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Chemesthesis from volatile organic compounds: Psychophysical and neural responses

William S. Cain [a,*], Nam-Soo Lee [a], Paul M. Wise [a,1], Roland Schmidt [a], Byung-Hoon Ahn [a,2], J. Enrique Cometto-Muñiz [a], Michael H. Abraham [b]

[a] *Chemosensory Perception Laboratory, Department of Surgery (Otolaryngology), Mail Code 0957, University of California, San Diego, La Jolla, CA 92093-0957, USA*

[b] *Department of Chemistry, University College London, 20 Gordon St., London WC1H 0AJ, UK*

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Abstract

In Experiment 1, subjects sought to localize the nostril stimulated, left or right, in tests with nine esters (acetates, propionates, and butyrates) at concentrations meant to trigger chemesthesis (pungency, irritation). The task produced psychometric functions for chemesthetic detection unconfounded by olfactory sensations. The functions indicated a sharp transition from no detection to perfect detection, rather uniform across the esters, which themselves varied in potency by two log units. The correlation between the thresholds for the eight materials that yielded thresholds and predictions from a published linear free energy relationship (LFER) equaled 0.99. In Experiment 2, amplitude of the negative mucosal potential (NMP) was recorded from the septum. The resulting functions also increased with concentration sharply. Against a criterion amplitude of the NMP, thresholds measured in the first experiment (and predictions from the LFER) correlated 0.99. The NMP seems to offer an adequate objective measure of sensory irritation. The LFER, although effective predictively, could stand to have a parameter to anticipate that molecules beyond a certain size fail to trigger irritation. In the present case, a cut-off of chemesthetic potency occurred between butyl butyrate and hexyl butyrate for the group of subjects, with some variation of the boundary among individuals.

Keywords: Irritation; Chemical senses; Chemesthesis; Psychophysics; Neurophysiology; Negative mucosal potential; Linear free energy relationship

1. Introduction

1.1. Chemesthesis vs. olfaction

Volatile organic compounds (VOCs) may trigger sensations via olfaction or chemesthesis, chemically-stimulated "feel" [1]. In the mucosa of the nasal cavity, chemesthesis arises from stimulation of the trigeminal nerve. For VOCs not chemically reactive against tissue, the chemesthetic threshold for pungency or irritation occurs at concentrations as low as one and as high as six orders of magnitude above the olfactory threshold [2,3].

Unlike olfaction, which compresses output relative to input, chemesthesis expands it [4–7]. Over a span hardly more than an order of magnitude, chemesthetic sensation may go from barely detectable to painful irritation.

Always compressive of input, olfaction exhibits different degrees of compression for different VOCs [8]. The variation shows some association with potency. VOCs of greater potency, i.e., lower thresholds, generally have shallower psychometric functions relating detection to concentration and shallower psychophysical functions above threshold [8–10]. Results in rats and monkeys indicate the same [11,12]. Chemesthesis may or may not exhibit similar characteristics.

Unlike olfaction, which relies upon stimulation of hundreds of types of receptors to give the spectrum of odor quality, chemesthesis for nonreactive VOCs appears to rely upon stimulation of a small variety [13,14]. One VOC might accordingly behave like another with respect to its psychometric

* Corresponding author. Tel.: +1 858 622 5831; fax: +1 858 458 9417.
E-mail address: wcain@ucsd.edu (W.S. Cain).
[1] Current address for Dr. Wise, Monell Chemical Senses Center, 3500 Market St., Philadelphia, PA 19104, USA.
[2] Current address for Dr. Ahn, Department of Otolaryngology, Keimyung University, Dongsan Medical Center, Daegu, Korea.

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function. The present study addresses this issue via the question: Does the psychometric function for detection of feel vs. concentration change systematically among homologous stimuli that differ in potency, as it does in olfaction?

Very few psychometric functions for chemesthesis from VOCs appear in the literature. They have been much steeper than the psychometric functions for odor detection for the same substances [15,16]. When plotted in normal-deviate coordinates against log concentration, the chemesthetic functions had slopes of approximately three, which means that a 10-fold change in concentration traversed virtually the entire range from undetectable to perfectly detectable, whereas the functions for odor had slopes less than half that size [15,16]. Such values provide a frame of reference for the present study.

1.2. Quantitative structure–activity relationship (QSAR)

Despite the relative absence of psychometric functions for chemesthesis, there do exist numerous chemesthetic thresholds, i.e., single values on such functions [2,3,17–22]. Thresholds gathered by uniform methodology for more than 40 VOCs led to creation of a QSAR in the form of a linear free energy relationship (LFER) [23–25]:

$$\log SP = c + eE + sS + aA + bB + lL \quad (1)$$

where SP represents sensory potency, E excess molar refraction of the VOC (solute), S its dipolarity/polarizability, A and B its overall or effective hydrogen-bond acidity and basicity, and L the Ostwald solubility coefficient on hexadecane (L^{16}) at 298 K.

According to the LFER, chemesthetic potency derives from a physical process, transport of a VOC to a receptor phase. It describes the physicochemical equilibrium between the VOC in the initial (gas) phase and at the receptor phase. Whereas the variables E, S, A, B, and L reflect properties of the VOCs, the coefficients e, s, a, b and l represent the complementary properties of the receptor phase. Importantly, the coefficients render a description similar to that of known biophases [25,26]. Eq. (1) has accounted for 96% of the variance in measured potency over a span of six orders of magnitude and has predicted potency for VOCs not involved in its creation [21].

The present stimuli comprise various esters: acetates, propionates, and butyrates. By predictions from the LFER, the VOCs should vary moderately in potency, about a 100-fold. Ability to predict variation in threshold over a limited range would endorse the worth of a QSAR.

1.3. Negative mucosal potential (NMP)

Pungent stimulation can elicit a surface potential from the nasal respiratory mucosa [27]. Because of its predominant negative peak, with amplitude up to hundreds of microvolts, the response has become known as the negative mucosal potential. Recorded from the septum, the signal represents most likely the aggregate receptor potential of many thousands of free nerve endings of the trigeminal nerve. Theoretically, it could also represent axon reflexes of trigeminal stimulation. Subsequent work ruled out various epiphenomenal sources, such as blood flow, olfaction, and activity from sympathetic fibers [27–29]. The finding that the NMP correlates closely with feelings of irritation, expressed in ratings of magnitude, argues for a trigeminal source [27,30,31].

If the NMP reflects perception, it should follow any differences in psychophysically measured potency across VOCs. Furthermore, the potential should become just discernible approximately when a stimulus becomes just detectable, though not necessarily in the range of mere probabilistic detection.

2. Experiment 1: psychometric functions

Research on the chemesthetic potency of VOCs began in earnest more than a decade ago with measurement of thresholds in persons without olfaction, i.e., anosmics [17,18]. Since VOCs stimulate olfaction, persons with normal olfaction could not give blinded thresholds. Anosmic subjects could. Thresholds obtained from them have formed the principal data base to model potency.

Despite advantages of the study of anosmics, the scarcity of such persons made it desirable to find a way to obtain criterion-free thresholds for chemesthesis from people with normal olfaction. Research showed that normosmic persons could localize the nostril stimulated by a chemical only when it triggered chemesthesis [32,33]. Olfactory stimulation offers no clues as to whether a stimulus has gone into the right nostril or the left. Fortunately, the concentration at which a person can localize the nostril coincides almost exactly with the concentration for chemesthetic detection [20,34]. The present study takes advantage of this virtual parity to study normosmic subjects.

3. Method

3.1. Subjects

Thirty-nine screened subjects (23 males and 16 females; ages 18 to 36) participated after they provided informed consent. For this experiment, as for the next, the protocol had approval from the Human Subjects' Committee of the University. Screening eliminated subjects with a history of nasal-sinus disease, pulmonary disease, a recent infection, or drug or alcohol abuse. Subsets of 10 subjects participated for each of the nine materials. Tests of sensitivity to a given material required four hours of participation from a subject in two sessions. Only a few subjects participated in sessions for most or all of the materials. The subjects earned $8/h.

3.2. Stimuli

The study employed binary dilutions in mineral oil of nine reagent-grade esters (Aldrich), three acetates, viz., ethyl acetate, butyl acetate, and hexyl acetate, three propionates, viz., ethyl propionate, butyl propionate, and hexyl propionate and three butyrates, viz., ethyl butyrate, butyl butyrate, and hexyl butyrate.

Glass vessels with volumes of 1.9 L held 200-mL reservoirs of liquid concentrations in successive twofold dilutions from neat VOC. The vessels had Teflon tops penetrated by two open Teflon tubes that served, respectively, to bring incoming air just to the surface of the liquid reservoir and to deliver stimulus material from the headspace above the liquid to the nostril [35]. A tight connection between nostril and the delivery spout insured no dilution of the vapor. As explained further below, a subject inhaled headspace from two vessels simultaneously, one that fed vapor to the right nostril and another that fed it to the left nostril. One vessel contained a concentration of VOC whereas the other contained just diluent.

A gas–liquid chromatograph (GLC) (Hewlett-Packard 5890) with a flame ionization detector provided means to calibrate headspace. Samples from the headspace above the liquid dilutions were injected from gas-tight syringes (250 μL cap.) onto the column (HP-FFAP, 30 m × 0.53 mm diam., 1.0 μm film) in three to five replicates. The median coefficient of variation of the replicates equaled 5.9%. A calibration curve obtained from injections of liquid served to convert mass of vapor samples into concentration (ppm v/v). Concentrations equaled 3981 to 79,432 ppm for ethyl acetate, 398 to 8128 ppm for butyl acetate, 30 to 1380 ppm for hexyl acetate, 1122 to 28,840 ppm for ethyl propionate, 110 to 3236 ppm for butyl propionate, 10 to 307 ppm for hexyl propionate, 389 to 10,965 ppm for ethyl butyrate, 28 to 631 ppm for butyl butyrate, and 3 to 145 ppm for hexyl butyrate.

3.3. Procedure

In a session, testing began at the lowest concentration for two trials and then proceeded progressively toward higher concentrations each given for two trials, essentially an ascending method of limits [36]. Forty-five second separated the trials. As indicated above, the subject sniffed from two vessels, one that fed headspace to the right nostril and one that fed it to the left. A sniff lasted on average about 2 s. The subject indicated the nostril with the greater "feel," guessing when unsure. An algorithm generated a random order of left-correct and right-correct for each session.

When the subject reached a concentration he or she could readily localize, or the highest concentration available, a 2-min time-out began. Testing then resumed at the lowest concentration and progressed upward again. Repetition of this regimen seven times gave 14 trials per concentration in a session. Two sessions with the same material gave 28 trials, which formed the basis for a psychometric function for the person. The order of the testing with the various materials varied irregularly among subjects.

4. Results

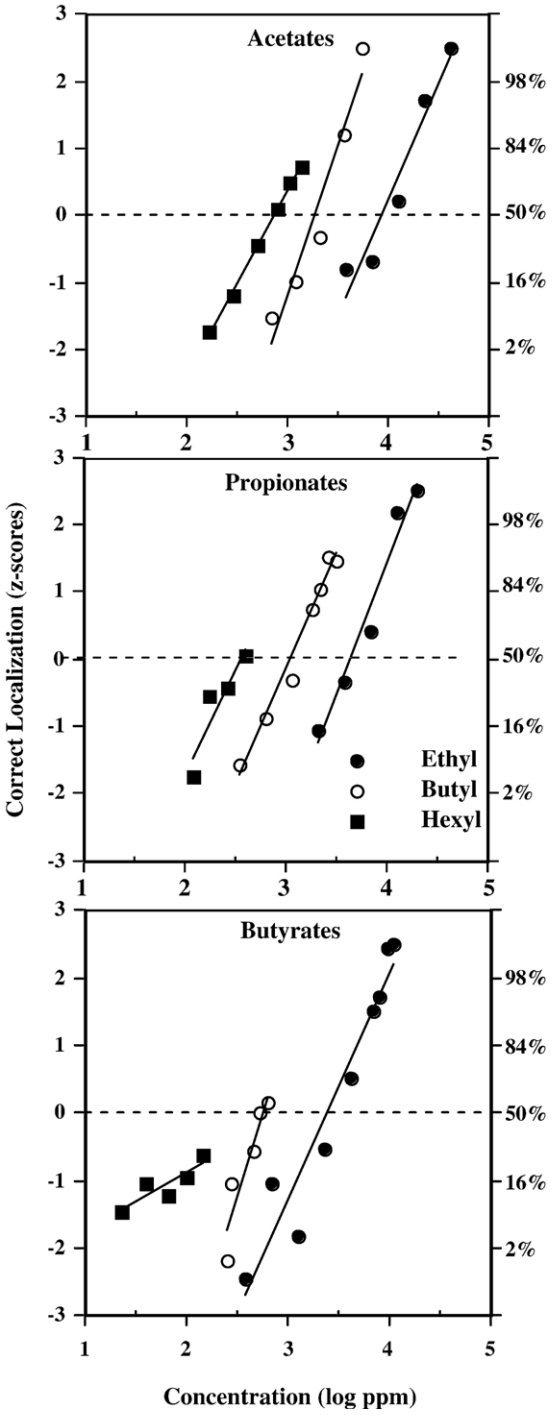

Fig. 1. Correct localization, in normal deviate scores (z), after correction for chance, vs. concentration for the nine esters. Each point summarizes 280 judgments. Averages at chance (z = negative infinity) and perfect performance (z = positive infinity) were excluded. Right ordinate shows percent equivalents to z-scores. Standard error across subjects averaged eight percentage points. The dashed line intersects the functions at the concentration defined as threshold, halfway between chance and perfect localization.

Fig. 1 depicts psychometric functions, chance corrected, for the nine esters plotted in normal deviate units (z-scores). The adequacy of the straight lines fitted to the data implies that to a first approximation a log-normal distribution governs variation in sensitivity. (The functions would plot as S-shaped ogives with probability as the ordinate [36].) The median slope of 3.4 indicates that 92% of the range from infrequently detectable to perfectly detectable chemesthesis occurs over just a 10-fold range in concentration. The hexyl compounds yielded on average somewhat lower slopes than the ethyl and butyl

compounds. Does this indicate that the underlying stimulus–response relationship between concentration and detection differs among VOCs?

The lower slopes for the hexyl compounds occurred in part because some subjects failed to achieve consistent detection of the longer chain-length molecules. The functions of these subjects sometimes exhibited slopes no different from zero and thereby reduced steepness. Slope showed less apparent systematic variation across compounds when computed in terms of the fitted psychometric functions for individuals who achieved at least 50% correct localization above chance; see columns for average threshold, its standard deviation, and average slope in Table 1. For chemosensory thresholds, these have very low variability, about ten times below that for olfactory thresholds. The median geometric standard error equaled just 11%.

Did variation in the ability to localize larger molecules reflect the normal random, and generally small, variations in sensitivity seen for the smaller molecules? Apparently not, since subjects who gave thresholds at the mean for smaller molecules sometimes gave indeterminate results for larger molecules. Fig. 2 illustrates the point: Subject J exhibited the same sensitivity as Subjects B and M until butyl acetate. For larger molecules, he gave indeterminate thresholds. The same occurred for Subject B, but later in the series. In no instance did a subject who produced an indeterminate threshold for a molecule of a given size yield a threshold for a larger molecule. These data illustrate a phenomenon seen previously in studies of chemesthesis in homologous series, viz., a cut-off [13].

The LFER shown in equation 1 has yielded the following coefficients for a data set of 48 compounds:

$$\log(1/\mathrm{NPT}) = -8.080 + 1.767S + 3.298A + 1.076B + 0.857L \quad (2)$$

where NPT represents nasal pungency threshold [25].

The correlation coefficient between predicted and obtained values for the present esters equaled 0.98 for the aggregate thresholds shown in Fig. 1 and 0.99 for the thresholds computed from individual psychometric functions (Table 1). The obtained values lay below those predicted, typically by a factor of 2 to 3, an outcome that comports with a difference found previously between results from the glass vessels used here and plastic bottles used in the studies that led to the equation [35].

5. Experiment 2: stimulus–response functions for the NMP

If the NMP reflects psychophysically assessed potency, then it should prove measurable at concentrations comparable to those found detectable in Experiment 1. As a measure of magnitude of signal, the NMP will most likely become apparent at concentrations above those detected with low probability. Differences in potency between esters, approximately 100-fold, offer a large enough span to examine whether comparability occurs or not. Because of the need to collect the NMP with precise timing, Experiment 2 employed a more sophisticated means to control and deliver the VOCs. The need for such timing also dictated a different way to introduce the VOC into the nostril. Whereas subjects inhaled the VOCs in Experiment 1, they had it introduced into one nostril as a flowing stream in Experiment 2. Such procedural differences seemed unlikely to obscure the broad agreement anticipated between the psychophysical and neural outcomes, since the two methods of delivery have already given comparable results [37].

6. Method

6.1. Subjects

Ten healthy young volunteers (seven males, three females; ages 19 to 37 years) participated. Subsets of 5 or 6 subjects from among the group of 10 participated in testing for any given ester.

Subjects were screened for relevant medical history, as in Experiment 1, and had a physical examination of the nasal passages by an otolaryngologist. Criteria for the exclusion via the examination included deviation of the septum, chronic hypertrophic rhinitis, polyposis, and signs of acute or chronic infection.

A subject participated on average in 13 sessions. A session lasted approximately 2 hours. Subjects earned $8/h.

6.2. Stimuli

Eight of the nine esters served as stimuli: ethyl acetate (9131 to 26,523 ppm), butyl acetate (2053 to 5250 ppm), hexyl acetate (358 to 676 ppm), ethyl propionate (5527 to 15,160 ppm), butyl propionate (1128 to 2126 ppm), hexyl propionate (219 to

Table 1
Group thresholds and slopes of psychometric functions from Fig. 1, average thresholds and slopes from those subjects (*n*) who achieved threshold, and predictions of thresholds from the LFER

Ester	Group threshold (log ppm)	Group slope	Average threshold (log ppm)	Standard deviation (log ppm)	Average slope	*n*	Predicted threshold (log ppm)
Ethyl acetate	3.94	3.51	4.05	0.104	3.79	10	4.56
Ethyl propionate	3.63	3.85	3.70	0.100	3.84	10	4.23
Ethyl butyrate	3.38	3.37	3.44	0.128	3.87	10	3.83
Butyl acetate	3.27	4.38	3.3	0.132	4.65	10	3.71
Butyl propionate	3.05	3.42	2.98	0.014	3.42	10	3.36
Butyl butyrate	2.75	5.09	2.57	0.187	6.99	5	3.01
Hexyl acetate	2.87	2.75	2.67	0.221	3.33	7	2.86
Hexyl propionate	2.56	3.09	2.26	0.272	3.42	3	2.53
Hexyl butyrate	–	0.87	–	–	–	–	2.17

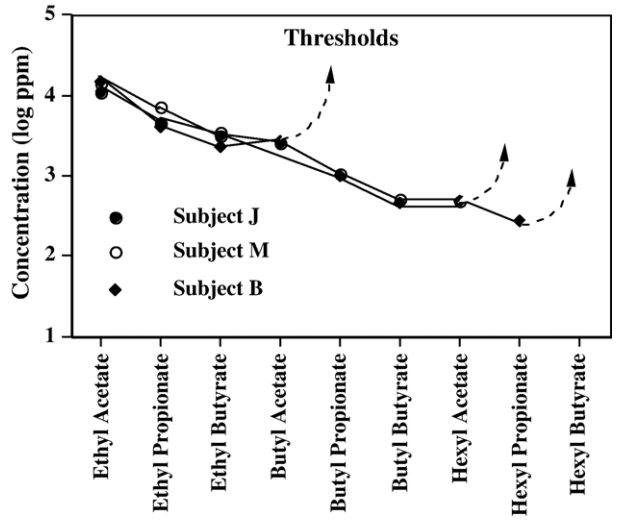

Fig. 2. Showing thresholds for three subjects over the series of esters. The thresholds for the three declined in unison with increases in the size of the molecules until first J, then M, then B reached molecules he could not detect. The curved lines depict the transition point between detection of the last member that a subject could detect and the rest of the set. Such individual differences as these have appeared in a study of eye irritation, as well [13].

401 ppm), ethyl butyrate (2054 to 5539 ppm), and butyl butyrate (313 to 485 ppm). Hexyl butyrate evoked too little pungency for inclusion.

A flow-dilution olfactometer delivered the stimuli to the nasal passage that bore the electrode [37]. Nitrogen sparged through 200 ml of liquid-phase material provided a feed stream. The vapor was diluted with air humidified to 80% RH and warmed to 36 °C. Flow rate of the final stream equaled 8.8 L/min. This emanated from a Teflon tube of 30-mm length by 3-mm i.d. placed inside the nares. The stream entered and exited the nostril by force of its own flow. The subject did not inhale the material, as explained below.

LabView software controlled the dilution and timing of the stimulating vapors, as well as the acquisition of the NMP. Dilution within the olfactometer could vary over the range 1000:1 via mass flow controllers. Rise-time of stimulus in the stream equaled approximately 20 ms. Injection into the flowing stream of dilution-air occurred virtually seamlessly by means of a switching scheme devised by Kobal [27,38]. By this scheme, opening a remote solenoid valve associated with a vacuum source removed a portion of the carrier stream and simultaneous closing of another solenoid valve associated with the vacuum replaced the same portion with vapor-saturated nitrogen. Hence, if the concentration desired on a particular trial equaled one-tenth saturated vapor, a stream of 0.88 L/min entered the background flow for 2 s. Simultaneously, background flow decreased by 0.88 L/min for 2 s. Placement of the solenoid valves and vacuum source far from the experimental room ensured noiseless switching at the experimental set-up.

The experimenter calibrated concentration of the vapors off-line by means of the GLC. Samples taken directly with a gas-tight syringe from the output of the delivery device were injected onto the column. A liquid calibration curve for each substance allowed conversion of the response of vapor samples to mass, and thence to concentration. The geometric average coefficient of variation of the concentration of the vapor samples equaled 7.7%.

The NMP was recorded from the antero-medial portion of the left nasal septum by means of a Teflon tubular electrode filled with Ringer-agar (1%) that bridged to a Ag/AgCl wire (impedance 2–8 kΩ at 1 kHz in 0.9% NaCl). The experimenter placed the electrode onto the septum under direct rhinoscopy and fixed it in place with an adjustable clip attached to eyeglass frames that the subject wore during testing. Reference and ground disk electrodes (Ag/AgCl) were placed at the right bridge of the nose and right mastoid area, respectively. Responses were fed through an S75-07 Coulbourn Instrument Direct Coupled Bioamplifier (d.c. mode), a Coulbourn Bandpass Biofilter (full band 1–40 Hz), and a National Instruments a/d converter over 13 s for storage on a Macintosh computer. The signal was digitized into 1-ms intervals. An epoch was recorded 1 s before delivery of stimulus and 12 s after. Records were monitored continuously to detect drifts in baseline or artifacts, such as eye blink, movement, and swallowing. Such artifacts disqualified records from consideration.

6.3. Procedure

Subjects began with a session of orientation to familiarize them with procedures (e.g., application of the electrodes) and teach them velopharyngeal closure, the technique whereby they breathed through the mouth and maintained the air in the nasal cavity static [27]. (Such closure occurs in everyday life during speech, swallowing, blowing and whistling.) Through velopharyngeal closure, a subject avoided any inhalation of the stimulus.

Subjects participated in three sessions per ester. A session comprised four presentations of each of four or five concentrations, depending upon the ester, plus blanks, which did not give discernible responses. Duration of stimulation equaled 2 s, with a 2 min interstimulus interval. In general, testing proceeded in an ascending order with respect to concentration.

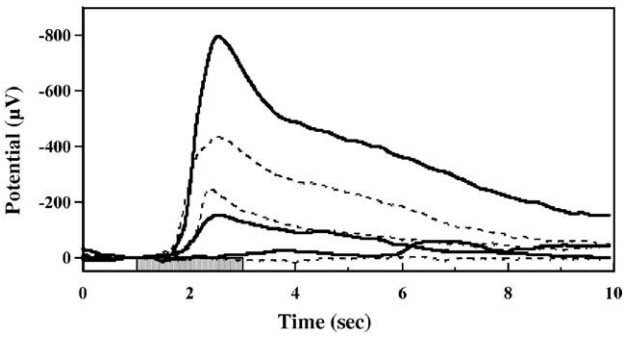

Fig. 3. Showing how amplitude (μV) measured via the septal electrode varied over time with stimulation by three concentrations of butyl acetate, 3.45, 3.58, and 3.72 log ppm. The records represent averages from the same subject in two sessions (dashed lines for one session and continuous lines for the other). The onset of the 2-s stimulus occurred at 1 s.

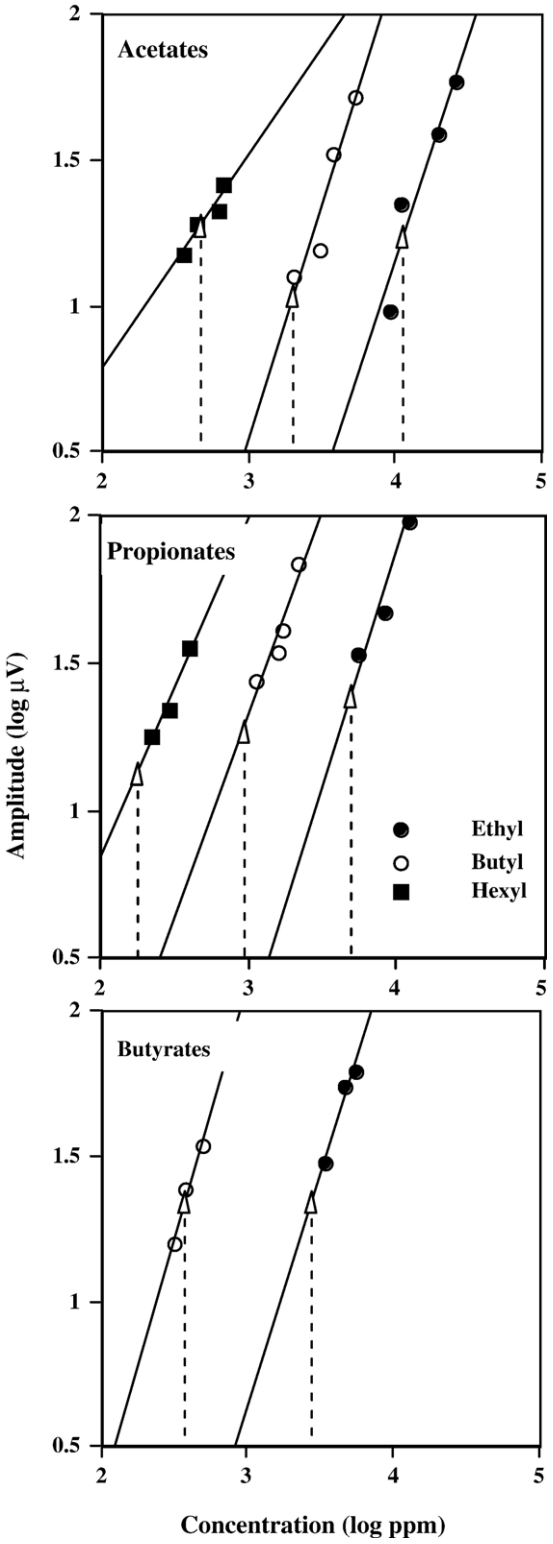

Fig. 4. Showing how the amplitude of the negative potential varied with concentration for the various esters. The arrows show the thresholds from column four of Table 1. The average standard error of the points in the figure equaled 0.11 log units.

Average NMPs were calculated for a subject's replicate responses within a session (see Fig. 3). The amplitude of the negative peak with respect to baseline then served as the datum for an average across sessions and across subjects.

7. Results

The NMP displayed itself in customary form as a negative potential with a return toward zero (Fig. 3). The final return often outlasted the full epoch.

Fig. 4 displays how the maximum amplitude of the negative wave varied with concentration. The latency to the maximum of the negative wave equaled 1.7±0.4 s. Although some differences in latency occurred between esters, they proved uninformative.

The functions for the NMP and those for localization in Fig. 1 show considerable similarity of order. That is, the esters seen as more potent from threshold measures also gave NMPs at lower concentrations. The thresholds from column 4 from Table 1 provide a more exact picture. These values appear on the abscissae of Fig. 4 where they intersect the lower ends of the functions. The correlation between those threshold values and any criterion level in the functions equaled 0.99 (Fig. 5). The correlation between predicted thresholds from the LFER [24] and the functions also equaled 0.99.

The slopes of the functions for the NMP averaged 1.42± 0.33, which implies expansion of output over input. In only one case, viz., for hexyl acetate, did the slope of a fitted power function fall below 1.0.

8. Discussion

8.1. Correspondence between thresholds and the NMP

The most striking finding concerned the agreement between the psychophysical and neural data. The NMP arose at concentrations in the vicinity of the chemesthetic threshold, which indicates that the potential has sensitivity very similar to that obtained psychophysically. Rarely does a human neural

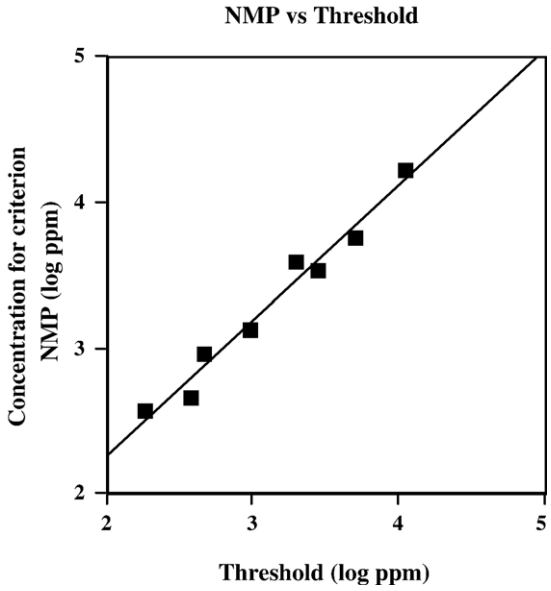

Fig. 5. Showing the association between concentrations that yielded an amplitude of 30 μV and threshold concentrations measured in Experiment 1 (Table 1, col. 4).

measure have such sensitivity. Admittedly, though, an exact comparison of sensitivity would require measurements of both responses in the same subject and by the same means of stimulation.

The average exponent of the power functions fitted to the amplitude of the NMP exceeded 1.0 and thereby implied expansion of output over input, just as seen psychophysically. Scaling of chemesthesis has entailed principally vapors of carbon dioxide, an odorless irritant. The average exponent of the psychophysical power function over five studies equaled 1.66±0.30 [4–7,39]. The average value of 1.42±0.33 for the NMP in the present case compares quite favorably. The agreement suggests that the psychophysically measured exponent arises from a peripheral transformation with essentially no further transformation by the CNS.

There seems little doubt that the NMP parallels chemesthetic sensations and can thereby offer an objective index of nasal chemesthesis. Such an index holds interest as a tool to assess the local toxicity of VOCs, a matter of concern in industrial and environmental toxicology and medicine. To illustrate, more than half the threshold limit values (TLVs) for VOCs in the industrial workplace stand upon a criterion of acute irritation [40]. In some instances, assays of irritation from animals, with extrapolation to human beings, guide the choice of a TLV [41]. In other instances, anecdotal reports from humans guide the choice. An objective index of irritation could add precision to setting such standards.

8.2. Slopes of psychometric functions: an interpretation

Psychometric functions for VOCs that varied in chemesthetic potency showed little indication of underlying systematic variation in slope. In this respect, they contrast with functions for olfaction. We speculate that systematic variation in slope arises from the diversity of olfactory receptors stimulated by even a single VOC. The perception of mixtures offers potential insight here [42,43]; the more complex a mixture, the more compression, or mutual suppression of components, will it exhibit [44,45], presumably because more complex mixtures stimulate wider varieties of receptors. The outputs from different receptor neurons most likely exhibit mutual inhibition upstream [46,47].

From the standpoint of olfaction, even a single VOC comprises a mixture since it will stimulate a variety of receptors, as will a mixture. The VOC with a low threshold will most likely stimulate a wider spectrum of receptors than one with a higher threshold. The greater the variety of receptors, the stronger might be the inhibition. In chemesthesis, by comparison, nonreactive VOCs may depend upon interaction of molecules with just a few types of receptors. The VOC would therefore present itself as either not a mixture or as a very simple one. This would minimize the differences between psychometric functions and give a picture of uniformity.

8.3. The LFER

The linear free energy relationship derived to account for thresholds from anosmics showed excellent ability to predict thresholds for chemesthesis assessed by localization. The outcome reinforces the conclusion that localization by normosmics can stand for detection, while it also endorses the value of the approach based upon solvation. The LFER implies that transport to a receptor site governs potency. Because the thresholds and the NMP showed close agreement, the LFER predicted the NMP as well as it predicted threshold.

Despite the accuracy of the linear free energy relationship, it makes no prediction that molecules above a certain size may have indeterminate thresholds. Not just for chemesthesis, but for other biological phenomena (e.g., anesthesia) as well, there may come a point where no further gain or a notable loss of potency accompanies an increment in molecular size [48]. In measurements of chemesthesis in the aliphatic series of alcohols, for instance, potency increased progressively through the series up to 1-heptanol, whereupon subjects failed to detect the stimulus 8% of the time even at saturated vapor concentration [17]. For 1-octanol, the next higher member of the series, subjects failed 25% of the time. For 1-nonanol, subjects would most likely have failed 100% of the time. For the acetates, indications of a cut-off began at octyl acetate [18]. For the alkyl benzenes, indications began at butyl benzene [19]. For ketones, they began at 2-nonanone [2].

Although the pattern suggests that size of the molecule determines the point of the cut-off, various physicochemical properties covary with size and the conclusion therefore requires caution [13,49]. A limitation based upon the size of what Franks and Lieb [48] have called the “binding pocket” on the receptor protein, which can account for a cut-off in inhibition of anesthesia to VOCs [50,51], may have relevance to chemesthesis as well [13,52]. Experiments that vary molecular size and shape with more rigid molecules than those studied here could help to characterize the receptor. With a parameter to describe the cut-off, the equation could presumably account for chemesthetic detection of molecules of any size [53]. Efforts to include such a parameter in a QSAR have begun, both for olfaction and chemesthesis [13,25,49,53].

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