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Dynamics of Nasal Irritation from Pulsed Homologous Alcohols

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Abstract

Relatively, few studies have focused on how nasal irritation changes over time. To simulate the rhythm of natural respiration, subjects received 3-s pulses of volatile organic compounds interspersed with 3-s pulses of clean air. Each trial, subjects received 9 pulses of a chemical vapor over about 1 min. Subjects rated nasal irritation from each pulse using magnitude estimation. Within a trial, compound and concentration were fixed. Compound (ethanol, *n*-butanol, or *n*-hexanol) and concentration (4 levels for each compound) varied across trials. For all stimuli, rated irritation decreased over time (adaptation). Plots of log-rated intensity versus elapsed time were approximately linear (intensity decreased by a fixed ratio per unit time). Interestingly, the slopes of intensity versus time functions differed very little: Regardless of concentration and compound, rated irritation decreased by about 32% over the 9 pulses. The basic mechanism of short-term adaptation may be the same for the 3 alcohols studied. Regardless, these data suggest that very simple models might be able to describe some aspects of perceptual dynamics quite well.

Key words: chemesthesis, exposure, inhalation toxicology, VOC

Introduction

Airborne chemicals can stimulate somatosensory nerves, causing sensations such as burning, warming, cooling, pungency, irritation, and stinging (Bryant and Silver 2000; Doty and Cometto-Muñiz 2003; Cometto-Muñiz et al. 2010). The eyes and upper airways are more sensitive than the dry keratinized skin that covers most of the body because mucus membranes offer easier access to nerve endings and molecular receptors. Mild to moderate sensory irritation is vital to our enjoyment of many beverages, foods, and personal products (Cardello and Wise 2008). On the other hand, irritation from environmental exposure can constitute a material impairment of health, and government regulators set many occupational exposure limits accordingly (NIOSH 1994; Cain 1996; Fisk and Rosenfeld 1997). Thus, basic data on the relationship between stimulus and sensation are of great interest, particularly in humans.

How molecular properties relate to sensation qualifies as one important concern (Doty and Cometto-Muñiz 2003; Abraham et al. 2010). Within an aliphatic series of molecules, which share a common functional group but vary in the number of methylene units in the base chain, irritant potency tends to increase with carbon chain length (Cometto-Muñiz et al. 1998; Cain et al. 2006; but also see Cometto-Muñiz et al. 2007). One parameter that increases with chain length is lipid solubility, an important predictor in some successful structure–activity models of irritant potency (Abraham et al. 2003; Hau et al. 1999). That lipid solubility matters makes sense, given that molecules must pass into lipid-rich tissue to reach nerve endings (Finger et al. 1990). Regardless, valid models of irritant potency could be valuable to regulators in government and industry responsible for setting limits for environmental and occupational exposures.

Stimulus dynamics, or how stimuli are distributed over time, is another important concern (Shusterman et al. 2006; Wise, Zhao, and Wysocki 2009). Most of the literature on the relationship between irritant potency and molecular parameters is based upon brief exposures in the laboratory, often a single sniff or brief pulse from an olfactometer (Wise, Zhao, and Wysocki 2009). Yet, with continuous exposure, irritation tends to wax over time, plateau, and may eventually wane as adaptation or desensitization occurs (Cain et al. 1986; Anton et al. 1992; Hempel-Jorgensen et al. 1999; Shusterman et al. 2003; Wise et al. 2003). The time course of irritation clearly varies across compounds (reviewed in Shusterman et al. 2006; Wise, Zhao, and Wysocki 2009). However, to the best of our knowledge, there have been

few, if any, systematic structure–activity studies of how the dynamics of nasal irritation varies with molecular properties. Thus, current models of irritant potency, lacking information on how people experience compounds over time, may provide incomplete information.

The current study will begin to address this issue by measuring how nasal irritation changes over time for a model group of homologous irritants, namely aliphatic *n*-alcohols. Eventually, it would be desirable to bridge the gap between very brief exposures in the laboratory and natural exposures, for example, up to 8 h in the workplace. Of course, perfectly natural, whole-body exposure entails less control over stimulus parameters, for example, how quickly and deeply subjects inhale, whether they inhale through the mouth or only through the nose, which tissues are exposed, and how concentration varies over time. In the current study, which represents a very early stage in the effort to bridge the gap between the laboratory and workplace, we chose to maintain tight control of the stimulus by injecting air laden with a volatile organic compound (VOC) into the nose using an air-dilution olfactometer. Vapor was pulsed in 6-s cycles to roughly simulate the rhythm of natural respiration: Three seconds of VOC were followed by 3 s of clean air. Subjects received 9 cycles to simulate exposures of up to about 1 min, such as might occur when a worker enters a contaminated room to complete a brief task.

Materials and methods

Subjects

Seventeen (9 female) healthy nonsmokers (22–38 years of age, average = 26.8) participated. Subjects provided written informed consent on forms approved by a University of Pennsylvania Institutional Review Board. Most subjects were employees of the Monell Center. Others were recruited from the local community. Employees had no special knowledge regarding the research beyond the information provided to all subjects during the informed consent procedure. All had previous experience with psychophysical testing, including evaluations of odor and nasal irritation.

Stimuli

Stimuli included ethanol (CAS# 64-17-5) at 1367, 2269, 3753, and 5868 ppm, *n*-butanol (CAS# 71-36-3) at 560, 735, 972, and 1271 ppm, and *n*-hexanol (CAS# 111-27-3) at 4.0, 8.3, 17.5, and 38.6 ppm. These values were targets, but actual values varied by 5% or less (see Calibration, below).

Based upon pilot work and previous findings using the same apparatus (Wise et al. 2007), the lowest concentration of each compound was selected to fall just above irritation threshold, that is, the lowest concentration that most subjects can reliably lateralize with 3.0–4.0 s presentations (methods described in Wise et al. 2006, 2007; Wise, Toczydlowski, et al. 2009). Additional pilot work suggested that these low concentrations were 1) approximately matched in perceived intensity across compounds, 2) more irritating than blanks (clean air), but 3) substantially less irritating than a standard stimulus (headspace above a 12.5% v/v aqueous solution of ethanol; see Procedures). The highest concentration of each stimulus was selected to cause moderate nasal irritation, roughly matched in intensity across the 3 compounds. Intermediate concentrations were selected by creating 2 logarithmically spaced steps between the low and high concentrations. Thus, we selected 4 concentrations of each stimulus that spanned the range from fairly weak to moderate nasal irritation, with comparable irritation levels across compounds.

Apparatus

Stimuli were delivered via a computer-controlled air-dilution olfactometer described in previous reports (Wise et al. 2005, 2006, 2007; Wise, Toczydlowski, et al. 2009). Air was dried and filtered before passing into a temperature-controlled enclosure. In the enclosure, the air was rehumidified. Some of the rehumidified flow passed through glass vessels containing pure liquid VOC. This VOC-laden air was then mixed with additional rehumidified air to form the desired stimulus concentration. A system of 3-way solenoid valves could gate a stimulus (either VOC-laden air or a clean air blank) to either nostril. Stimuli entered the nostrils at 5 (±0.05) L/min, 37 (±0.5) °C, and 90 (±3) % relative humidity. Stimuli were embedded in a steady (background) flow of air with the same flow rate, temperature, and humidity as the stimuli, which allowed a focus on chemical stimulation of somatosensory nerves. The device could switch between clean and odorized air rapidly (within ~15 ms) with little change in temperature, flow, or humidity.

Stimulus presentation

Subjects practiced velopharyngeal closure, a breathing technique in which the soft palate is used to isolate the nasal cavity from the rest of the airways to help prevent fluctuations in pressure and flow from respiration (Kobal and Hummel 1991). Subjects practiced closure until they could breathe for up to a minute without fogging a mirror held under the nose, though closure was not monitored during experimental trials. The olfactometer injected stimuli into the nose through flexible, 4.0-mm outer diameter Tygon tubes, which extended about 0.75 cm into the nostrils. Flow exited the nostrils around the tubes.

Calibration

All parameters were measured at the output of the olfactometer. Experimenters measured flow rate (Gillibrator 2 flowmeter; Gillian Instrument Corp.), humidity (Digitron 2020R hygrometer; Topac Instruments), and temperature (BAT-12 thermocouple reader; Physiotemp Instruments). A fast-response pressure transducer (CyQ line, custom made;

Cybersense) was used to verify that minimal changes in flow occurred during presentation of VOCs. Vapor phase concentration of the VOC to be studied was adjusted daily to the desired value using photoionization detectors (MiniRAE 2000 for ethanol and *n*-butanol; ppbRAE Plus for *n*-hexanol; both from RAE Systems). Standards were created by injecting known masses of VOC into air-filled Tedlar gas sampling bags. The standards were used to convert PID readings to parts per million values.

Subject training

Most subjects expressed an understanding of the difference between odor and irritation. Regardless, during an initial test session, subjects were presented with beakers of ethanol. Subjects gently sniffed wafted vapor at arms length to experience odor, then approached the beaker more closely and sniffed more vigorously to experience irritation. Furthermore, experimenters discussed several examples of pure odor sensations, for example, those of coffee and rose, and sensations that also involve irritation, for example, those of acetone and ammonia. Subjects were told to rate the strength of irritation, for example, burning, stinging, prickling, pungency, and to ignore odor, throughout the experiment.

During the initial session, subjects also practiced magnitude estimation with a modulus. The modulus, or standard, consisted of a 5 cm line on a piece of paper and was assigned a value of "100." Subjects were instructed to rate the length of other lines proportional to the standard, for example, a line half as long should be rated as "50," whereas a line twice as long should be rated as "200." An experimenter verified that ratings of several lines were roughly proportional to length to ensure that subjects understood the magnitude estimation procedure. Finally, subjects rated irritation from a VOC (randomly selected concentration and compound) in 6 practice trials, using the methods described in Procedures.

Procedures

Subjects were instructed to rate nasal irritation proportional to the irritation from a modulus, namely the headspace above 20.0 mL of a 12.5% v/v aqueous solution of ethanol. The standard stimulus, presented in a 250-mL glass bottle, was replaced several times per week to maintain potency. At the beginning of each experimental session, subjects took a single sniff of the standard through a Teflon nosepiece attached to the cap of the bottle. The (mild) irritation the stimulus caused was assigned a value of "100." This standard helped ensure that different subjects used comparable ranges of numerical values and that subjects maintained comparable criteria across experimental sessions. A pause of about 5 min followed the sniff of the standard.

During an experimental session, subjects received a fixed concentration of a single VOC. Subjects were not told that the concentration of the stimulus remained the same during a session. Subjects were told that the intensity of irritation may or may not change during a trail and session. During each trail, subjects placed the output tubes of the olfactometer in their nostrils, established velopharangeal closure, and clicked a mouse to start. After a warning tone, a series of 9 pulses began. Pulses consisted of 3 s of VOC followed by 3 s of clean air to simulate the rhythm of natural breathing (Figure 1). A tone accompanied each pulse so that subjects were familiar with the rhythm of stimulation. During each session, subjects completed 6 trials, with at least 5 min elapsing between trials. During 2 trials, the steady stream of air in one nostril (right in one trial, left in the other) was periodically replaced with a clean air blank. During 4 trials, the steady stream of air in one nostril was periodically replaced with a fixed concentration of a particular VOC (2 left and 2 right). The 6 trials occurred in semirandom order, with the constraint that a particular nostril could not receive odorized air in consecutive trials. In all trials, subjects were aware of the nostril to be stimulated. The main purpose of presenting stimuli to one nostril was to help avoid adaptation, that is, to present fewer stimuli to each nostril during an experimental session. Subjects rated the intensity of each stimulus pulse by writing a numeric response on a pad of paper.

Subjects were instructed to avoid eating or drinking (except for water) for at least 1 h before experimental sessions. Concentration and compound varied in an irregular fashion between sessions. In total, subjects completed 13 experimental sessions: 3 compounds × 4 concentrations, plus a training session. Sessions were conducted over 10 weeks.

Data analysis

Replicate ratings (2 per combination of nostril, compound, concentration, and pulse number) were averaged using the arithmetic mean. These average ratings were log-transformed prior to further analyses because magnitude estimates are usually log-normally distributed (Lawless 2007). Effects were assessed via repeated measures analysis of variance (ANOVA), using Statistica software (Version 8.0, Statsoft). Initial analyses found violations of sphericity, so both univariate analyses with corrected degrees of freedom (Greenhouse and Geisser 1959) and multivariate analyses of variance (Wilk's test) (Gill 2001) were conducted. Both approaches

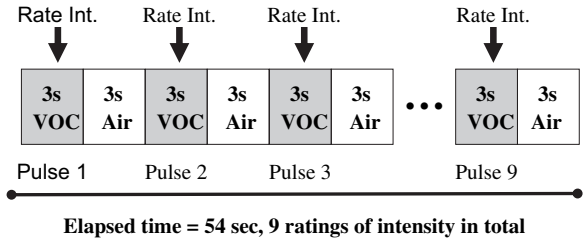

Figure 1 Time course of a trial. Trials lasted 54 s, with cycles of 3 s of VOC-laden air followed by 3 s of clean air (or, for blanks, 3 s of clean air followed by 3 s of clean air). Subjects rated the intensity of nasal irritation from each VOC pulse via magnitude estimation.

supported the same conclusions, hence we only report the univariate results below (significance criterion of $P < 0.05$). When needed, post hoc contrasts with a Bonferroni correction for multiple comparisons were used to examine effects in more detail.

Results

Ratings of the blanks (clean air)

Initial analyses focused on ratings of irritation from the blanks (clean air). The modal response was "0" or no reported irritation. The average rating was 3.9 (standard deviation [SD] = 6.7). Considering that the headspace above a 12.5% ethanol solution (the standard) was assigned a value of 100, most ratings for the blanks were essentially null. Furthermore, according to ANOVA, ratings for blanks did not vary systematically with time, concentration, or compound. Accordingly, data for the blanks were not considered further.

Ratings of VOCs

Next, ratings for VOCs were submitted to a 4-way ANOVA: Nostril (left vs. right) × Compound (ethanol, butanol, hexanol) × Concentration (4 levels) × Time (pulses one through 9). The effect of Concentration was significant, $F_{1.71,\ 27.43} = 166.02$, $P < 0.000001$, demonstrating an expected increase in rated irritation with concentration. The effect of Time also was significant, $F_{1.63,\ 26.14} = 69.10$, $P < 0.000001$. Rated intensity tended to decrease over time (Figure 2). Finally, the effect of compound reached significance, $F_{1.68,\ 26.91} = 3.71$, $P < 0.05$), indicating that the 3 compounds were not perfectly matched in intensity. Contrasts showed that subjects rated butanol as stronger than the other 2 compounds, though the difference was not large. Average (across concentrations) intensities were 74.1, 95.5, and 81.3 for ethanol, butanol, and hexanol, respectively. The remaining main effect, that of Nostril, failed to reach significance.

In contrast to most of the main effects, none of the interactions were significant. To a first approximation, regardless of concentration, compound, or nostril, perceived intensity seemed to decrease in a consistent fashion; however, the reader should note that the Concentration × Time interaction approached significance, $F_{4.75,76.05} = 2.11$, $P < 0.08$. Inspection of Figure 2 suggests that intensity may decrease more sharply over time at the lowest concentrations.

Decline in intensity over time

Linear fits to plots of log-rated intensity versus pulse number (Figure 2) accounted for an average of 94.3% (SD = 0.05%) of the variance in log intensity. Thus, intensity appeared to decrease by a constant factor per unit time. As suggested by the ANOVAs described above, differences in slopes appeared modest. Based on the fitted functions, intensity decreased by an average of 32.2% (SD = 0.06%) from the first pulse to the last. Under the current conditions, there was no clear indication of nonmonotonic effects of time, that is, sensitization followed by desensitization.

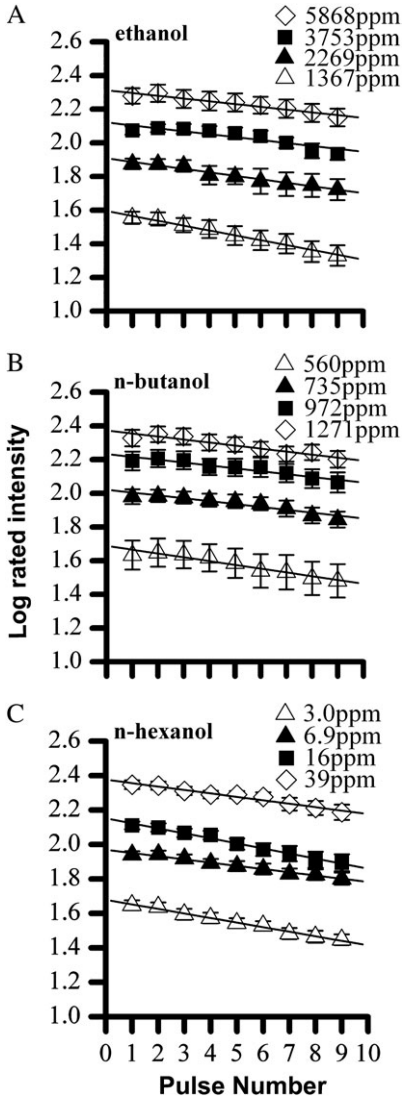

Figure 2 Ratings of intensity as a function of pulse number (elapsed time) and concentration. *x* axis: pulse number (elapsed time). *y* Axis: log-rated intensity ("2" is the value assigned to a standard of 12.5% v/v ethanol). **(A)** Ethanol. **(B)** *n*-Butanol. **(C)** *n*-hexanol. In each graph, the 4 data series represent different stimulus concentrations. The lines represent linear fits (least squares regression) to functions of log intensity versus pulse number. Error bars represent standard errors of the means.

Discussion

For all concentrations and compounds, intensity decreased over the course of 9 simulated inhalations (about 1 min). The rate at which intensity decreased did not differ greatly between concentrations of a given compound or between

compounds. To a first approximation, rated irritation was about 32% lower after 9 simulated inhalations, regardless of concentration or compound. Furthermore, though the experiment was not specifically designed to examine this issue, the concentration needed for a comparable level of irritation decreased with carbon chain length (Figure 2), which is consistent with past structure–activity work on irritant potency (Doty and Cometto-Muñiz 2003; Abraham et al. 2010). If these findings generalize to other VOCs, then it may be possible to predict how nasal irritation changes over time using relatively simple extensions of existing structure–activity models, at least during exposures of up to about 1 min.

Dynamics of nasal irritation

An earlier set of experiments examined the effect of stimulus duration on absolute detection of nasal irritation from the same aliphatic alcohols (Wise et al. 2007). Subjects were able to reliably detect nasal irritation at progressively lower concentrations as stimulus duration increased, at least up to about 4.0 s. Whether subjects might detect irritation from even lower (subthreshold) concentrations by integrating across inhalations remains an open question with considerable relevance for indoor air quality. However, based on the monotonic decrease in perceived intensity over time observed in the current experiment with weak to moderate suprathreshold concentrations, integration across inhalations seems less likely, at least for exposures up to about 1 min.

In addition, the previous study on absolute detection found a clear effect of carbon chain length: integration over time became more complete (closer to a perfect trade-off in which a 2-fold increase in duration could compensate for a 2-fold decrease in concentration) as carbon chain length increased (Wise et al. 2007; also see Wise, Toczydlowski, et al. 2009). In contrast, carbon chain length had little or no impact on dynamics in the current work. Absolute detection and suprathreshold ratings of intensity are very different paradigms (but see Wise et al. 2005). Still, we speculate that the biophysics of diffusion and transport in the nasal mucosa might matter more for detection of very brief stimuli, whereas the dynamics for longer suprathreshold exposures might be determined by changes in neural response, with a common mechanism of adaptation among the 3 compounds.

Considering that other suprathreshold studies generally find increasing irritation during the first phase of exposure (reviewed in Brand and Jacquot 2002; Shusterman et al. 2006; Wise, Zhao, and Wysocki 2009), the current monotonic decrease in intensity may seem surprising. However, many past studies have employed longer exposures and sampled rated irritation more coarsely, for example, one rating per minute. Again, different mechanisms, such as accumulation of algogenic peptides released from nociceptors (Bryant and Silver 2000), may come into play at longer durations.

Of course, the results may be particular to aliphatic alcohols. Ethanol, in particular, has wide-ranging effects on neural function, including anesthesia (Weight 1992; Catlin et al. 1999). Furthermore, repeated application of ethanol to the tongue did not cause a build-up of burn, unlike repeated application of the hot chili principle capsaicin (see Green 1990). It would be unwise to generalize the current results even to other nonreactive VOCs without further work on additional compounds.

Though we have chosen the current stimulus duration and interstimulus interval to roughly simulate natural respiration, it would be informative to vary the rhythm of stimulation. In both the mouth and the nose, the next application of a given irritant may feel either more or less intense than the previous application, depending on the interstimulus interval (Green 1990; Hummel et al. 1994; Hummel et al. 1996; Brand and Jacquot 2002). It seems reasonable to suggest that one might observe both waxing and waning of irritation for most compounds, depending on stimulus dynamics. Ultimately, dynamics must be explored in detail for a full understanding of chemical irritation.

Limitations and future directions

The current method of stimulus presentation, namely passive injection of stimuli into the nose, is clearly not physiological. Flow rates and patterns of flow in the nasal cavity, which can influence deposition and absorption of volatile compounds (e.g., Frederick et al. 1994, 1998; Morris 2001; Kurtz et al. 2004), probably differed from those of natural breathing. In addition, our regular 6-s cycles, with changes in concentration that approximated a temporal square wave, probably did not match natural breathing. Though we favor the tight stimulus control that our methods offer at this early stage of investigation, additional studies using more natural breathing techniques would complement the current results.

Readers should also consider the possibility that the odors of the stimuli influenced ratings of irritation, though subjects received training in this regard. There is evidence that subjects can in fact focus on irritation, though the contribution of odor to perceived irritation is not perfectly understood (Doty et al. 1978; Kendal-Reed et al. 1998). It would be valuable to repeat the experiment with a sample of subjects who lack a functional sense of smell (anosmics). This approach also has limitations in light of evidence that anosmics and normal controls might differ in their sensitivity to nasal irritation (Walker et al. 2001; Hummel et al. 2003; Frasnelli et al. 2010). Regardless, tests in anosmics and normal controls could complement one another well.

Finally, though we have focused on factors associated with the stimulus (molecular properties, concentration, and dynamics), other factors influence the time course of sensation as well. Future studies could examine the influence of expectations, beliefs about stimuli, personality factors, and individual differences in underlying physiology on the time course of sensation (Stevens 1990; Dalton et al. 1997; Shusterman 2002). Ultimately, we must account for the interaction

between stimulus- and subject-driven factors to achieve a complete understanding of chemical irritation.

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