Temporal Integration in Nasal Lateralization of Homologous Alcohols

Paul M. Wise, Sean E. Toczydlowski, and Charles J. Wysocki

Monell Chemical Senses Center, 3500 Market Street, Philadelphia, Pennsylvania 19104-3308

Received April 10, 2007; accepted May 25, 2007

Through temporal integration, sensory systems accumulate stimulus energy, e.g., photons, acoustic energy, or molecules, over time to detect weaker signals than they otherwise could. Past studies found imperfect temporal integration in detection of nasal irritation: To maintain a fixed level of detection, one must increase stimulus duration by more than twofold to compensate for cutting concentration in half. Despite this generality, integration varied widely among compounds, from nearly perfect, i.e., an increase in duration of slightly more than twofold could compensate for cutting concentration in half, to highly imperfect. How do such differences relate to molecular parameters? Perhaps molecules that more readily dissolve into the lipid-rich perireceptor environment will accumulate, and therefore integrate, better over time. To test this hypothesis, studies compared temporal integration for three compounds that differ systematically in lipid solubility: \(n\)-ethanol, \(n\)-butanol, and \(n\)-hexanol. Subjects were healthy, adult humans. Nasal lateralization was used to measure irritation threshold. Subjects received a fixed concentration of a single compound within each experimental session, and stimulus duration was varied to find the briefest stimulus subjects could reliably lateralize. Concentration and compound varied across sessions. Consistent with the hypothesis, integration did become closer to perfect as lipid solubility increased. That just one molecular parameter can help predict degree of integration suggests that a structure-activity approach to understanding temporal integration shows promise.

**Key Words:** chemical irritation; pungency; chemesthesis; volatile organic compound; inhalation toxicology.

Airborne chemicals can stimulate somatosensory nerves. Chemical somesthesia, or chemesthesia (Green et al., 1990), includes sensations such as stinging, pungency, cooling, warming, irritation, and burning (Bryant and Silver, 2000; Doty and Cometto-Muñiz, 2003). Chemesthesia in the eyes, nose, and parts of the mouth is mediated by the trigeminal nerve. Under some circumstances, government regulators treat chemical irritation as a material impairment of health and set occupational exposure limits based on irritation (Cain, 1996; NIOSH, 1994). Research has increased our understanding of chemesthesia in recent decades (Bryant and Silver, 2000; Doty and Cometto-Muñiz, 2003; Doty et al., 2004). Nevertheless, basic data that relate stimulus to sensation remain limited, especially for humans.

Data concerning the dimension of time in nasal chemesthesia are particularly limited. Sensory systems sum stimulus energy over time to detect weaker signals than they otherwise could (Baumgardt, 1972; Garner and Miller, 1947). At the supra-threshold level, a given perceived intensity may come from a brief presentation of a strong stimulus or a longer presentation of a weaker stimulus. To fully understand any sensory system, one must study how it integrates stimuli over time, i.e., temporal integration.

Above threshold, irritation grows with stimulus duration over the course of seconds or even minutes (Anton et al., 1992; Cain et al., 1986; Cometto-Muñiz and Cain, 1984; Fraselli et al., 2003; Hempel-Jorgensen et al., 1999; Wise et al., 2003). Work at threshold level has been more limited but is also important. Researchers often wish to know the minimum concentration that will cause detectable irritation. Thresholds give the best answer to this question. Further, subjects often have trouble distinguishing between odor and chemesthesia when making ratings of intensity (Wysocki and Wise, 2003). Do ratings reflect annoyance with an odor rather than chemesthesia? This point is especially salient given that expectations and beliefs about stimuli influence how rated irritation builds over time (Dalton et al., 1997). It is important to understand these influences, but it would also be useful to obtain more objective, performance-based data.

Nasal lateralization is performance based. Subjects simultaneously receive clean air in one nostril and chemical vapor in the other and must identify the nostril that received chemical vapor. Humans have little or no ability to lateralize odors, but we can lateralize chemicals that stimulate somatosensory nerves (Doty and Cometto-Muñiz, 2003; Wysocki and Wise, 2003). Lateralization can be used to measure chemesthetic thresholds for odorous chemicals, even though subjects usually smell concentrations too low to cause detectable irritation.

Wise et al. (2004, 2005, 2006) measured the briefest stimulus durations that allowed reliable lateralization for three model irritants: \(\text{CO}_2\) (\(10,000–65,000\) ppm), \(\text{NH}_3\) (37–721 ppm), and ethanol (1650–5000 ppm). For all three compounds, a fixed-ratio increase in stimulus duration could compensate for...
TEMPORAL INTEGRATION IN NASAL LATERALIZATION 255

a fixed-ratio decrease in concentration to maintain threshold level lateralization. These findings suggest that detection depends in some simple way on total mass delivered to the nose, i.e., a product of time (T) and concentration (C). Haber’s rule, a model commonly used in toxicology, states that T multiplied by C equals a constant for a fixed outcome (see Miller et al., 2000).

For all three model compounds, however, the simple form of Haber’s rule failed to describe lateralization: It required more than a twofold increase in stimulus duration to compensate for a twofold decrease in concentration. These findings suggest imperfect mass integration, which can be modeled by a more general form of Haber’s rule: \( C^nT^m = \text{constant} \), where the exponent \( n \) indicates degree of integration (see “Data analysis” section for more details) (Miller et al., 2000). This model described lateralization of \( \text{CO}_2 \), \( \text{NH}_3 \), and ethanol quite well over the range of concentrations studied (Wise et al., 2004, 2005, 2006).

If this simple model of integration works for other nasal irritants, researchers could characterize entire time-concentration trading functions by measuring a few, carefully selected points. The current experiments replicate the findings for ethanol and extend them to include the homologous alcohols butanol and hexanol. The fact that the three alcohols vary systematically in structure, i.e., in the number of methylene units, also allows an initial structure-activity investigation of integration. Since molecules must diffuse through lipid-rich tissue to reach nerve endings (Finger et al., 1990), we begin with the hypothesis that more lipophilic molecules might accumulate better in the mucosa over time and therefore demonstrate integration that is closer to perfect. Within an aliphatic series, lipid solubility increases with the number of methylene units. Accordingly, the hypothesis predicts that integration should be closest to perfect for hexanol, less perfect for butanol, and furthest from perfect for ethanol.

MATERIALS AND METHODS

Materials. Subjects received \( n \)-ethanol (CAS# 64-17-5) at 1800, 2250, 2800, 3550, and 4500 ppm, \( n \)-butanol (CAS# 71-36-3) at 470, 635, 870, 1200, and 1645 ppm, and \( n \)-hexanol (CAS# 111-27-3) at 2.5, 3.6, 5.3, 7.7, 11.2, and 16.3 ppm. These concentrations were target values, but actual concentrations deviated from targets by less than 5\% (see “Calibration” section). Concentrations were selected, based on previous work and pilot testing, to span a range from detectable with presentations of about 0.2 s to the lowest that subjects could detect with pulses less than 10 s. An extra concentration was included for \( n \)-hexanol because pilot work was less conclusive regarding an appropriate range.

Subjects. A total of 26 (14 females) healthy, adult, nonsmokers participated. Ages ranged from 22 to 55 (average = 30). Subjects provided written informed consent on forms approved by the Institutional Review Board of the University of Pennsylvania before they participated in any experiments. All subjects were paid, except for P.M.W. and S.E.T. The authors were blind to any conditions that could cue responses trial by trial. Data from the authors resembled data from the other subjects, and analyses that excluded data from the authors supported the same conclusions. The experiment started with an ideal of a completely within-subjects design. However, changes in subject availability made this ideal impossible. Ten subjects contributed data for all three compounds, three subjects contributed data for two compounds, and 13 subjects contributed data for only one compound. Subject samples included 17 for ethanol, 16 for butanol, and 16 for hexanol.

Apparatus. An air dilution olfactometer offered tight control of timing, with very rapid onset and offset of stimuli (Fig. 1). Other reports describe the general design in detail (Wise et al., 2005, 2006). In short, air was dried and filtered before passing into a temperature-controlled enclosure. In the enclosure, the air was humidified. Some of the humidified flow passed through glass vessels containing pure, liquid volatile organic compound (VOC). This VOC-laden air was then mixed with additional humidified air to form the desired stimulus concentration (target to be lateralized). A system of three-way solenoid valves could gate a stimulus (either VOC-laden target or a clean air blank) to either nostril. Stimuli entered the nostrils at 5 (± 0.05) \( \text{l/min} \), 37 (± 0.5)\(^\circ\)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.

Stimulus presentation. During stimulation, subjects practiced velopharyngeal closure. This breathing technique helps prevent fluctuations in pressure and flow in the nasal cavity from respiration (Kobal and Hummel, 1991). Subjects use the soft palate to isolate the nasal cavity from the rest of the airways. The olfactometer injected stimuli into the nose through flexible Tygon tubes (4 mm outer diameter) which extended about 0.75 cm into the nostrils. Flow exited the nostrils around the tubes.

Calibration. Calibration was done at the output of the olfactometer. Experimenters checked flow rate (Gillibrator 2 flow-meter; Gillian Instrument Corp., Wayne, NJ), humidity (Digitron 2020R hygrometer; Topac Instruments, Hingham, MA), and temperature (BAT-12 thermocouple reader; Physiotemp Instruments, Clifton, NJ). A fast-response pressure transducer (CyQ line, 5.5\% 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.

Stimulus presentation. During stimulation, subjects practiced velopharyngeal closure. This breathing technique helps prevent fluctuations in pressure and flow in the nasal cavity from respiration (Kobal and Hummel, 1991). Subjects use the soft palate to isolate the nasal cavity from the rest of the airways. The olfactometer injected stimuli into the nose through flexible Tygon tubes (4 mm outer diameter) which extended about 0.75 cm into the nostrils. Flow exited the nostrils around the tubes.

Calibration. Calibration was done at the output of the olfactometer. Experimenters checked flow rate (Gillibrator 2 flow-meter; Gillian Instrument Corp., Wayne, NJ), humidity (Digitron 2020R hygrometer; Topac Instruments, Hingham, MA), and temperature (BAT-12 thermocouple reader; Physiotemp Instruments, Clifton, NJ). A fast-response pressure transducer (CyQ line, 5.5\% 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.

Stimulus presentation. During stimulation, subjects practiced velopharyngeal closure. This breathing technique helps prevent fluctuations in pressure and flow in the nasal cavity from respiration (Kobal and Hummel, 1991). Subjects use the soft palate to isolate the nasal cavity from the rest of the airways. The olfactometer injected stimuli into the nose through flexible Tygon tubes (4 mm outer diameter) which extended about 0.75 cm into the nostrils. Flow exited the nostrils around the tubes.

Calibration. Calibration was done at the output of the olfactometer. Experimenters checked flow rate (Gillibrator 2 flow-meter; Gillian Instrument Corp., Wayne, NJ), humidity (Digitron 2020R hygrometer; Topac Instruments, Hingham, MA), and temperature (BAT-12 thermocouple reader; Physiotemp Instruments, Clifton, NJ). A fast-response pressure transducer (CyQ line, 5.5\% 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.

Stimulus presentation. During stimulation, subjects practiced velopharyngeal closure. This breathing technique helps prevent fluctuations in pressure and flow in the nasal cavity from respiration (Kobal and Hummel, 1991). Subjects use the soft palate to isolate the nasal cavity from the rest of the airways. The olfactometer injected stimuli into the nose through flexible Tygon tubes (4 mm outer diameter) which extended about 0.75 cm into the nostrils. Flow exited the nostrils around the tubes.

Calibration. Calibration was done at the output of the olfactometer. Experimenters checked flow rate (Gillibrator 2 flow-meter; Gillian Instrument Corp., Wayne, NJ), humidity (Digitron 2020R hygrometer; Topac Instruments, Hingham, MA), and temperature (BAT-12 thermocouple reader; Physiotemp Instruments, Clifton, NJ). A fast-response pressure transducer (CyQ line, 5.5\% 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.

Stimulus presentation. During stimulation, subjects practiced velopharyngeal closure. This breathing technique helps prevent fluctuations in pressure and flow in the nasal cavity from respiration (Kobal and Hummel, 1991). Subjects use the soft palate to isolate the nasal cavity from the rest of the airways. The olfactometer injected stimuli into the nose through flexible Tygon tubes (4 mm outer diameter) which extended about 0.75 cm into the nostrils. Flow exited the nostrils around the tubes.

Calibration. Calibration was done at the output of the olfactometer. Experimenters checked flow rate (Gillibrator 2 flow-meter; Gillian Instrument Corp., Wayne, NJ), humidity (Digitron 2020R hygrometer; Topac Instruments, Hingham, MA), and temperature (BAT-12 thermocouple reader; Physiotemp Instruments, Clifton, NJ). A fast-response pressure transducer (CyQ line, 5.5\% 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.

Stimulus presentation. During stimulation, subjects practiced velopharyngeal closure. This breathing technique helps prevent fluctuations in pressure and flow in the nasal cavity from respiration (Kobal and Hummel, 1991). Subjects use the soft palate to isolate the nasal cavity from the rest of the airways. The olfactometer injected stimuli into the nose through flexible Tygon tubes (4 mm outer diameter) which extended about 0.75 cm into the nostrils. Flow exited the nostrils around the tubes.
custom made; Cybersense, Nicholasville, KY) verified that minimal changes in flow occurred during stimulus presentation. Each day, vapor-phase concentration of the VOC to be studied was adjusted to the desired value using photoionization detectors (MiniRAE 2000 for n-ethanol and n-butanol; ppbRAE Plus for n-hexanol; both from RAE Systems, Sunnyvale, CA). Standards were created by injecting known masses of VOC into air-filled Tedlar gas sampling bags. The standards were used to convert Photoionization detector reading to ppm values.

Procedure. To start each trial, subjects placed the tubes in their nostrils and established velopharyngeal closure. When ready, subjects clicked a mouse to begin a countdown of 10 s. The last 3 s of the countdown were accompanied by beeps, after which the computer presented a variable-duration stimulus. The nostril that received the target was selected at random trial by trial. After the stimulus ended, subjects remained in position for 3 s, then recorded which nostril received the target. After a 45-s intertrial interval, the computer prompted the subject to begin the next trial. Including the countdown, more than 55 s elapsed between stimulus presentations.

Concentration was fixed within an experimental session. The computer executed a forced choice, ascending method of limits to find duration thresholds (Cain et al., 1988; Wise et al., 2006). Runs started at durations that were at least three 3-duration steps below threshold for most subjects (according to pilot work). After an incorrect response, duration increased by a single, 0.10 log10 duration step. Duration remained the same after a correct response. Runs terminated when subjects achieved five consecutive correct responses at a given concentration. If a subject achieved five correct at the starting duration (a rare occurrence), starting duration was cut in half and the run began again. This method was designed for reasonably rapid data collection. A previous study supported the validity of the method by showing that it produced results essentially equivalent to those of a more intensive psychophysical procedure (Wise et al., 2006). Runs required about 10–15 min, on average. After a break of at least 5 min, subjects completed a replicate threshold run using the same procedure.

Subjects completed one session for practice, using an intermediate concentration. Next, on subsequent days, subjects completed a single session for each concentration, in irregular order. Subjects completed no more than one session on a given day and completed all sessions for a given compound within 1 month. The compounds were tested in the following (randomly selected) order: butanol, ethanol, hexanol.

Data analysis. Thresholds were defined as the duration at which the subject first achieved five consecutive correct responses (average of the two runs for each concentration for a given compound). Experimenters plotted threshold duration versus concentration, i.e., a time-concentration trading function, in log-log coordinates. In the imperfect integration model described above (see “Introduction” section), solving for $T$ yields: $T = kC^{-1}$. This equation is a power function. Accordingly, plots of log duration versus log concentration can be fit with a simple linear equation:

$$\log(T) = -n\log(C) + k$$

“$T$” represents the threshold stimulus duration required for lateralization, “$C$” represents concentration, and $k$ is a constant. A slope, $n$, of $-1$ indicates perfect integration or perfect time-concentration trading. A slope less than $-1$ indicates imperfect integration, and a slope of greater than $-1$ indicates greater than perfect integration.

Slopes were compared across compounds using two techniques. First, data were averaged across subjects and time-concentration trading functions were fit using least-squares regression. Regression generated 95% confidence intervals (CIs) for the slopes to facilitate comparison. If, for example, the 95% CI of the slope for ethanol did not include the average slope for butanol and the 95% CI for butanol did not include the average slope for ethanol, the difference in slope was considered statistically significant. This standard for significance roughly corresponds to a series of $t$-tests with an alpha level of 0.05 (two tailed), i.e., that the means differ by at least 2 SEs (adjusted for sample size). Second, functions were fit to data from individual subjects. Having a slope for each subject allowed a one-way, between-subjects, ANOVA to test the overall effect of number of methylene units. Differences between individual compounds were assessed using pairwise $t$-tests (with a Bonferroni correction for multiple comparisons).

RESULTS

Analysis of Group Functions

For all three compounds, subjects could lateralize increasing weaker concentrations if stimulus duration increased (Fig. 2). Some subjects failed to lateralize the lowest concentrations reliably with pulses as long as 10 s (one for ethanol, four for butanol, and five for hexanol). In addition, for hexanol, one subject failed to lateralize the second lowest concentration. Linear functions fit group data reasonably well, accounting for 98% of the variance in thresholds for ethanol, 99% of the variance for butanol, and 98% of the variance for hexanol. Slopes of best-fit linear functions, with 95% CIs in parentheses, were $-2.75 (3.46$ to $-1.98)$ for ethanol, $-1.90 (2.29$ to $-1.51)$ for butanol, and $-1.26 (1.48$ to $-1.04)$ for hexanol. Accordingly, to compensate for a twofold increase in concentration, one would need to increase duration by about $1.26\log C + 4.07$, $R^2 = 0.98$.
6.5-fold for ethanol, about 3.7-fold for butanol, and about 2.4-fold for hexanol. By the criterion that the 95% CIs should not include means for other compounds, slopes increased monotonically with number of methylene units.

Analysis of Slopes from Individual Subjects

Linear fits to data for individual subjects (not shown) accounted for an average of 83% of the variance in thresholds for ethanol, 73% of the variance in thresholds for butanol, and 77% of the variance in thresholds for hexanol. Average slopes, with standard deviations in parentheses, for the three compounds follow: \( -2.70 \) (0.92) for ethanol, 1.92 (0.73) for butanol, and 1.28 (0.53) for hexanol. Accordingly, slopes from analysis of individual data agree well with those from analysis of group data. In a one-way ANOVA, the effect of compound reached significance, \( F(2,46) = 15.11, p < 0.001 \) (preliminary analyses had revealed no significant violations of the assumptions of ANOVA). Pairwise tests revealed a significant difference between ethanol and butanol, \( t(31) = 2.69, p = 0.012 \) (two tailed), a significant difference between ethanol and hexanol, \( t(31) = 5.47, p < 0.001 \), and a significant difference between butanol and hexanol, \( t(30) = 2.85, p < 0.01 \). As an additional note, post hoc analyses found no significant gender differences in slope for any compound or any significant gender differences in duration threshold for any concentration of any compound (\( p > 0.10 \)).

DISCUSSION

A Model of Short-Term Integration in Nasal Chemesthesia

In past studies, a simple but imperfect mass-integrator model described short-term integration in nasal lateralization quite well (Wise et al., 2004, 2005, 2006). This finding held true for \( \text{CO}_2 \), which stimulates by acidifying tissue (see Shusterman and Avila, 2003), for the base \( \text{NH}_3 \), and for the nonreactive VOC ethanol. The good linear fits in Figure 2, all with slopes less then \( -1 \), show that a simple but imperfect integration model also described detection in the current experiment. In this respect, current results replicate findings for ethanol and extend them to additional nonreactive VOCs, viz., butanol and hexanol. Simple but imperfect integration has also been found in some studies of suprathreshold irritation (Cometto-Muñiz and Cain, 1984; Shusterman et al., 2006; Wise et al., 2005).

Taken together, extant data support the more general form of Haber’s rule (Miller et al., 2000) as a model of short-term integration in nasal chemesthesia (\( C^nT = k \), see “Introduction” section). Until research uncovers rules that predict how well a given compound will integrate over time, time-concentration trading functions must be determined empirically. The simple integration model can accelerate this process.

Differences among Compounds in Degree of Integration

Simple but imperfect integration describes detection of nasal chemesthesia for all model stimuli tested thus far, but compounds differ in degree of integration. It required a 3.1-fold increase in duration to compensate for cutting \( \text{CO}_2 \) concentration in half (Wise et al., 2004). Integration was better for \( \text{NH}_3 \), requiring a 2.5-fold increase in duration, and much worse for ethanol, requiring an increase in duration of about sixfold (Wise et al., 2005, 2006). The reasons for the differences among compounds remain unclear, but the current studies begin to shed some light on the matter. We hypothesized that more lipophilic molecules would accumulate more readily in the lipid-rich perireceptor environment and thus integrate better over time. The finding that slopes of time-concentration trading functions fell monotonically as number of methylene units increased is consistent with this hypothesis.

The finding also extends a growing literature on chemesthetic thresholds. For a diverse group of nonreactive VOCs, potency increases (irritation threshold decreases) as lipid solubility increases (see Abraham et al., 2001; Cain et al., 2006; Doty and Cometto-Muñiz, 2003). Indeed, lipophilicity is the most important parameter in several structure-activity models (Abraham et al., 2003; Hau et al., 1999). This literature is based on brief presentations in the laboratory where stimulus duration is either uncontrolled (e.g., a single sniff) or fixed using an olfactometer. Due to differences among compounds in slopes of integration functions, sampling at a fixed duration would provide at best an incomplete picture of structure-activity relationships. The current study does not invalidate past findings. The finding that entire time-concentration trading functions moved toward lower concentrations as number of methylene units increased is consistent with past results. However, current findings do suggest that one must carefully consider stimulus duration in any effort to develop methods for investigating structure-activity relationships in nasal chemesthesia. Ideal studies would include multiple durations.

With respect to underlying mechanisms of integration, the current results suggest that transport of molecules from vapor phase to the receptor phase (i.e., to the nasal mucosa where endings of the trigeminal nerve are located) plays an important role in integration. The research discussed in the previous paragraph leads to similar conclusions regarding detection of irritants in more traditional paradigms (Abraham et al., 2001; Cain et al., 2006; Doty and Cometto-Muñiz, 2003). Models of irritant sensitivity based on transport to the nasal mucosa fail to account for some data (e.g., Cometto-Muñiz et al., 2007; Kasanen et al., 1998; Thierauf et al., 1999). Furthermore, as discussed in detail elsewhere (Cain, 1990; Wise et al., 2004, 2005), factors such as neural integration (either central or peripheral) or progressive recruitment of different types of fibers might also play a role. These possibilities are neither exhaustive nor mutually exclusive.

Limitations

Previous reports discuss general limitations of the experimental paradigm more fully (Wise et al., 2004, 2005). In brief,
the simple model of integration described above covers all events from injection of the stimulus into the nose to execution of the response. More experiments, including physiological studies, will be needed to elucidate the various components of this “black box.” Pharmacokinetic-type studies of concentration in the nasal mucosa might prove informative. Current results are consistent with the idea that detection depends on some function of area under the concentration-time curve rather than on peak concentration. Studies using, e.g., an acidic stimulus together with a pH-sensitive dye or electrode might help test this hypothesis (Shusterman and Avila, 2003). Studies that investigate possible enzymatic metabolism of irritant compounds in the nasal mucosa might also prove informative (Zhang et al., 2005).

The method of stimulus presentation creates another limitation. Passive injection of stimuli into the nose, with tubing inserted into the nasal cavity to a limited depth and with subjects practicing velopharyngeal closure, probably creates different flow rates and patterns of flow through the nasal cavity than does natural breathing. Patterns and rates of flow affect deposition and absorption of compounds in the nasal cavity (e.g., Frederick et al., 1994, 1998; Kurtz et al., 2004; Morris, 2001). Our methods allow tight control of stimulus parameters, but studies using natural breathing techniques could complement the current findings. Finally, our focus has been on short-term integration, i.e., over less than 10 s. Other rules of integration might apply over minutes or longer.

In addition to these general limitations, stimuli were run in a fixed order for all subjects. The need to clean the olfactometer between stimuli, a process that involved replacing a great deal of tubing, made it impractical to interleave stimuli. We cannot rule out order effects. However, time-concentration trading slopes for ethanol in the current experiment (−2.75) agree reasonably well with slopes from a previous experiment using the same psychophysical procedure (−2.66) and with another experiment using a more intensive psychophysical procedure (−2.54) (Wise et al., 2006). The fact that data for ethanol (tested second in the current study) replicate well somewhat alleviates concerns regarding order effects.

Another limitation concerns the sample of subjects. There were no significant gender differences, but a larger sample might reveal such differences. Further, our sample consisted of only healthy nonsmokers, who may differ in sensitivity compared to other populations, e.g., smokers, anosmics, and those with chronic rhinitis (reviewed in Shusterman, 2002). It might prove interesting to determine whether patient populations differ from healthy controls with respect to temporal integration. Further, it might prove interesting to determine how integration relates to consumption of alcohol: We collected no information on consumption.

CONCLUSIONS

To the best of our knowledge, the current results constitute the first data on structure-activity relationships in temporal integration in detection of nasal irritation. That integration improved monotonically with number of methylene units within an aliphatic series suggests that at least some aspects of sensory dynamics can be predicted based on molecular parameters. The structure-activity approach to understanding integration shows promise.

FUNDING

Term Chair in Chemosensory Psychophysics at Monell of Kraft Foods and National Institute of Environmental Health Sciences (5R03ES013969) to P.M.W.

REFERENCES


