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**Perception of odor and nasal pungency from homologous series of
volatile organic compounds**

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Abstract

We tested nasal detection thresholds for airborne chemicals in a group of anosmics (i.e., subjects lacking a functional sense of smell) and in a group of age-, gender-, and smoking-status-matched normosmics (i.e., subjects with normal olfaction). Anosmics provided odor unbiased nasal pungency (irritation) thresholds. Normosmics provided odor thresholds. Homologous series of alcohols, acetates, and ketones served as stimuli. Eye irritation thresholds were also measured for selected acetates. Most substances evoked pungency (i.e., were detected by the anosmics). All sensory thresholds decreased systematically with carbon chain length. The gap between pungency and odor grew larger with increasing carbon chain length. Pungency thresholds — but not odor thresholds — showed a uniform linear relationship of slope close to unity with saturated vapor concentration, irrespective of chemical functionality or carbon chain length. This suggests that pungency from nonreactive airborne chemicals rests heavily on a relatively unspecific physical interaction with a susceptible biophase. Of relevance to indoor environments, such an interaction opens the possibility for a high degree of sensory addition of pungency from individual components of complex mixtures resulting in noticeable irritation even when each component is at a level well below threshold.

Key words: Odor Pollution - Smell - Sensory Irritation - Volatile Organic Compounds - Anosmia - Nasal Sensory Thresholds

Introduction

Sensory irritation and odor are frequently cited as adverse responses in indoor air quality complaints (e.g., see Cometto-Muñiz and Cain, 1992; Mølhave, 1991). At the same time, these sensory responses are more amenable to quantification than other symptoms — like headache, tiredness or difficulty in concentration.

Odor sensations arise from the olfactory epithelium — in the upper back portion of the nose — and are carried to the Central Nervous System (CNS) by the olfactory nerve (Cranial Nerve I). What we like to call "**pungent**" sensations are elicited in the mucosae of the face (ocular, nasal, and oral) through chemical stimulation of free nerve endings from the trigeminal nerve (Cranial Nerve V), which also carry thermal, tactile, and pain sensations. The term "**common chemical sense**" (CCS) is often employed to refer to the detection of chemicals through any exposed mucosa — or even through the skin below the epidermis (Keele, 1962) — resulting in sensations that are not properly odors or tastes (Green et al., 1990). Such common chemical or pungent sensations (or, simply, **pungency**) include: piquancy, tingling, prickling, irritation, stinging, burning, and freshness, among others.

The vast majority of chemicals will elicit both nasal sensations: odor and pungency. It is generally true that at low concentrations odor predominates and at high concentrations pungency predominates (Cometto-Muñiz et al., 1989; Cometto-Muñiz and Hernández, 1990). A critical question is: At what concentration each sensation begins to be elicited? As a rule, airborne chemicals evoke odor at levels below those at which they evoke pungency. In view of this, pungency thresholds would have to be measured against a sometimes quite strong odorous background. In this setting, there is ample room for

variation in the criterion used by each subject regarding when to call a nasal sensation barely pungent (pungency threshold) as opposed to strongly odorous.

We tackled this problem by using groups of subjects clinically diagnosed as anosmics, that is, persons lacking a functional sense of smell (Cometto-Muñiz and Cain, 1990; Cometto-Muñiz and Cain, 1991; Cometto-Muñiz and Cain, 1992; Cometto-Muñiz and Cain, 1993). Anosmics can only be aware of airborne chemicals through the pungency that such substances might evoke. In this way, their responses reflect "true" pungent sensations, unbiased by odors. On the other hand, subjects with normal olfaction (i.e., normosmics) will detect airborne chemicals present at near threshold levels only through the odor that they evoke. We complemented our approach by employing homologous series of chemicals as stimuli. In these series, physicochemical properties change in a systematic fashion. In principle, gathering data for such series with a uniform and standardized methodology would allow the build up of quantitative structure-activity relationships (QSARs) for both odor and nasal pungency. QSARs for upper respiratory tract irritation have been based, so far, exclusively on animal data (Abraham et al., 1990).

Here we report the results of nasal detection thresholds in a group of anosmics (pungency thresholds) compared to a group of age-, gender-, and smoking-status-matched normosmics (odor thresholds) towards homologous series of alcohols, acetates, and ketones, as well as towards secondary and tertiary alcohols and acetates. For selected acetates we also gathered eye irritation thresholds.

Materials and Methods

Stimuli. All substances employed were analytical-grade reagents. The alcohols included: methanol through 1-octanol, 2-propanol, 2-butanol (sec-butyl alcohol), 2-methyl-2-propanol (tert-butyl alcohol), and 4-heptanol. The acetates included: methyl through octyl acetate, decyl acetate, dodecyl acetate, sec-butyl acetate, and tert-butyl acetate. The ketones comprised: 2-propanone (acetone), 2-pentanone, 2-heptanone, and 2-nonanone. Deionized water served as the solvent for methanol, ethanol, 1-propanol, and 2-propanone. Mineral oil served as the solvent for all the rest.

Dilution series were prepared for each stimulus, starting with the pure compound (100% v/v), labeled dilution step 0. Successive dilutions comprised up to dilution step 15. Typically each step represents a three-fold dilution. Stimuli were presented in 250-ml capacity, squeezable, polyethylene or polypropylene bottles (Amoore and Ollman, 1983), each containing 30 ml of solution. The bottle closure had a pop-up spout that allowed testing each nostril separately (Cain et al., 1988). To measure eye irritation thresholds, the same bottles were used. In this case, the top of the bottle contained a 25-ml roughly conical reservoir chamber the rim of which was placed around the eye. A squeeze of the bottle delivered a puff of vapor directly to the eye. The vapor concentration in the headspace of each bottle was measured by gas chromatography (photoionization detector), using a gas sampling valve. For every substance, chromatographic readings were taken from the headspace of each bottle in the series, including the bottle containing saturated vapor at room temperature (23 °C). The concentration corresponding to saturated vapor for each compound is known from handbooks or databases on physical properties. Knowledge of the concentration of saturated vapor and its associated chromatographic reading allowed conversion of the readings from the other bottles into concentration units, and a calibration curve was derived.

Subjects. Typically a total of eight subjects participated in the evaluation of each chemical series. Half of them were clinical anosmics (patients from the Connecticut Chemosensory Clinical Research Center, University of Connecticut, or Yale-New Haven Hospital) as determined by the CCCRC olfactory test (Cain et al., 1988). The other half were age-, gender-, and smoking status-matched normosmics. The anosmic group employed in the study of each series included congenital and head trauma anosmics. Subjects tested for eye irritation were normosmics.

Procedure. Participants delivered the stimulus and blanks (water or mineral oil) to themselves by placing the pop-up spout inside the designated nostril and squeezing the bottle as they sniffed. They rapidly learned to squeeze and sniff with constant vigor across trials. In the case of eye irritation testing, subjects placed the rim of the reservoir around the eye and squeezed the bottle while keeping the tested eye open.

The method employed was a two-alternative, forced-choice, ascending method of limits. Briefly, the subject started by using one nostril or eye to compare the intensity of the lowest concentration of a substance (e.g., dilution step 15) to a blank and deciding (forced-choice) which one was stronger. A correct choice led to the presentation of the same concentration (from another bottle) also paired with a blank. An incorrect choice led to the presentation of the next dilution step (a concentration three times higher: dilution step 14) paired with a blank. This continued until five correct choices were made in a row, in which case that step was taken as the threshold. The same procedure was then repeated with the other nostril or eye. After that, testing began with another substance in the series in identical manner. The ascending concentration approach to the threshold and the alternate use of each nostril helped to minimize the effects of the commonly found phenomenon of olfactory adaptation (e.g., Cain, 1974).

In the case of nasal testing, sessions lasted between two and three hours. They were repeated until 12 thresholds (6 for each nostril) per subject were obtained for each compound. In the case of eye irritation testing, sessions lasted between 15 and 45 min and were repeated until 6 thresholds (3 for each eye) per subject per compound were obtained. The order of presentation of the chemicals within each series differed from subject to subject. The number of times that the right or left nostril (or eye) was tested first for a certain substance was counterbalanced for each subject.

Data analysis. The individual thresholds for each participant, expressed as dilution steps, were averaged. These averages were then converted to headspace concentrations (ppm) with the gas chromatography-derived calibration curve. Finally, thresholds (in ppm) were averaged geometrically across subjects in each group (anosmic and normosmic).

Results

Figure 1 depicts the average odor and pungency threshold for members of homologous alcohols, acetates, and ketones. Both sensory thresholds tend to decline as the chemical series progresses. Nevertheless, odor and pungency did not decline at the same rate: The decline of odor thresholds — at least for the first few members of each series — was steeper than the decline of pungency thresholds.

Insert Figure 1 about here

Eye irritation thresholds were tested only for acetates with an even number of carbons in the variable chain, and the thresholds came close to those of nasal pungency (Figure 1).

Anosmics were able to detect almost all chemicals, albeit at a much higher concentration than normosmics. Only four compounds failed to be detected at all by one or more anosmics: 1-octanol, and octyl, decyl, and dodecyl acetate.

Traditionally, the low molecular weight, high vapor pressure members of each series are considered more irritant than their high molecular weight, low vapor pressure counterparts. Nevertheless, the results clearly show that the latter substances elicit threshold pungency in the anosmic group at concentrations (expressed in ppm) two or more orders of magnitude below the former.

On the basis of the overall outcome we can point out two reasons that might contribute to that distorted traditional view. The first reason is that the lower members of each series achieve the pungency threshold not much above the odor threshold (about one order of magnitude higher). On the contrary, the higher members achieve the pungency threshold at levels much higher than the odor threshold (from 2.5 up to 4 orders of magnitude higher). The second reason comes from comments made by the anosmics regarding the particular "type" of pungency experienced from lower versus higher members in each series. The lower members had more "bite" or "sharpness" in the sensation they evoked, while the higher members were more "dull" or "pastel".

In summary, the closeness of both nasal thresholds (odor and pungency) and the sharpness of the pungency that characterize the first members of the series help to explain

why these substances are usually regarded as more irritating than the last members, whose pungency is in fact elicited at lower concentrations (in ppm).

The standard deviations depicted in Figure 1 show that anosmics and normosmics do not superimpose in their thresholds, and that the variability of nasal pungency thresholds is substantially lower than that of odor thresholds.

Discussion

In order to explore how well simple physicochemical properties can explain the results obtained, we plotted — for all compounds studied — both sensory thresholds as a function of saturated vapor at room temperature ($\approx 23^{\circ}\text{C}$). Figure 2 illustrates the outcome.

Insert Figure 2 about here

Nasal pungency thresholds from the three homologous series conform well to a single linear function (slope = 1.02, $r = 0.98$), parallel to the saturated vapor identity line, but shifted downwards. The outcome indicates that, irrespective of the chemical functionality or length of the carbon chain, these substances begin to elicit nasal pungency at a fairly constant percentage of vapor saturation ($\approx 32\%$). Thus, the results suggest a broadly tuned physicochemical interaction between the stimulus and the receptive biophase.

Odor thresholds, on the other hand, do not conform to a single function. In fact, odor thresholds from some chemical series tend to show a linear relationship with vapor

saturation (e.g., alcohols) while those from other series show a sigmoid relationship (e.g., acetates). Nevertheless, even those showing linearity have a slope that differs from unity (in the case of the alcohols the slope is 1.62). Overall, the outcome indicates that olfaction is more finely tuned to the molecular features of the stimulating compounds than is the CCS.

There is a robust relationship between pungency and odor thresholds (Figure 3). Decyl and dodecyl acetate have been excluded from the figure given that only one out of the four anosmics tested was able to detect these two substances. The results show that the gap between the odor and the pungency threshold for a particular substance becomes smaller as the odor threshold grows higher. That is, for compounds with a relatively low odor threshold (e.g., 10^{-2} ppm) the gap is in the order of four orders of magnitude. For compounds with a relatively high odor threshold (e.g., 10^4 ppm) the gap closes to only one order of magnitude.

Insert Figure 3 about here

Our studies probe into the basic stimulus-response characteristics of the common chemical and olfactory senses. Nevertheless, the results bear importance to crucial aspects of indoor air quality. Measuring nasal thresholds in anosmics has provided, for the first time, an insight into the ability of substances to produce nasal pungency in the absence of olfaction. This is particularly important since sensory irritation (pungency) of the nose, eyes, and throat are widely cited among indoor air quality complaints.

Pungency and odor thresholds obtained with a uniform and standardized methodology — such as ours — and employing a variety of homologous chemical series constitute a convenient human data set in which to base QSARs for irritation and odor

from airborne chemicals. Many of the nonreactive compounds studied here are commonly present indoors (cf. Mølhave et al., 1986).

Another relevant issue for indoor air quality is that of the odor and pungency thresholds of substances presented alone versus presented in mixtures. If the pungency from airborne chemicals relies on a broad, relatively unspecific physicochemical interaction with the receptive biophase, it is reasonable to expect considerable sensory additivity from mixtures of compounds. In the case of indoor environments, where dozens of chemicals are simultaneously present, it should come as no surprise that such complex mixtures have the potential for irritating the mucosae of the face even at levels where no individual component has reached its pungency or odor threshold. In our laboratory, we are beginning to investigate how anosmics and normosmics respond to mixtures of VOCs.

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Figure Legends

Figure 1. Thresholds for nasal pungency (filled squares), odor (empty squares) and eye irritation (triangles). Only n-members (i.e., unbranched members) of the series are joined by a line. Bars indicate standard deviations.

Figure 2. Pungency (filled squares) and odor (empty circles, squares, and triangles) thresholds for all chemicals studied as a function of saturated vapor concentration at room temperature. The saturated vapor identity line (slope=1.00, $r=1.00$, no symbols) is shown for reference. The function for pungency has a slope=1.02 and $r=0.98$.

Figure 3. Relationship between pungency and odor thresholds in humans for 26 nonreactive VOCs.

FIGURE 1

FIGURE 2

FIGURE 3

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