘nasal irritant sensitivity’. Finally, we consider an experiment aimed at underlying the biological mechanisms of inter-individual variability.

Anatomy and innervation of the upper airway

The nasal cavity is invested with a highly vascular lining, which, in combination with the extended surface area conveyed by the turbinates, facilitates the transfer of heat and moisture to inspired air. The complex anatomy of the turbinates also optimizes filtration of large particles (by the process of impaction). The presence of a ciliated epithelium further provides for the transport and elimination of these particles, either to the anterior nares or to the nasopharynx (where they are either expectorated or swallowed).

Beyond this ‘air conditioning’ and filtering function, the large surface area of the upper airway provides for the clearance of gaseous/vapor phase pollutants (‘scrubbing’) with surprising efficiency. For example, a single breath of chlorine gas, at up to

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Table 1 Epidemiologic risk factors for symptom-reporting in 'problem buildings'

	Female	Younger age	Nasal allergies
Brasche <i>et al.</i> ⁶	X	X	X
Cummings <i>et al.</i> ⁷			X
Hall ⁸	X		X
Mendell ¹⁰	X		X
Menzies and Bourbeau ¹¹	X	X	X
Stenberg and Wall ¹²	X		

Reproduced, with permission, from *Int Arch Occup Environ Health*.²⁸

three parts/million concentration, will be removed from the inspired airstream supraglottically with >95% efficiency.¹⁵ This scrubbing function is, in turn, dependent upon the water solubility and chemical reactivity of the pollutant in question, such that increasing solubility provides for early activation of mucous membrane irritant sensors, alerting individuals to avoid prolonged exposure (Figure 1). The ability of an air pollutant to produce immediate upper airway/mucous membrane irritation, along with its olfactory potency, is an important component of its 'warning properties'.

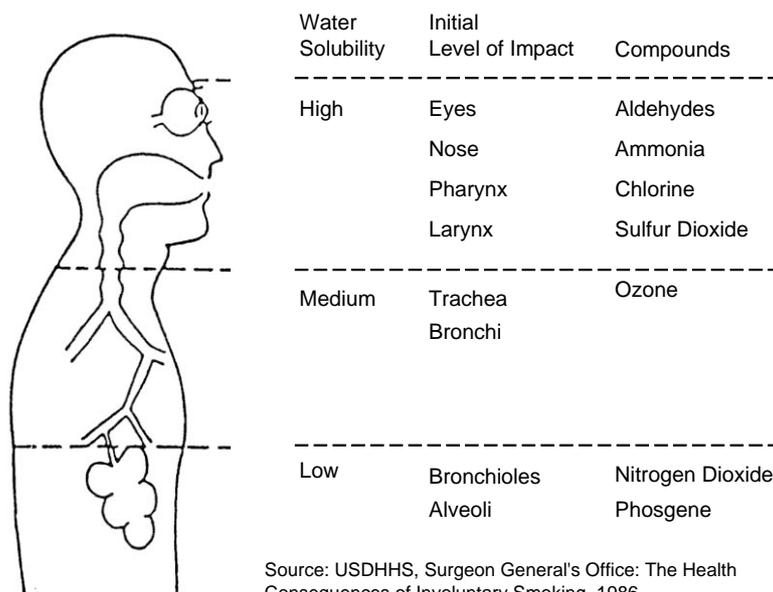
Of note, many of the air pollutants encountered in indoor environments are both highly water soluble and chemically reactive. Principal among these are aldehydes (from building materials, cigarette smoke, or produced by indoor chemical reactions). Further, common cleaning products used in indoor settings, including ammonia, sodium hypochlorite (bleach), and phenolic disinfectants area, share these physico-chemical properties and also produce initial warning sensations in the upper airway. Thus, the

predominance of upper versus lower airway symptoms in problem buildings is understandable given both the anatomy of the upper airway and the nature of the pollutants present.

The neural apparatus stimulated by these pollutants includes two main structures: the olfactory nerve (cranial nerve I – providing for the sense of smell), and the trigeminal (cranial nerve V – providing for the sense of irritation in the eyes, nose, oral cavity, and nasopharynx). In addition, the glossopharyngeal and vagal nerves (cranial nerves IX and X) convey the sense of irritation for the hypopharynx and larynx. Just as our appreciation of flavors involves a combination of the senses of taste and smell, our appreciation of many inhaled compounds involves aspects of olfaction and trigeminal stimulation. The latter carries sensations ranging from 'freshness' or 'cooling' (in response to menthol), to burning or stinging (as elicited by ammonia or chlorine).¹⁶

Techniques for documenting 'nasal irritant sensitivity'

Numerous techniques have been devised for studying the effects of airborne irritants on the upper airway of humans. The endpoints involved include epidemiologic, psychophysical, behavioral (including respiratory behavior), physiologic (including the study of reflex changes in airway caliber and airway secretions), biochemical/molecular biologic, electrophysiologic, and brain metabolic (ie, functional CNS imaging). This range of techniques suggests a voluminous literature, a review of which is beyond



Source: USDHHS, Surgeon General's Office: The Health Consequences of Involuntary Smoking. 1986

Figure 1 Water solubility and site of initial impact of airborne irritants. (Source: US Department of Health and Human Services, Surgeon General's Office: *The Health Consequences of Involuntary Smoking*, USGPO, 1986).

the scope of this paper, but for which the reader is referred to a recent comprehensive review.¹⁷

Virtually all animal experimental work in this area is predicated upon the pioneering work of Yves Alarie, who distinguished between 'sensory irritants' and 'pulmonary irritants', based on water solubility and pattern of response in respiratory behavior.¹⁸ In Alarie's scheme, upper respiratory, or 'sensory', irritants produce a slowing of respiration, and lower respiratory tract, or 'pulmonary' irritants, produce rapid, shallow breathing. This system has given rise to a functional index of sensory irritation – the RD₅₀ or concentration of a pollutant producing a 50% slowing of respiration – which, in turn, has shown interspecies relevance via a comparison with irritancy-based occupational exposure hazards.¹⁹ Analogies have been drawn between the RD₅₀ and the threshold for 'transient reflex apnea' in humans.²⁰ Alarie's work was amplified on mechanistically by Nielsen, who examined both the structure-activity relationships and the imputed receptor mechanisms in sensory irritation.²¹

In our experiments, 'nasal irritant sensitivity' has been defined dually, as: (1) 'sensory acuity' (the ability to distinguish an irritant from a control [clean air] stimulus), and (2) 'physiologic reactivity' (the tendency of an individual to exhibit reflex changes in nasal airway caliber and/or secretions in response to irritant provocation). The ensuing discussion is limited to the former dimension (ie, sensory acuity), although the interested reader is referred to published studies pertaining to the second dimension.^{22,23}

Psychophysical studies of nasal irritation in the laboratory require special attention to olfaction as a potential confounder. In everyday experience, it is not unusual for individuals to refer to 'an irritating odor', when in doing so, they are integrating input from two different sensory modalities (olfaction and trigeminal chemoreception). In practice, studies attempting to document nasal trigeminal responses in isolation often rely on the use of limited numbers of anosmic subjects.²⁴ Other approaches involve the use of the odorless irritant, carbon dioxide, which, given its lack of odor cueing, can be presented in a forced-choice temporal discrimination task versus air.²⁵ Finally, odorous volatile organic compounds (VOCs) can be studied in normosmic individuals by the lateralization method, which exploits the ability of humans to localize a unilateral irritant source by nostril, but their inability to do so by odor alone.^{26,27} The latter two methods were used in the series of experiments summarized below.

Methods

The studies described below were approved by the Committee for Human Research at the University of California, San Francisco, CA. Subjects signed informed consent documents prior to testing, and were reimbursed for their participation in these studies.

Descriptive experiment

As described in detail elsewhere, a descriptive study was conducted involving a sample of 60 paid volunteers, stratified by age (19–68 years), and roughly balanced by gender and allergy status.²⁸ Subjects underwent replicate measures of nasal irritant sensitivity (sensory acuity) on separate days in a climate-controlled environment (22°C/40% relative humidity) via: (1) CO₂ detection, and (2) VOC localization (see details below). Sessions were counter-balanced for order (ie, CO₂-VOC-CO₂-VOC versus VOC-CO₂-VOC-CO₂) within each age-gender-allergy stratum (eg, allergic rhinitic females, aged 35–52). Seasonal allergic rhinitic subjects were tested outside their relevant aeroallergen season, and testing was postponed for at least 1 week for subjects with symptoms consistent with an acute upper respiratory tract infection.

Carbon dioxide detection thresholds

The CO₂ dilution apparatus has been described in detail elsewhere.²⁵ Briefly, purified air and CO₂ were delivered to flow meters via electronically-controlled solenoid valves, to deliver 0 and 15–45% CO₂ vol/vol (5% steps) at a total rate of 5 L/min. The mixed output of these flow meters was delivered to both nostrils via a disposable nasal cannula, the right nostril of which was equipped with a respiratory flow thermocouple to permit synchronization of applied stimuli with spontaneous respiration, as noted below.

Trials involved pairs of 3-s stimuli – one air and the other CO₂ diluted in air – synchronized with inspiration. The two stimuli were presented in random order with an inter-stimulus interval of 12–15 s and an inter-trial interval of 60 s. CO₂ stimuli were presented in an ascending series, beginning at 0% concentration ('blanks'), with five trials at each concentration. Subjects were blinded with respect to stimulus order. The 'CO₂ detection threshold' was defined as the lowest concentration at which the subject correctly identified all five CO₂ stimuli as being 'more irritating' than control (clean air) stimuli.

VOC localization thresholds

Procedures for VOC localization have also been detailed elsewhere.²⁸ Polypropylene squeeze bottles (240 mL) contained *n*-propanol dilutions in deionized water, as well as blanks containing an equal volume of water alone. Stimuli and blanks (headspace from the squeeze bottles) were conducted from these bottles to both nares via 15 cm lengths of 1.5 mm ID flexible plastic tubing, capped with perforated foam earplugs, which anchored the tubes in subjects' nostrils during trials. Stimulus duration was approximately 0.5 s.

n-Propanol concentrations in water were adjusted to achieve a geometric progression of headspace vapor concentrations (target concentration ratio = $1.30 \times$ from step-to-step). Headspace vapor concentrations were determined on a weekly basis using an Agilent Technologies model 6850 gas chromatograph. Mean headspace concentrations for the seven steps in the dilution series ranged from 4800 to 22 700 ppm, the latter being saturated vapor from the undiluted solvent. Actual step-to-step concentration ratios averaged 1.29 ± 0.02 (mean \pm SEM).

The VOC testing protocol involved forced-choice localization with the ascending vapor concentration series described above. Subjects communicated their breathing pattern to the tester using hand movements and, at the end of expiration, were instructed to sniff gently. Stimulus and blank bottles were then compressed simultaneously, delivering approximately 30 mL of headspace into each nostril. After a few seconds, subjects were asked to indicate which side experienced the most 'irritation'. Six trials were conducted per stimulus level, with an inter-trial interval of 60 s. Subjects were not informed of stimulus order. The lowest stimulus concentration at which a subject correctly identified the laterality of all six stimuli defined the 'VOC localization threshold'.

Individual CO₂ detection and VOC localization thresholds were taken as the means of the two replicate determinations. Aggregate data were checked for normality and log-transformed as needed prior to analysis, using analysis of variance (ANOVA).

Mechanistic experiment

Study design

A study was conducted to investigate the source of inter-individual variability in sensory acuity to CO₂.²⁹ CO₂ is hydrated to carbonic acid in an enzyme-catalyzed step, involving the mucosal enzyme, carbonic anhydrase (Figure 2). To gain insight into this process of stimulus activation, the method

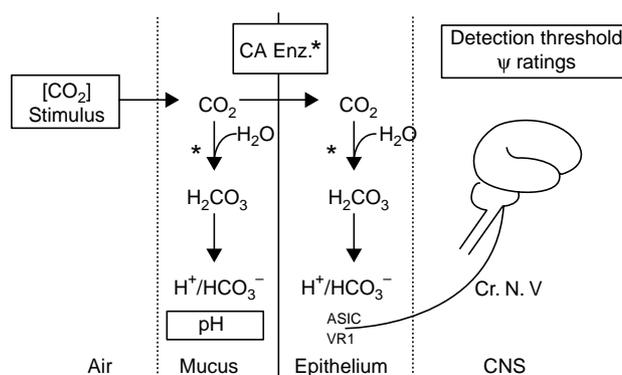


Figure 2 Theoretical framework for studies relating applied stimulus concentration [CO₂], Δ pH, CO₂ detection threshold, and suprathreshold rating of sensory irritation ψ . CA, carbonic anhydrase enzyme activity; ASIC, acid-sensitive ion channel; VR1, vanilloid (capsaicin/H⁺/heat) receptor (also referred to as TRPV1); Cr. N. V., fifth (trigeminal) cranial nerve. (Adapted, with permission, from *Chem Senses*).²⁹

of obtaining CO₂ detection thresholds, detailed above, was modified by inserting a flexible glass-tipped pH probe into one nostril during testing. The question to be examined was whether individuals, who differed consistently in their sensory acuity to CO₂, did so because of differences in stimulus activation (ie, conversion of CO₂ to carbonic acid, hence hydrogen ion), or in their efficiency in detecting a given CO₂-induced pH excursion.

Eight non-smoking, non-asthmatic subjects, between the ages of 21 and 56 years (including six males and four allergic rhinitics) participated. All subjects had previously participated in chemosensory studies, half of whom had demonstrated either consistently high (>30%) or low (<20%) CO₂ detection thresholds on two previous testing sessions, at least 2 months apart. The high threshold group (average age 48 years) consisted entirely of males, whereas the low threshold group (mean age 33 years) was equally divided between males and females.

Real-time pH monitoring

Nasal mucosal pH was measured utilizing a flexible glass-tipped pH probe, normally used for monitoring esophageal pH (Probe M3; Medical Instruments Corporation, Solothurn, Switzerland). The probe drove a pH meter with analog output (Model 6171; Jenco Instruments, San Diego, CA). Output from the pH meter was digitized using an A/D convertor board (DI-195B; DataQ Instruments, Akron, OH) on a Windows-compatible laptop computer (Dell Computers, Roundrock, TX). Data were acquired and analysed utilizing WinDaq (DATAQ Instruments) with a 10-Hz sampling rate. The probe and pH meter were calibrated (at pH 4.0 and 7.0) on a daily basis.

The probe was then introduced 4 cm along the floor of the right nasal cavity and maintained in position using paper tape applied to the nose and forehead.

CO₂ stimulation

In a single testing session, nasal pH was measured along the floor of the right anterior nasal cavity during CO₂ stimulation. Three-second stimulus pulses, paired with 3 s air pulses in random order (12–15 s interstimulus interval; 60 s inter-trial interval) were administered bilaterally by nasal cannula (No. 1606; Salter Labs, Arvin, CA) at 5 L/min, synchronized with inspiration. CO₂ stimuli, with five trials per level, were administered in an ascending concentration series (starting with 0% or 'sham', and progressing to 15, 20, 25, 30, 35, 40 and 45%). In each trial, subjects were asked to identify the more irritating of the two stimuli, as well as to rate the more irritating pulse using a computer-based version of Green's 'labeled magnitude scale'.³⁰ The lowest concentration at which a subject identified all five CO₂ stimuli as more irritating than the paired air pulses was defined as the CO₂ detection threshold. Psychophysical ratings of nasal irritation (ψ , 0–100) were entered directly onto the computer using data acquisition software (LabView, National Instruments, Austin, TX).

Results

Descriptive experiment

The data distributions of both outcome variables (CO₂ detection and VOC localization) differed significantly from normal; hence, data were log-transformed before being subjected to ANOVA. Age range predicted both VOC localization thresholds ($P < 0.0001$) and CO₂ thresholds ($P < 0.05$), with younger age predicting lower thresholds. Female gender predicted lower CO₂ detection ($P < 0.05$), but not VOC localization thresholds ($P = 0.10$). Nasal allergies predicted lower VOC localization ($P < 0.05$), but not CO₂ detection thresholds ($P = 0.52$).²⁸ The observed patterns were largely consistent with the *a priori* hypotheses derived from symptom reporting patterns in field studies (see above).

Mechanistic experiment

All subjects showed phasic drops in pH (Δ pH) associated with CO₂ – but not air – stimulation. Averaged by trial, Δ pH ranged up to 0.26 pH units. Applying linear regression to data from all subjects combined, a positive relationship was apparent between applied CO₂ concentration and Δ pH ($P < 0.0001$). Stratified by historical CO₂ sensitivity, the regression lines for the high- and low-threshold

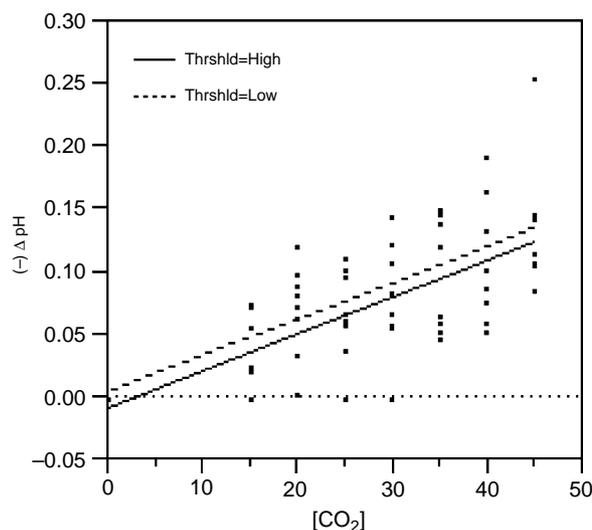


Figure 3 Individual mean values of Δ pH (inverted scale) as a function of applied [CO₂] ($P < 0.0001$ for all subjects combined). Stratified by historical CO₂ threshold, there was no significant difference in regression lines between low- and high-threshold subjects. Each symbol (•) represents the mean of five observations, within individual and stimulus series. (Reproduced, with permission, from *Chem Senses*).²⁹

groups were parallel (0.0029 pH units/% CO₂), and not significantly displaced from one another ($P = 0.25$; Figure 3).²⁹

For all subjects combined, a positive relationship was apparent between applied CO₂ concentration and ψ ($P < 0.0001$). Stratifying by historical CO₂ sensitivity, the regression for the high- and low-threshold groups had significantly different slopes, with ψ increasing more steeply in the low-threshold than in the high-threshold group ($P < 0.01$; Figure 4). ψ and Δ pH were, in turn, significantly inter-related

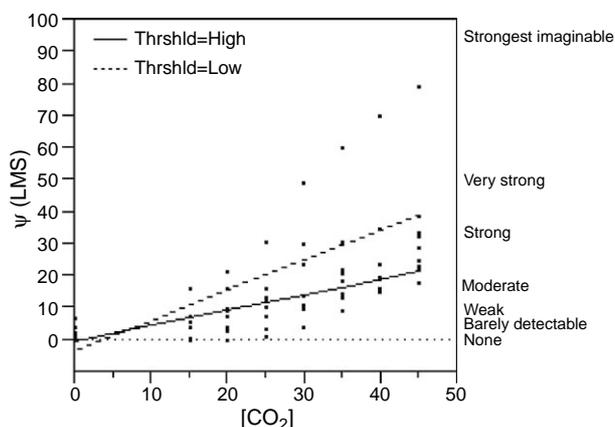


Figure 4 Individual mean values of ψ (LMS scale) as a function of applied [CO₂] ($P < 0.0001$ for all subjects combined). Stratified by historical CO₂ threshold, low-threshold subjects had a significantly steeper regression line than high-threshold subjects ($P < 0.01$). Each symbol (•) represents the mean of five observations, within individual and stimulus series. (Reproduced, with permission, from *Chem Senses*).²⁹

($P < 0.001$). Stratifying by historical CO_2 sensitivity, the regressions for the high- and low-threshold groups had significantly different slopes, with ψ increasing more steeply in the low-threshold group than in the high-threshold group ($P < 0.05$; Figure 5).

ΔpH was also measurable at threshold for six of eight subjects, including three each in the 'low threshold' and 'high threshold' groups. Among these six subjects, there was a significant positive relationship between log-transformed $[\text{CO}_2]$ and mean ΔpH at threshold (Figure 6; $P < 0.05$).

Discussion

Descriptive experiment

Significant age-related decrements were apparent in both CO_2 detection and VOC localization, with younger subjects performing better in tests of sensory acuity. Gender, on the other hand, predicted differences in CO_2 detection only (females more sensitive), and rhinitis status predicted VOC localization only (allergic rhinitics more sensitive). Thus, age emerged as the most robust predictor of nasal irritant sensory acuity, with gender and nasal allergies being less powerful explanatory variables. These observations agree with experimental data published elsewhere.³¹

The reasons for – and mechanistic bases of – the apparent differential associations (not necessarily 'effects') of the demographic variables studied are unclear. Age can be postulated as a predictor of neurodegeneration, and in fact, skin biopsies and electrophysiologic studies in an aging population show selective dropout of $\text{A}\delta$ fibers, responsible for

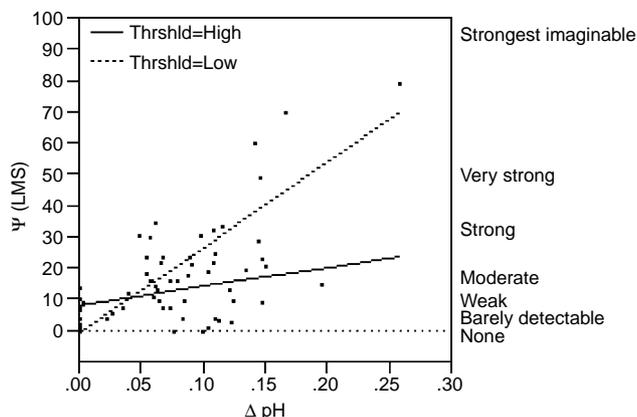


Figure 5 Relationship between individual mean ΔpH and ψ , averaged by stimulus level ($P < 0.001$ for all subjects combined). Stratified by historical CO_2 threshold, low-threshold subjects had a significantly steeper regression line than high-threshold subjects ($P < 0.05$). Each symbol (•) represents the mean of five observations, within individual and stimulus series. (Reproduced, with permission, from *Chem Senses*).²⁹

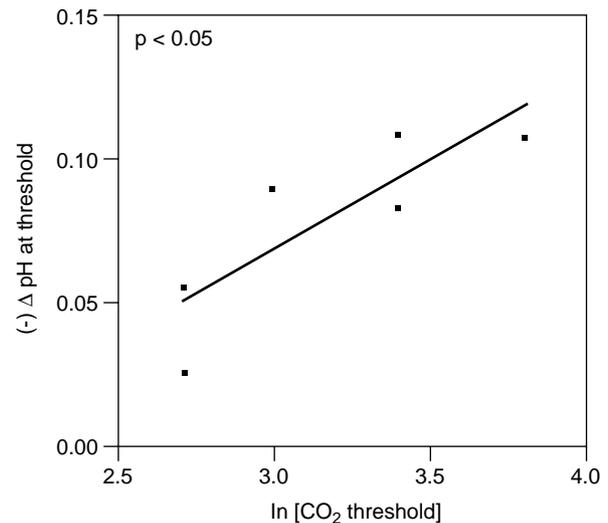


Figure 6 Relationship between [log-transformed] CO_2 concentration and ΔpH at threshold for six of eight subjects in which measurable pH fluctuations were observed at that stimulus step. ΔpH at threshold increased significantly with increasing [log-transformed] CO_2 detection threshold ($P < 0.05$). (Reproduced, with permission, from *Chem Senses*).²⁹

the 'sharp' quality of acute pain.³² Of the other two variables studied, gender and allergy status, only the former was associated with differences in CO_2 detection thresholds, and only the latter with differences in VOC localization. Consistent with our findings, two other laboratories have found a lack of association between gender and VOC localization thresholds, whereas another found gender differences in suprathreshold CO_2 rating.^{33–35} In our sample, which included females aged 19–68, there was no diminution of gender effect, but rather the difference was actually accentuated with age. This implies that a hormonal etiology for the observed gender differences is unlikely.

Allergic inflammation as a predictor of neural excitability is a well-established phenomenon in experimental animals and, increasingly, in humans. Udem and others have established animal models showing that the mediators of allergic inflammation acutely and subacutely alter neuronal excitability, efferent reflex function, and autonomic ganglion transmission in airway nerves.³⁶ These observations have recently been extended to humans by Hummel's group, which showed acute changes in responsiveness to 20% (relatively low-level) CO_2 on chemo-somatosensory event-related potentials (CSERPs) in allergic rhinitics post-allergen challenge.³⁷ (Of note, in this study a differential electrophysiologic response to CO_2 by allergy status was observed, but no subjective irritant rating data were recorded.) Finally, augmentation of suprathreshold rating of VOCs was apparent in a study by Kjaergaard, who found that allergic

rhinitics reported more (combined) eye, nose and throat irritation when exposed to a mixture of airborne VOCs (the 'Molhave cocktail'), than non-allergic controls.³⁸

Mechanistic experiment

The mechanistic study of CO₂-induced sensory irritation compared a group with 'high' thresholds with a group with 'low' thresholds. Consistent with our earlier descriptive study, the high-threshold group was both older and predominantly male than the low-threshold group.^{28,29} Significant differences between the two subgroups involved the relationship between [CO₂] and ψ (psychophysical slope) and the relationship between Δ pH and ψ . However, the relationship between [CO₂] and Δ pH (stimulus activation) did not differ significantly by subgroup. Further, examination of Δ pH, measured at the CO₂ detection threshold, confirmed that minimum detectable Δ pH was lower in those with lower CO₂ thresholds. Thus, our data suggest that high- and low-threshold individuals differ in their threshold and suprathreshold response to a given pH excursion, rather than in their activation or buffering of CO₂ pulses. This implies that intrinsic differences in neural sensitivity (in this case, to H⁺) may play a role in chemesthetic variability. Whether this finding applies to other, non-acidic, irritant air pollutants remains to be determined.

If this experiment had been confined to suprathreshold data, the issue of cognitive bias would have been operative, particularly since the high- and low-threshold groups differed demographically. However, examination of Δ pH *at threshold*, in an experiment in which a force-choice paradigm was used for threshold determination effectively addresses the potential for cognitive bias. Thus, whatever cognitive factors may have been operative in the *suprathreshold* data, the *threshold* data imply a biological effect that transcends the demographic dimension.

Overall, this experiment implies that signal transduction, rather than stimulus activation, is responsible for inter-individual differences in CO₂ detection. At the level of transduction, CO₂ detection involves acid-sensing, a task that is shared by acid-sensitive ion channels (ASIC/DRASIC) and the capsaicin receptor (TRPV1). Based upon nasal trigeminal electrophysiologic studies in rodents, using selective pharmacologic antagonists, these two channels appear to be roughly equipotent.³⁹ The mechanism of detection of VOCs, on the other hand, has yet to be elucidated, and has traditionally been treated as a non-specific membrane perturbation, mediated by the physico-chemical properties of the

VOC.⁴⁰ Increasing evidence derived from structure-activity and stereospecificity studies, however, points to the operation of specific VOC receptors.⁴¹ Thus, one could hypothesize that differential associations between demographic variables (gender and allergies) and distinct sensory endpoints (CO₂ detection and VOC localization), may reflect differential associations between these variables and membrane receptor populations. As trigeminal receptors are elaborated in the brainstem and transported peripherally, testing of this hypothesis in humans would involve not only further elucidation of a putative VOC receptor, but also biopsy of the peripheral (airway) nerves for immunohistochemical analysis.

Summary

The work reviewed in this paper suggests that, whatever additional psychosocial cofactors may be identified in problem indoor environments, differential symptom-reporting patterns related to age, gender, and allergy status have at least *some* biological basis. Mechanistically, it appears that differential neural sensitivity may be responsible for variability in one of the two test systems used in this research. A biological basis for altered airway neuronal function in allergic airway disease – termed 'neuromodulation' – has been identified in various animal models.³⁶ Age-related decrements in nociceptive function have also been postulated from electrophysiologic studies involving peripheral nerves.³² With regard to gender, the fact that differential sensitivity versus males is actually more prominent among older than younger subjects suggests that hormonal factors are unlikely to be responsible. Notwithstanding, given the considerable variability in chemosensory performance that is apparent even after accounting for age, gender and allergy status (residual variance being approximately 70% of the total), the issue of biological mechanisms underlying nasal chemesthetic variability remains largely unexplored.

Acknowledgements

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