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REVIEW

Individual Factors in Nasal Chemesthesis

Dennis Shusterman

Division of Occupational and Environmental Medicine, University of California—San Francisco, San Francisco, CA, USA

Correspondence to be sent to: Dennis Shusterman, Upper Airway Biology Laboratory, 1301 So. 46th Street, Bldg 112, Richmond, CA 94804, USA. e-mail:dennis@itsa.ucsf.edu

Abstract

Population variability in nasal irritant (chemesthesic) sensitivity has been postulated by both clinicians and epidemiologists studying indoor and ambient air pollution. Among experimentalists, however, limited attention has been paid to variance in this trait. Candidate susceptibility markers include age, gender, presence or absence of nasal allergies or olfactory dysfunction, cognitive bias and self-reported pollutant reactivity. For most of these markers, conflicting data exist. This review distinguishes between functional subcomponents of nasal irritant sensitivity (sensory acuity versus physiologic reactivity), catalogs psychophysical and physiological methods for their study and examines the current evidence for variation in this trait. In general, interindividual variability has been an under-studied phenomenon.

Introduction

The premise that humans exhibit significant inter-individual variation in nasal irritant sensitivity and/or reactivity is one that has been suggested on both clinical and epidemiologic grounds. The experimental evidence, however, is mixed. This paper summarizes existing data pertaining to nasal chemesthetic variability and briefly reviews potential pathophysiological mechanisms which may underlie any observed variance in this trait.

Analytic models

The everyday concept of 'nasal irritant sensitivity' can be divided into a number of sub-constructs. The first refers to the ability of an individual to detect an irritant gas or vapor against a background (unpolluted) atmosphere and might properly be termed 'nasal irritant sensory acuity' (in psychophysicists' terms, this constitutes true 'sensitivity'). Loosely related to the first class of metrics would be the tendency of individuals to rate the intensity of supra-threshold stimuli as strong or weak (in psychophysicists' terms, 'sensory responsiveness'). The second major construct is the tendency of individuals to experience reflex-mediated physical symptoms when exposed to irritants (e.g. nasal congestion, rhinorrhea, post-nasal drip) and is referred to as 'nasal irritant physiologic reactivity'. On the other hand, 'subjective reactivity' to odorous/irritating air pollutants (including odor hedonics, 'annoyance' and emotional responses) is beyond the scope of this review, except to the extent that it influences primary perceptual endpoints. For a discussion of subjective issues, the reader is referred to reviews on odorous air pollution (Shusterman, 1992, 1999, 2001). In this paper, the distinction between olfaction and nasal trigeminal chemoreception, although somewhat artificial by everyday standards, will be maintained and the term 'sensitivity' will be used as a global descriptor, consistent with lay usage.

Implicit in the above model are a number of underlying questions. First, do individuals who show greater sensory acuity/physiologic reactivity to a given irritant (or class of irritants) tend to show greater acuity/reactivity to other irritants? Secondly, are sensory acuity and physiologic reactivity linked, or do they vary independently? Finally, are these traits stable and reproducible within individuals over time? All of these questions should be addressed empirically before the term 'nasal irritant sensitivity' can be used with precision. In addition, should nasal irritant sensitivity prove to be a useful construct, it would be useful to know what personal characteristics—for example age, gender, smoking status, allergies, or olfactory impairment—might predict variations in this trait.

Epidemiologic evidence for chemesthetic variability

Epidemiologically, eye, nose and throat irritation (trigeminally mediated sensations) are among the acute symptoms most frequently reported by individuals exposed to environ-

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mental tobacco smoke, workers in problem buildings and residents living near selected industrial emission sources (Kreiss, 1989; Bascom *et al*., 1991; Cummings *et al*., 1991; Shusterman *et al*., 1991; CDC, 1992; Fisk *et al*., 1993; Hall *et al*., 1993; Wallace *et al*., 1993; Kharrazi *et al*., 1994). Irritant-associated symptoms of the upper respiratory tract, including nasal congestion and rhinorrhea, may mimic an allergic response, but are not characterized by the same biochemical markers evident in allergy (Bascom *et al*., 1991). Nevertheless, both clinically and epidemiologically, many observers have linked nasal reactivity to environmental irritants with pre-existing allergic rhinitis (Bascom *et al*., 1991; Cummings *et al*., 1991; Hall *et al*., 1993; Wallace *et al*., 1993). If this link is real, it has important implications for both clinicians and environmental regulators since, for instance, up to 20% of the US population suffers from allergic rhinitis and could therefore constitute a susceptible subgroup for irritant air pollutants (Settipane, 1991). By this same logic, differential sensitivity by gender (females typically reporting more symptoms) would have even more profound risk assessment implications (Kreiss, 1989; Hall *et al*., 1993; Wallace *et al*., 1993).

Experimental approaches

Experimental studies examining nasal irritant sensitivity have focused upon psychophysical endpoints, physiologic measures, or some combination thereof. In some cases, the focus of attention has been the group mean sensory threshold (or structure–activity relationships underlying such group means), such that individual variability has only been incidental to the study and can only be teased out retrospectively. In other cases, inter-individual variation is an explicit focus of study, with or without hypothesized markers of sensitivity.

Differences in the operational definition of 'nasal irritation' are crucial in understanding the literature on this subject. The first distinction to be made is between primary and secondary indices of nasal irritation, the former referring to the sensation of irritation *per se* and the latter referring to irritant-induced physiologic reflexes/symptoms, including variations in breathing pattern, facial (orbital) response, nasal congestion, rhinorrhea and post-nasal drip. The second distinction, as noted above, is between psychophysical and physiological metrics, the psychophysical being based upon a behavioral response and the physiological often including some type of biomedical instrumentation. A matrix of study methods based upon these distinctions appears in Table 1.

In studies of nasal chemesthesis based upon a psychophysical approach, varied strategies have been employed to address the potential confounding effect of odor. One approach has been to estimate an irritation threshold among anosmic subjects only, the presumption being that what we commonly identify as irritation requires only intact trigeminal function (Cometto-Muniz and Cain, 1990, 1991, 1993, 1994, 1998; Cometto-Muniz *et al*., 1998a,b, 2000). Another approach has been to study suprathreshold nasal irritation in normosmics, eliciting standardized irritation ratings ('isoresponse levels') and allowing subjects to integrate as much or as little olfactory information into that rating as is customary for them (Kendal-Reed *et al*., 1998, 2001). Still another approach has been to estimate irritation thresholds by finding the lowest stimulus concentration at which the laterality of a unilateral stimulus source can be identified, since irritation, but not olfaction, can be reliable lateralized psychophysically (Kobal *et al.*, 1989; Wysocki *et al*., 1992, 1997a; Cometto-Muniz and Cain, 1998). Finally, the issue of odor confounding in nasal irritant testing can been circumvented by employing the odorless (or near-odorless) test irritant, carbon dioxide (Cometto-Muniz and Cain, 1982; Dunn *et al*., 1982; Stevens *et al*., 1982; Cometto-Muniz and Noriega, 1985; Stevens and Cain, 1986; Cain, 1987; Anton *et al*., 1992; Lotsch *et al*., 1997; Mohammadian *et al*., 1997; Shusterman and Balmes, 1997a,b; Shusterman *et al*., 2001).

In recent years, it has also become possible to study primary nasal irritation instrumentally. Specifically, electrophysiologic measures have been developed to monitor both peripheral and central nociceptive events. Peripherally, one can measure the so-called negative mucosal potential ('NMP'), a brief, irritant-induced voltage spike recorded from the septal area of the nasal cavity (Kobal, 1985; Thurauf *et al*., 1991, 1993; Hummel *et al*., 1996b, 1998b; Hummel 2000). Centrally, electrophysiologists can document

Table 1 Classes of endpoints and measures in nasal chemesthesis

Endpoint	Measure	
	Psychophysical/perceptual	Physiological
Primary (sensory irritation)	threshold measures, suprathreshold rating	negative mucosal potential, chemosensory event-related potentials (CSERPs)
Secondary (irritant reflexes)	visual analog scales (VAS): nasal congestion, rhinorrhea, post-nasal drip	respiratory pattern recording, orbital muscle response, rhinomanometry, quantification of nasal secretions, laser-Doppler flowmetry, mucociliary clearance tests, nasal lavage markers

so-called 'chemosensory event-related potentials' (CSERPs) by averaging electroencephalographic signals which occur in relationship to intermittent nasal stimuli. A further distinction has been made between cortical activity patterns related to trigeminal stimulation ('chemosomatosensory evoked potentials') and those occurring after olfactory stimulation ('olfactory evoked potentials') (Kobal and Hummel, 1988, 1994, 1998; Hummel *et al*., 1991, 1992, 1994, 1995, 1996b, 1998a,c; Hummel and Kobal, 1992; Kobal *et al*., 1992; Livermore *et al*., 1992; Barz *et al*., 1997; Hummel, 2000).

Perceptual measures of secondary nasal irritation (i.e. self-reported congestion, rhinorrhea and post-nasal drip) are frequently documented using visual analog scales. Instrumental measures of secondary irritation often focus on nasal patency (rhinomanometry, acoustic rhinometry, nasal peak flow measurement) and quantification of secretions (Solomon, 1995). Less obvious reflexes, however, include changes in nasal mucosal blood flow (as documented by laser-Doppler flowmetry), mucociliary clearance (saccharine clearance, radionuclide clearance, stereociliometry) and nasal inflammation (nasal lavage, cytology, or histology) (Anderson and Proctor, 1983; Corbo *et al*., 1989; Druce *et al*, 1989; Koren *et al*., 1990; Koren and Devlin, 1992; Lindberg and Runer, 1994; Peden, 1996). Irritant-related changes in respiratory behavior are classified here as a secondary measure of nasal irritation despite substantial differences in latency compared to the other secondary endpoints mentioned. [Changes in respiratory behavior are virtually instantaneous, whereas reflex changes in nasal caliber or secretions typically involve latency periods of at least a few minutes (Warren *et al*., 1992, 1994; Shusterman and Balmes, 1997a; Walker *et al*., 2001a,b).] Most recently, an index of facial (orbital) muscle response to nasal irritation has also been described (Jalowayski *et al*., 2001).

As a footnote to the above classification scheme, considerable potential for methodologic variation, even among nominally equivalent methods, should be readily apparent in this large matrix of study techniques.

Experimental evidence of variability

Experimental studies documenting interindividual variability in nasal irritant sensitivity—explicitly or implicitly—are discussed in the following paragraphs. Studies in which interindividual variability was explicitly examined are summarized in Table 2.

Psychophysical studies

Primary endpoint (nasal irritation)

Irritant threshold. In a number of experiments, Cometto-Muñiz and Cain have employed a standard psychophysical technique (forced-choice, ascending series, method of limits) to document detection thresholds for VOCs among anosmic and normosmic subjects (Cometto-Muniz and Cain, 1990, 1991, 1993, 1994, 1998; Cometto-Muniz *et al*., 1998a,b). As noted above, detection thresholds generated among anosmics have been presumed to extrapolate to trigeminal thresholds in the larger population. The focus of much of this work has been to elucidate structure–activity relationships for homologous series of VOCs (including acetates, aldehydes, alkylbenzenes, carboxylic acids and terpenes), rather than to examine inter-individual variability in chemoreception. Nevertheless, the authors noted that inter-individual variability in detection appears greater among normosmics than anosmics, implying that variability is more pronounced for olfaction than for trigeminal perception.

In an experiment in which the irritant thresholds of anosmics and normosmics were explicitly compared (i.e. detection thresholds in anosmics and localization thresholds in both anosmics and normosmics), no significant differences were found (Cometto-Muniz and Cain, 1998). However, when this methodology was extended to include full psychometric functions (i.e. differing detection probabilities), normosmics' performance emerged as superior at lower stimulus levels (Cometto-Muniz *et al*., 2001). This finding of 'convergence' in performance between the two groups at higher stimulus levels is echoed in the literature on suprathreshold rating (Kendal-Reed *et al*., 2001).

Stevens and Cain (Stevens and Cain, 1986) examined the detection of CO_2 stimuli (against a background of air) as a function of subject age. Subjects included 20 elderly (between 67 and 93 years of age) and 20 controls (between ages 19 and 31 years). In contrast to their results for CO_2-induced respiratory disruption (see below), they found no systematic effect of age for this task.

Anton *et al*. (Anton *et al*., 1992) determined the threshold for nasal irritation on 12 healthy adults using 2 s pulses of CO_2 applied unilaterally via nasal cannula. Subjects breathed orally, having practiced velopharyngeal closure prior to the onset of the experiment. The stimulus progression mode combined the method of limits and the staircase method. Subjects reported uncued painful stimuli, as any mechanical or auditory cues were masked by this apparatus. The final distribution of irritant thresholds spanned from 35 to 55% v/v CO_2 (mean, 47%), with a relatively even distribution among (5%) concentration intervals. Retesting on a separate occasion yielded a similar data distribution, with no significant change in individual thresholds. No systematic attention was given to variation in thresholds within the group, however.

Shusterman and Balmes (Shusterman and Balmes, 1997a) utilized paired CO_2 and air stimuli in a forced-choice, ascending series, method of limits protocol. Pulses were of 3 s duration, applied unilaterally, synchronized with inspiration during normal nasal breathing, with a 12–15 s interstimulus interval and 45 s inter-trial interval. Among the 30 healthy adult subjects studied (aged 19–79 years), CO_2 detection thresholds ranged from 20 to 50% v/v

Table 2 Studies of variability in nasal chemesthesis

Reference	Test agent	Psychophysical (perceptual) endpoint(s)	Physiological (instrumental) endpoint(s)	Subjects stratified by	Significant variability?[a]
(Anton *et al*., 1992)	CO_2	detection threshold		random (normosmics)	yes
(Barz *et al*., 1997)	CO_2		CSERP amplitudes	Parkinson's disease status	no
(Bascom *et al*., 1991)	ETS	nasal irritation, congestion	nasal airway resistance	historical ETS sensitivity	yes/yes
(Bascom *et al*., 1996)	ETS	nasal congestion, rhinorrhea	nasal airway resistance	historical ETS sensitivity	no/no
(Cometto-Muñiz and Cain, 1982)	CO_2	suprathreshold rating	'transient reflex apnea'	smoking status	yes/yes
(Cometto-Muñiz and Noriega, 1985)	CO_2	suprathreshold rating		gender	yes
(Cometto-Muñiz and Cain, 1998)	alcohols	localization versus detection		olfactory dysfunction	no
(Cometto-Muñiz *et al*., 1998b)	terpenes	localization versus detection		olfactory dysfunction	no
(Cometto-Muñiz *et al*., 2001)	butyl acetate, toluene	localization versus detection		olfactory dysfunction	yes[b]
(Dalton *et al*., 1997)	acetone	suprathreshold rating		risk expectation	yes
(Dunn *et al*., 1982)	CO_2		'transient reflex apnea'	smoking status	yes
				gender	yes
(Hummel *et al*., 1996a)	CO_2		CSERP amplitudes	olfactory dysfunction	yes
(Hummel *et al*., 1996c)	CO_2		CSERP amplitudes	idiopathic environmental intolerance	yes
(Hummel *et al*., 1998a)	CO_2	suprathreshold rating	CSERP amplitudes	age	no/yes
(Kendal-Reed *et al*., 1998)	propionic acid	'isoresponse rating'		random (normosmics)	yes
(Kendal-Reed, 2000)	propionic acid	'isoresponse rating'		olfactory dysfunction	yes
(Kendal-Reed *et al*., 2001)	propionic acid	'isoresponse rating'	tidal volume	olfactory dysfunction	yes/yes
(Kjaergaard *et al*., 1995)	VOCs (mixture)	eye, nose, throat irritation	nasal volume	seasonal allergic rhinitis	yes/no
(Mattes and DiMeglio, 2001)	ethanol	localization threshold		gender	no
(McLean *et al*., 1979)	NH_3		nasal airway resistance	seasonal allergic rhinitis	no
(Shusterman and Balmes, 1997a)	CO_2	detection threshold		age	no
				gender	no*
				smoking status	yes
			historical ETS sensitivity		no
(Shusterman *et al*., 1998)	Cl_2	nasal irritation, congestion	nasal airway resistance	seasonal allergic rhinitis	yes/yes
(Shusterman *et al*., 2001)	CO_2	detection threshold		gender	yes
				seasonal allergic rhinitis	no
		n-propanol	localization threshold		gender
				seasonal allergic rhinitis	yes
(Stevens *et al*., 1986)	CO_2	detection threshold	'transient reflex apnea'	age	no/yes
(Willes *et al*., 1998)	ETS	nasal congestion, rhinorrhea, nasal irritation, rhinorrhea	nasal airway resistance	historical ETS sensitivity	yes/no
				gender	yes/no
(Wysocki *et al*., 1997b)	1-butanol	localization threshold		age	yes

[a](Psychophysical/physiological) endpoint.

[b]Difference apparent at lower detection probabilities only.

*$P = 0.06$ for gender effect.

(geometric mean, 27%), with a distribution skewed toward lower values. On multivariate analysis, cigarette smoking was associated with higher detection thresholds and the gender difference (females tending toward lower thresholds than males) approached statistical significance ($P = 0.06$). On the other hand, no age trend was apparent for CO_2 detection thresholds and neither self-reported reactivity to environmental tobacco smoke nor self-reported 'vasomotor rhinitis' symptoms predicted individual thresholds.

Shusterman *et al*. (Shusterman *et al*., 2001) obtained replicate measures of both CO_2 detection and VOC (*n*-propanol) localization from 16 subjects aged 19–37 years, evenly divided by both gender and allergic rhinitis status. Female gender predicted lower thresholds for both measures, whereas nasal allergies predicted lower thresholds for VOC localization only. On an intra-individual basis, the two measures (CO_2 detection and VOC localization) showed significant correlation ($r = 0.63$; $P < 0.01$).

Lotsch *et al*. (Lotsch *et al*., 1997) examined the issue of circadian rhythms in chemoreception, presenting five healthy male volunteers with 200 ms uncued CO_2 pulses at 30 s intervals using a staircase protocol. Six different test times—evenly spaced over a 24 h period—were employed and thresholds were obtained separately for each nostril. Overall, absolute CO_2 detection thresholds varied from ~30 to 60%, v/v. For irritant thresholds, no consistent circadian rhythms were apparent, either using individual or group data. Apart from the temporal analysis, the authors did not directly address the issue of the relative magnitude of between- versus within-subject test variability.

Wysocki *et al*. (Wysocki *et al*., 1997b) examined the effects of age on both olfactory and nasal trigeminal thresholds to 1-butanol among 142 subject aged 20–89 years. Both thresholds increased with age (olfactory more than trigeminal). The authors pointed out that, independent of age, olfactory impairment predicted elevated trigeminal localization thresholds. This observation, in turn, raised the possibility that the age–trigeminal connection may be indirect (i.e. may be mediated by a contribution of intact olfaction to trigeminal irritant perception).

Gudziol and colleagues (Gudziol *et al*., 2001) presented formic acid vapor in increasing concentrations to 72 anosmics and 96 healthy controls ranging in age from 19 to 88 years. Minimum concentrations eliciting a description of 'burning or stinging' on four successive trials were significantly higher in anosmics than normosmics. Due to the lack of a forced-choice paradigm or allowance for odor cueing, however, the study is of limited value in comparing trigeminal threshold between the two groups.

Mattes and DiMeglio (Mattes and DiMeglio, 2001) tested 25 male and 25 female light-to-regular alcohol consumers, aged 21–50 years, with regard to their olfactory, taste and trigeminal thresholds for ethanol. Using the technique of localization to document nasal irritation, they found no significant difference in threshold by gender.

Suprathreshold scaling of irritation. Stevens *et al*. (Stevens *et al*., 1982) compared suprathreshold rating of nasal irritation from CO_2 among younger (age 18–25 years) and older (age 65–83 years) subjects, using the method of magnitude matching. For given stimulus strengths (CO_2 concentration range, 24–100% v/v), older subjects, on average, gave significantly lower subjective irritation ratings than did younger subjects.

Cometto-Muñiz and Noriega (Cometto-Muñiz and Noriega, 1985) examined gender differences in suprathreshold rating of nasal irritation from CO_2. After being presented with 2–3 s unilateral pulses of CO_2 in the 21–60% (v/v) range, subjects rated stimuli using the method of magnitude estimation. Investigators found that females exhibited a steeper psychophysical function than did males (slope, 2.2 versus 1.6). In a second (cross-modality) procedure, in which nasal CO_2 stimuli were magnitude matched to oral sucrose stimuli, females similarly showed higher absolute pungency ratings and steeper psychophysical functions, on the average, than did males.

Dalton *et al*. (Dalton *et al*., 1997) explored the role of cognitive bias in modifying responses—including perceived irritation—in a controlled exposure study to an odorous air pollutant. Ninety adults were exposed for 20 min to 800 p.p.m. acetone in a climate-controlled chamber; control exposure was to a non-irritating odorant, phenylethyl alcohol. Three subgroups of 30 each were given differing instructions prior to exposure. Pre-exposure characterization of the compounds involved included a positive bias ('natural extracts'), neutral bias ('standard odorants') and a negative bias ('industrial solvents'). The neutral and negative bias groups combined reported more acetone-related symptoms, including nose and throat irritation, lightheadedness, nausea and drowsiness, than did the positive bias groups. These findings are in agreement with earlier epidemiologic observations near hazardous waste sites, at which the prevalence of sensory irritation symptoms was predicted by both frequency of perceived environmental odors and degree of 'environmental worry' (Shusterman *et al*., 1991). The relative roles of cultural background, personality and risk perception/communication on the overall response to odorous/irritating air pollutants (including hedonic and emotional responses) is reviewed in detail elsewhere (Shusterman 1992, 1999, 2001).

Kendal-Reed *et al*. (Kendal-Reed *et al*., 1998) examined the endpoint of subjective nasal irritation from proprionic acid, comparing the response of 31 normosmic and four anosmic subjects. The experimental protocol involved 15 s occlusive exposure by facemask to concentrations of vapor ranging from peri-threshold in normosmics to suprathreshold in anosmics. Subjects were asked to rate nasal irritation (and odor, in the case of the normosmics) independently on a visual analog scale with two anchors: 'slight' and 'previous high'. Four so-called 'isoresponse' levels, consisting of the interpolated stimulus concentration producing a predeter-

mined interval between the two above-noted anchors, were calculated for each subject and means and confidence intervals calculated using a bootstrapping technique. The investigators found: (i) normosmic subjects apparently integrated odor information into their estimation of irritation (i.e. they showed lower concentrations for each irritant isoresponse level than did anosmics); (ii) the degree of inter-individual variance in concentration for a given irritant isoresponse decreased with increasing intensity in normosmics, but increased with increasing intensity in anosmics; and (iii) inter-individual differences in isoresponse level for irritation in normosmics were as large as—or larger than—the corresponding differences for odor and were much larger than the inter-individual differences for irritation in anosmics.

Kendal-Reed *et al.* (Kendal-Reed *et al.*, 2001) examined inter- and intra-individual (within- and between-session) variability in nasal irritation using the endpoint of the isoresponse level to propionic acid (see above). Included were 31 normal and four anosmic subjects. Except at the highest isoresponse level, anosmics exhibited lower irritant sensitivity than did normosmics. Anosmics tested at all levels showed lower intra-individual (between-session) variation than did normosmics. Among normosmics, intra-individual variance decreased as stimuli progressed from lower to higher concentrations. The authors interpreted their data to support a contribution of intact olfaction to perceived irritant magnitude, particularly at lower stimulus concentrations.

Mohammadian and colleagues (Mohammadian *et al.*, 1997) examined the effect of acute nasal 'inflammation'—defined as the acute mucosal state induced by the pre-application of cold, dry air to one nostril—on the suprathreshold rating of CO_2-induced pain. Nineteen normal adult subjects completed a study in which 200 ms pulses of CO_2 at a concentration of 65% v/v (36 total) were applied to the left nostril on an uncued basis, with an interstimulus interval of 30 s and with subjects exercising velopharyngeal closure. Nasal irritation was rated using a visual analog scale and the experiment was repeated under conditions in which the cold, dry air was pre-applied either ipsilaterally or contralaterally to the CO_2. The experimenters found that pre-application of cold, dry air for 6 min prior to CO_2 challenge increased the suprathreshold rating of CO_2-induced irritation, including when rating was performed contralateral to the side on which cold air was applied. Although confidence limits were presented for all group data, the extent of inter-individual variability was not an explicit focus of this study.

Several studies have examined perceived nasal irritation—as well as such secondary symptoms as congestion and rhinorrhea (see below)—in provocation experiments designed primarily to examine physiologic endpoints. Bascom and colleagues (Bascom *et al.*, 1991) initially exposed 21 healthy adult subjects to high-level sidestream tobacco smoke (STS) for 15 min and obtained sensory ratings on a category scale for a number of symptoms pre- and post-exposure. The intensity of exposure was documented using the surrogate measure carbon monoxide, which was regulated to ~45 p.p.m. The subjects were subdivided into 10 historically sensitive to environmental tobacco smoke (ETS-S) and 11 historically non-sensitive (ETS-NS). Whereas subjects, as a whole, reported significant exposure-related increases in combined nose–throat irritation, ETS-S subjects reported significantly greater increases than ETS-NS subjects. In a similarly designed study with 13 ETS-S and 16 ETS-NS subjects exposed at multiple STS concentrations (0, 1, 5 and 15 p.p.m. CO) for 2 h, no difference in self-reported nasal irritation was apparent until the highest STS concentration was reached, at which point the ETS-NS group reported more intense symptoms (Bascom *et al.*, 1996). In a third study along these lines, 14 ETS-S and nine ETS-NS subjects were exposed to 'moderate' levels of STS (15 p.p.m. CO) for 2 h and again the ETS-NS subjects reported greater exposure-related nasal irritation (Willes *et al.*, 1998). A possible confounder in interpreting the results of these three studies is the varying proportion of subjects with evidence of allergic disease between the (ETS-S and ETS-NS) subgroups in each study (see discussion below).

Kjaergaard and colleagues (Kjaergaard *et al.*, 1995) exposed 18 'hayfever' and 18 normal subjects to a mixture of 22 different VOCs at an aggregate concentration of 20 mg/m^3 for 4 h. Exposure to control conditions—'clean air'—occurred on a separate day. Hayfever subjects showed greater increases in combined subjective (eye–nose–throat) irritation over the course of the exposure than did non-allergic subjects.

Shusterman and co-workers (Shusterman *et al.*, 1998) compared the response of eight seasonal allergic rhinitic (SAR) and eight non-rhinitic (NR) subjects, to a 15 min exposure by nasal mask to chlorine at 0.5 p.p.m. The experiment was counterbalanced with respect to both subject gender and order of exposure (chlorine versus control first) and SAR subjects were tested out of season. After chlorine provocation, SAR subjects showed more significant increases in self-rated nasal irritation than did NR subjects.

Secondary endpoints (irritant-related reflex symptoms)

As noted above, numerous studies whose primary focus has been physiologic measures have, in addition, examined perceptual rating of secondary (reflex) symptoms. In two of three of Bascom's STS studies mentioned above, for example, (historically) ETS-sensitive subjects reported significantly greater exposure-related increases in perceived nasal congestion and rhinorrhea than did non-sensitive subjects (Bascom *et al.*, 1991, 1996). In Kjaergaard *et al.*'s (Kjaergaard *et al.*, 1995) VOC provocation experiment, subjects with seasonal allergic rhinitis ('hayfever') showed significantly greater exposure-related increases in self-reported rhinorrhea than did controls (non-rhinitics). In

Shusterman *et al.*'s (Shusterman *et al.*, 1998) chlorine-provocation experiment, seasonal allergic rhinitic subjects reported more significant exposure-related increases in nasal congestion than did non-rhinitic subjects. Together, these reports suggest that self-reported pollutant reactivity and/or skin-test proven allergy status may, under some circumstances, predict reflex symptoms in response to nasal irritant provocation.

Physiological studies

Primary endpoint (nasal irritation)

Peripheral electrophysiologic measures. A number of published studies explore the electrophysiologic response of the nasal mucosa to painful stimulation, referred to as the 'negative mucosal potential' or 'electrotrigeminogram' (Kobal, 1985). Methodologic variables influencing the magnitude and latency of such potentials include the concentration and duration of applied stimuli, the time interval involved in repetitive stimulation and pre-medication of the mucosa with local anesthetics, ganglion blockers, or capsaicin (Thurauf *et al.*, 1991, 1993; Hummel *et al.*, 1996c). Unfortunately, no studies have appeared to date that explicitly examine inter-individual variability in this endpoint.

Central electrophysiologic measures. Summated and averaged electroencephalographic (EEG) potentials occurring in relationship to intermittent nasally applied chemical stimuli have been referred to as either 'chemosensory evoked potentials' or CSERPs (Hummel *et al.*, 1991, 1992, 1994, 1995, 1996a, 1998a,b; Hummel and Kobal, 1992; Kobal *et al.*, 1992; Livermore *et al.*, 1992; Barz *et al.*, 1997; Kobal and Hummel, 1994, 1998). As noted above, topographic distinctions have been made between cortical activity related to trigeminal stimulation ('chemosomatosensory evoked potentials') and that related to olfactory stimulation ('olfactory evoked potentials'). Specifically, activity is most prominent in the vertex after trigeminal stimulation and in parieto-central recording sites after olfactory stimulation. Further, unilateral stimulus presentation produced bilaterally symmetrical cortical activity with odorant stimuli, but asymmetric (predominantly contralateral) activity with irritants (Hummel and Kobal, 1992). In contrast to the situation for the negative mucosal potential, several studies have examined inter-individual variation in this response as a function of personal/demographic traits, including gender, age and disease state (olfactory loss, Parkinsonism and epilepsy). These studies are reviewed below.

Hummel and colleagues (Hummel *et al.*, 1998c) recorded cortical activities and perceptual ratings to phenyl ethyl alcohol and CO_2 among 17 young adult subjects (nine females and eight males). Women had significantly greater P2, N1P2 and N1P3 amplitudes than did men, but paradoxically tended to rate stimulus intensities as lower. On the other hand, the two groups did not differ in their degree of short-term adaptation to repetitive stimuli.

Hummel and co-workers (Hummel *et al.*, 1998a) examined the effects of age on odor detection, identification and discrimination, as well as on CSERPs elicited by two predominantly olfactory stimuli (H_2S and vanillin) and one predominantly trigeminal stimulus (CO_2). Gender-balanced groups of 16 subjects each represented the age ranges of 15–34, 35–54 and 55–74. Odor discrimination ability decreased significantly with age, whereas the decrement in odor identification was not statistically significant and there was no change in odor detection performance. With regard to trigeminal function, for all three test compounds, N1P2 (as well as P2) CSERP amplitudes decreased significantly—and N1 latency increased—with age. CO_2 intensity ratings, on the other hand, did not vary systematically by age.

Three studies have examined the effect of olfactory loss on trigeminally induced cortical activity. Hummel *et al.* (Hummel *et al.*, 1996a) recorded CSERPs in response to CO_2 stimuli among 16 patients with olfactory dysfunction of various etiologies (average age, 51 years) as compared to age- and sex-matched controls. Patients with olfactory dysfunction exhibited significantly lower P1N1 amplitudes, as recorded at the Cz (predominantly trigeminal) location, although latencies were not different for the two groups. The authors proposed several competing explanations, including the possibility that cortical or thalamic interactions occur between the two systems, or that coincidental damage had occurred to the two systems during head trauma (which was responsible for olfactory loss in half of the patients). A separate study (Kobal and Hummel, 1998) emphasized the opposite aspect of trigeminal function among anosmics—that is, its relative preservation. The investigators used olfactory (vanillin and H_2S) as well as trigeminal (CO_2) stimuli to assess the responses of 44 patients giving a history consistent with anosmia and concluded that a lack of response to the former and a relatively intact response to the latter could be used objectively to validate the history. Finally, Hummel and co-workers (Hummel *et al.*, 1991) studied three patients with Kallmann's syndrome (congenital hypgonadism and anosmia) and found not only absent olfactory CSERPs (to vanillin or H_2S), but also augmented responses to trigeminal stimuli (CO_2 and menthol).

Barz and colleagues (Barz *et al.*, 1997) examined CSERPs in 13 Parkinson's disease (PD) patients taking antiparkinsonian drugs, 18 who were not on medication and 38 age- and sex-matched controls. Stimuli included vanillin and H_2S (predominantly olfactory) and CO_2 (predominantly trigeminal). Subjects and controls were also tested for odor identification ability. PD patients showed diminished odor identification ability, regardless of medication status and olfactory evoked responses showed slowing (increased latency) in this group. Trigeminal evoked responses,

however, appeared to be intact in PD patients, whether on or off medication.

Hummel *et al*. (Hummel *et al*., 1995) studied CSERPs in 22 patients with temporal lobe epilepsy: 12 with a left-sided focus and 10 with a right-sided focus. No control group was used. Vanillin and H_2S (predominantly olfactory) and CO_2 (predominantly trigeminal) were employed, with separate trials for left- versus right-sided stimulus presentation. Regardless of the laterality of the epileptic focus, CO_2 stimuli applied to the left nostril showed longer latencies than did stimuli to the right nostril (a finding that is difficult to interpret without a comparison group). Of equal interest is the fact that the laterality of the epileptic focus appeared to influence observed CSERP latencies for olfactory, but not trigeminal, stimuli.

Finally, Hummel *et al*. (Hummel *et al*., 1996b) and Vieregge *et al*. (Vieregge *et al*., 2000) measured CSERPs to olfactory (H_2S) and trigeminal (CO_2) stimuli among 23 patients diagnosed with 'idiopathic environmental intolerance' (IEI) and compared the results with age- and gender-matched controls. They found that IEI patients had smaller olfactory and trigeminal ERP amplitudes than did controls, as well as higher olfactory identification and discrimination thresholds. The authors concluded that IEI patients' self-reported augmented responsiveness to chemosensory stimuli may involve enhanced cortical processing of chemosensory events, rather than a primary sensory process.

Secondary endpoints (reflex changes)

Respiratory behavior studies. It has long been noted that experimental animals exhibit respiratory slowing in response to upper respiratory tract irritation (Alarie, 1973). Starting with work in the early 1980s, considerable attention has also been paid to irritant-induced changes in respiratory behavior in humans. In these studies the most frequently used test compound is high-level, pulsed CO_2 (which produces sensory irritation by generating carbonic acid in mucous membrane water, with little, if any olfactory stimulation). A smaller subset of studies has used volatile organic chemicals for this purpose, albeit without the advantage of isolating chemesthesis from olfaction. Although these studies examine an endpoint that is secondary (reflex) in nature, this classification is somewhat problematic, since (CNS-mediated) changes in respiratory behavior are of a very short latency compared to other (primarily biochemically mediated) reflexes. Classificational issues aside, several such studies have highlighted inter-individual chemesthetic variability, including studies examining age, gender, smoking status and presence or absence 'vasomotor rhinitis' symptoms.

Dunn *et al*. (Dunn *et al*., 1982) studied CO_2-induced respiratory disruption in 25 smokers and 26 nonsmokers (average age, 27 years; average cigarette consumption among smokers, one pack per day). CO_2 stimuli were self-administered by nasal cannula and subjects synchronized their breathing with a metronome in order to achieve consistent stimulus duration. Respiratory behavior was recorded by placing a thermocouple at the unstimulated nostril. Smokers exhibited a significantly higher mean threshold for respiratory disruption than did non-smokers (81 versus 60% v/v; $P < 0.001$) and males tended to show higher thresholds than females (77 versus 67%; $P = 0.05$). In addition, one in four smokers (but no non-smokers) tolerated pure CO_2 without manifesting a change in respiratory behavior.

Cometto-Muñiz and Cain (Cometto-Muñiz and Cain, 1982) expanded upon the above work by adding suprathreshold intensity rating of nasal irritation to the endpoint of respiratory disruption. In addition to replicating the previous findings of an elevated threshold for so-called 'reflex transitory apnea' among smokers, they found that smokers tended to rate a given stimulus as less irritating. When this effect was accounted for, they found that smokers exhibited respiratory disruption at the same level of perceived irritation as non-smokers. This observation was taken as support for the theory that some conductive factor (e.g. a thickened mucus layer) may be responsible for an apparent decrease in nasal irritant sensitivity in smokers.

As noted in a previous section, Stevens and Cain (Stevens and Cain, 1986) examined both the detection of CO_2 stimuli and CO_2-induced respiratory disruption as a function of subject age. Whereas they found no systematic effect of age on CO_2 detection (see above), the average threshold for CO_2-induced respiratory disruption among the elderly was 1.6 times the average among controls ($P < 0.00001$).

Shusterman and Balmes (Shusterman and Balmes, 1997b) compared the endpoint of CO_2-induced respiratory disruption with CO_2 detection thresholds among 20 healthy adult volunteers. Within the limitations of the study [maximum stimulus concentration, 70% (v/v); maximum perceptual rating of stimuli 'very strong'], clear-cut evidence of respiratory disruption was documented in only 13 (65%) of subjects. On the other hand, all subjects were able correctly to distinguish CO_2 from air in the requisite number of trials. Significant variability in individual responses was observed, with respiratory patterns including 'pleateauing', inspiratory pause, cough and forceful expiration. For several subjects, respiratory disruption appeared and disappeared irregularly during the ascending series of stimuli, implying that accommodation had occurred rapidly. The investigators concluded that the CO_2 detection task appeared to be a more reproducible measure of individual nasal irritant sensitivity than was the respiratory disruption threshold.

Warren and colleagues (Warren *et al*., 1992, 1994) exposed normosmics to various concentrations of VOCs and observed changes in respiratory pattern, as measured directly with a pneumotachometer. Exposures lasted 10 s and took place 1 min apart. In the first study, transnasal pressure was measured simultaneously with airflow, in order to derive nasal cross-sectional area (however, as this measure did not

change systematically with exposure, it was omitted from the second study). In the first study, the test compound employed was acetic acid (3–100 p.p.m.); in the second, amyl acetate and phenethyl alcohol were also used. In both studies, subjects showed a decrease in tidal volume with increasing acetic acid exposure concentration; this decrease mirrored increases in perceived irritation and odor intensity. Amyl acetate and phenylethyl alcohol yielded comparable odor but lower irritation ratings than did acetic acid and also had less profound effects on tidal volume. The authors concluded that irritation, not odor, was responsible for the respiratory disruptions observed. Although inter-individual variability of response was represented by error bars, it was not an explicit focus of analysis for either of these studies.

Walker *et al*. (Walker *et al*., 2001a) measured respiratory volume and duration during 15 s presentations of propionic acid vapor in 20 normosmic and four anosmic subjects, monitoring for decreases in inspiratory volume and duration. They found that normosmics, on average, responded to lower stimulus concentrations than did anosmics and did so with more profound changes in respiratory parameters. The authors argue that these observations support the case that odor is a contributor—not a confounder—in the study of nasal irritation.

Studies of nasal physiologic parameters. As noted above, Bascom and co-workers, in their studies of subjects who were historically ETS-S and ETS-NS, have also documented physiologic responses to STS. Physiologic markers have included nasal airway resistance (NAR, as measured by rhinomanometry), nasal cross-sectional area (by acoustic rhinometry) and a variety of biochemical and cellular markers (analyzed from nasal lavage fluid). In the first such study (Bascom *et al*., 1991), subjects were exposed to 'high-level' STS (45 p.p.m. CO × 15 min) and the 10 ETS-S subjects showed greater exposure-related increases in NAR after ETS provocation than did the 11 ETS-NS subjects. On the other hand, neither group showed evidence of a true 'allergic' (IgE-mediated) reaction, as evidenced by a lack of elevation of histamine, kinins, or albumin in nasal lavage fluid post-exposure. Seven of 10 ETS-S subjects (70%) were classified as atopic (>1 positive skin test), compared to only 3 of 11 ETS-NS subjects (27%). The authors concluded that the most likely response mechanism was neurogenic rather than allergic, but that pre-existing allergic inflammation may have up-regulated the neurogenic response.

In the second differential sensitivity study in this series, Bascom and colleagues (Bascom *et al*., 1996) studied 13 ETS-S and 16 ETS-NS subjects exposed to 'low-to-moderate' STS levels (1, 5 and 15 p.p.m. × 2 h). Differential responses were evident for NAR at 1 and 5 p.p.m., but not at 15 p.p.m. The pattern of differences was complex, in that the ETS-NS group showed more (rhinomanometrically measured) congestion at 1 p.p.m. and the ETS-S group showed more congestion at 5 p.p.m. The pattern of differences for nasal cross-sectional area was even more complex, depending upon the portion of the tracing targeted (anterior, mid-, or posterior nasal cavity). In this experiment, the two subgroups were comparable with respect to allergy status (i.e. the mean number of positive skin tests per subject).

In the most recent of this series of studies (Willes *et al*., 1998), 14 ETS-S and 9 ETS-NS subjects were exposed to STS (at 15 p.p.m. CO-equivalent for 2 h: 'prolonged, moderate levels') and nasal congestion was measured by rhinomanometry pre- and post-exposure. Interestingly, 8 of 15 STS-S subjects (53%) were judged to be atopic, but an even greater proportion of the ETS-NS subjects (seven of nine, or 78%) had evidence of allergies. Although seven of the eight subjects with the greatest STS-related increases in NAR were in the ETS-S group, the two groups did not differ significantly in their mean response to STS challenge.

Kjaergaard and co-workers (Kjaergaard *et al*., 1995), in their study of allergic rhinitic ('hayfever') and non-rhinitic subjects, examined changes in nasal volume (by acoustic rhinometry) after exposure to a mixture of VOCs simulating an indoor air quality problem. Although symptom reporting differed by subgroup (see above), rhinitics and non-rhinitics congested to an equal degree after VOC challenge, with no differential physiologic responsiveness being apparent.

McLean and colleagues (McLean *et al*., 1979) measured NAR among 33 seasonal allergic rhinitic and non-rhinitic subjects pre- and post- exposure to ammonia (100 p.p.m. × 5 s per nostril). Exposures were repeated at 15 min intervals, with successively longer durations of exposure (10, 15 and 20 s) in separate sub-experiments. Mean NAR increased after exposures and a dose–response relationship was evident for exposure duration; however, no difference was apparent in response by allergic rhinitis status.

Shusterman *et al*. (Shusterman *et al*., 1998) studied eight seasonal allergic rhinitic (SAR) and eight non-rhinitic (NR) subjects in a single-blinded crossover study with 15 min exposure to either: (1) filtered air, or (2) 0.5 p.p.m. chlorine in filtered air. Subjects had their NAR measured in triplicate before, immediately after and 15 min after the exposure. SAR subjects showed a significant congestive response (~20% increase in NAR after chlorine compared to control condition), whereas NR subjects showed no such response ($P < 0.05$).

Summary of the evidence for variability

A wide array of data bears on the issue of inter-individual variability in nasal chemesthesis. Despite conflicting—and sometimes confusing—findings, certain conclusions are possible, as follows.

1. Many published chemesthetic studies contain, but do not fully analyze or present, potential data pertaining to the issue of inter-individual variability.
2. Study methodologies which, on the surface, appear very

closely related (e.g. thresholds for CO_2 detection versus CO_2-induced changes in respiratory pattern) may yield differing conclusions regarding the importance of a given susceptibility marker, such as age (Stephens and Cain, 1986).
3. The predictive value of self-reported pollutant reactivity varies considerably by study. Not surprisingly, this variable more reliably predicts perceptual, rather than physiological, endpoints. For studies in which self-reported reactivity to air pollutants is used as an explanatory variable, it is desirable to control for the proportion of subjects in each subgroup who have nasal allergies, in order to allow each potential marker of susceptibility to be examined separately. This can be achieved either in the study design (balanced samples) or in the analysis (stratified or multivariate analysis).
4. Intact olfaction may contribute to both threshold and suprathreshold irritant perception. The differences observed between anosmics and normals, when present, tend to be greater at low stimulus concentrations.
5. In the majority of chemesthetic experiments in which subject gender has been explicitly examined, females tend to be more 'sensitive' (i.e. they detect irritant stimuli at lower concentrations, rate suprathreshold stimuli as stronger and react physiologically more markedly) than males.
6. In some, but not all, experiments in which allergic rhinitis ('hay fever') has been examined, rhinitics tend to exhibit more pronounced perceptual and/or physiological reactivity to irritant provocation than do non-rhinitics. The robustness of this finding deserves further attention.
7. Age has been examined as a predictor of nasal irritant sensitivity in only a limited number of studies to date and has yielded conflicting results.
8. In the limited number of studies in which cigarette smoking has been examined, smokers appear to have a blunted sense of nasal irritation compared to non-smokers.
9. Cognitive bias, particularly regarding the degree of toxicological risk posed by an exposure source, can influence such primary endpoints as perceived odor and irritation intensity. This bias may be influenced, not only by external events and risk communication, but also by personality variables predisposing to 'negative affectivity'.
10. There is only one published study addressing the issue of the generalizability of individual nasal irritant sensitivity across test compounds. This issue also deserves further study.

Potential mechanisms underlying variability

To the extent that inter-individual variability in nasal chemesthesis can be demonstrated—and personal markers identified—potential underlying mechanisms of susceptibility become of interest. Inter-individual variability in irritant-induced upper airway reflexes has been best studied for ETS. Self-reported nasal reactivity to ETS (defined as positive responses to questions regarding nasal irritation and congestion, rhinorrhea and postnasal drip in smoky environments) is more common among individuals with a prior history of atopy (allergies) than in non-atopics (Bascom *et al.*, 1991; Cummings *et al.*, 1991). Despite this empirical association with atopy, only a small proportion of historically ETS-S subjects have positive skin test reactivity to tobacco-leaf extract or tobacco smoke condensates (Stankus *et al.*, 1988).

Reinforcing the distinction between irritant-induced reflex symptoms and those of allergic rhinitis, the usual markers of IgE-mediated allergic response (including histamine and kinins) were not elevated in nasal lavage fluid after STS provocation (Bascom *et al.*, 1991). Assuming that these findings generalize to other types of chemical irritants, one implication to be drawn is that—although a prior history of respiratory allergies may be a risk factor for both perceptual and physiologic irritant reactivity—the actual mechanism of response probably does not involve true 'allergy' (mast cell degranulation/immediate hypersensitivity).

A potential explanation for this seemingly paradoxical relationship between upper respiratory tract chemesthesis and respiratory allergies is that allergy plays a modulatory role over the operation of another response system (Bascom, 1992). The most credible candidate for a non-allergic nasal response mechanism involves the irritant (nociceptor) receptor system of the trigeminal nerve (Cometto-Muñiz and Cain, 1992). Within this system, capsaicin-sensitive C (and Aδ) fibers innervate the nasal and oral cavities and give rise to both local (neuropeptide-mediated) and central (parasympathetic and sympathetic) reflexes (Baraniuk and Kaliner, 1990; Widdicombe, 1990; Raphael *et al.*, 1991; Baraniuk, 1992, 1994; Silver, 1992). In addition to responding to the model irritant, capsaicin, these sensory fibers are also sensitive to various irritant chemicals and to low pH (Lou and Lundberg, 1992; Nielsen and Hansen, 1993). Figure 1 illustrates the three alternative acute nasal response systems—one allergic and two neurogenic—as well as the principal non-invasive techniques available for studying them.

Animal experiments empirically support (and lend biological credibility to) a postulated allergy–chemoreception link. Using the model of the guinea pig sensitized to an exogenous protein (ovalbumin), it has been shown that antigen challenge of a tracheal preparation acutely decreases the threshold for mechanical stimulation necessary to produce a given frequency of afferent nerve impulses (Riccio *et al.*, 1996). Further, antigen challenge increases the efficiency of conduction of autonomic ganglia for efferent impulses (Weinreich and Undem, 1987). An additional potentiation of neurogenic reflexes occurs via inactivation of muscarinic

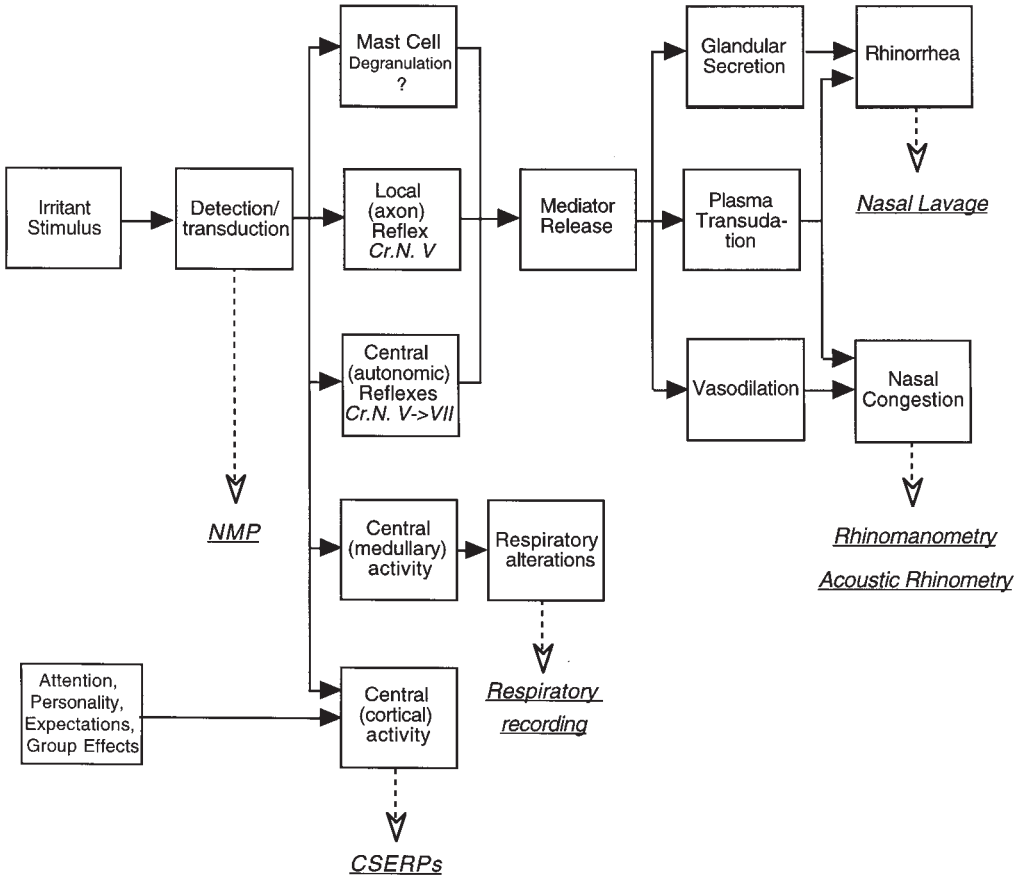

Figure 1 Potential mechanisms underlying the nasal reflex response to irritants (congestion, rhinorrhea and inflammatory cell influx). Italics indicate principal non-invasive study techniques for documenting both primary (sensory) irritation and secondary (reflex) responses. NMP, negative mucosal potential; CSERPs, chemosensory event-related potentials.

M_2 receptors, which have been shown to be sensitive to such insults as ozone exposure, viral infection and basic proteins associated with mast cell degranulation (Elbon *et al.*, 1995; Jacoby *et al.*, 1998). M_2 receptors, under normal circumstances, act as a negative feedback system in the parasympathetic nervous system and down-regulate post-ganglionic acetylcholine release; their inactivation would therefore potentiate cholinergic reflexes (Minette and Barnes, 1990). Thus, allergen challenge to susceptible (allergically sensitized) organisms may modulate both the afferent and efferent components of airway neurogenic reflexes. This model holds great promise for explaining not only upper and lower respiratory tract hyperresponsiveness after allergen challenge, but also after infection and high-level irritant exposures.

With respect to mechanisms underlying other suspected or confirmed markers of nasal irritant sensitivity (smoking status, gender, age), less can be said. As noted above, psychophysical data suggest that smokers manifest reflex respiratory disruption at a similar level of perceived irritation as do nonsmokers; however, a stronger stimulus appears to be necessary to produce that level of sensation (Cometto-Muniz and Cain, 1982). The authors interpreted this observation to indicate that a conductive factor (e.g. thickness or chemical characteristics of nasal mucus) was responsible, although impaired signal transduction (in smokers) could produce similar result. For gender differences in chemesthesis, speculation is possible regarding potential 'hormonal effects.' If this is an operative mechanism, then gender-related differences in chemesthesis should diminish with age (i.e. comparing post-menopausal women with similarly aged men). Finally, to the degree that age emerges as a significant (negative) predictor of nasal irritant sensitivity (a finding that is yet to be replicated in a sufficient number of studies), 'neurodegeneration' would likely emerge as the major candidate mechanism.

Summary

Patterns of symptom reporting in real-life air pollution situations point to individual factors in nasal chemesthesis. Experimental studies, in turn, document significant inter-individual variability, but generally not of as large a magnitude as is the case for the olfactory system. Functional definitions of nasal irritant sensitivity differ widely and even minor methodologic differences between experiments can lead to differing results and conclusions. Potential markers

of inter-individual variation which have received varying degrees of empirical support include gender (females more sensitive), upper respiratory tract allergies (rhinitics more sensitive), smoking (non-smokers more sensitive), age (younger subjects more sensitive) and self-reported pollutant sensitivity (historically sensitive individuals being more sensitive). Confounding may play a role in the predictive value of self-reported sensitivity, particularly if respiratory tract allergies are not taken into account. Mechanisms underlying observed differences in nasal chemesthesis are best understood for the case of respiratory tract allergies, which appear to modulate some neurogenic processes. Variability in nasal irritant sensitivity remains only partially investigated and for many published studies, potentially relevant data have been unexplored.

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