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SENSORY IRRITATION POTENCY OF VOCs MEASURED THROUGH NASAL LOCALIZATION THRESHOLDS

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ABSTRACT

In order to measure "odor unbiased" nasal pungency (e.g., sensory irritation) thresholds, we have resorted in the past to testing subjects with no olfaction (i.e., anosmics). The present study illustrates another way to gain insight into the separate response of the nasal trigeminal and olfactory nerves without resorting to anosmics. Thresholds for nasal localization of airborne n-alcohols to the right or left nostril, measured in normosmics, fell into register with nasal pungency thresholds measured in an anosmic, and with eye irritation thresholds measured in normosmics and the anosmic. As expected, odor thresholds fell well below the other three sensory thresholds.

INTRODUCTION

Our chemical senses play an important role in the perception of the quality of indoor air [1, 2]. In particular, olfaction and the common chemical sense (CCS) or chemesthesis [3] make us aware of the presence of airborne chemicals in our surroundings. The sense of smell, through the olfactory nerve (cranial nerve I), evokes **odor sensations**, whereas the CCS, through the trigeminal nerve (cranial nerve V), evokes **pungent sensations** in all the face mucosae: ocular, nasal, and oro-pharyngeal. What we call pungent sensations or pungency involves tingling, piquancy, burning, irritation, stinging, freshness, and prickling, among others. In the indoor air literature they are generally referred to as sensory irritation and they include eye, nose, and throat irritation.

Practically all odorous chemicals can also elicit pungency, and our research efforts over the past few years have been aimed at assessing the concentration gap between a purely olfactory sensation and an olfactory plus trigeminal sensation [4-8]. To achieve this goal we tested small groups of subjects lacking a sense of smell (i.e., anosmics), and obtained from them "odor unbiased" **nasal pungency (irritation) thresholds**. We similarly tested a group of subjects with a normal sense of smell (i.e., normosmics) — matched to the anosmics by age, gender, and smoking status — and obtained from them **odor thresholds**. Subjects were classified as anosmics or normosmics based on a standard clinical test [9]. The substances employed in the previous studies included members of various homologous chemical series: alcohols, acetates, ketones, and alkylbenzenes. Physicochemical properties in these series change in an orderly way, allowing us to relate such properties with sensory potency. As a result, we devised a quantitative structure-activity relationship (QSAR), in the form of a linear

solvation equation, that successfully described the nasal pungency potency in physicochemical terms [10].

In the present study we explore an alternative way to obtain odor unbiased nasal pungency thresholds. The method is based in the ability of subjects to localize the nasal sensation evoked by a chemical to the right or left nostril. A pioneer study concluded that the olfactory sense can localize odorants to one or the other nostril based on the time difference of stimulus arrival at each nostril and on the difference in sensation magnitude between the two nostrils [11]. Nevertheless, substances used in that investigation had significant pungency (i.e., trigeminal impact) and it was later shown that nasal localization can only be achieved through trigeminal stimulation [12, 13]. If this is the case, measuring **nasal localization thresholds** in normosmics might constitute an alternative to testing anosmics as a mean to obtain odor unbiased nasal pungency thresholds. Recent experiments addressed the issue of nasal localization using the almost odorless pungent stimulus CO₂ [14]. Here we have used the homologous n-alcohols 1-propanol, 1-butanol, 1-hexanol, and 1-octanol to measure thresholds for odor (in normosmics), nasal localization (in normosmics), nasal pungency (in an anosmic) and eye irritation (in both normosmics and anosmic).

METHODS

Stimuli and Apparatus. All substances used, 1-propanol, 1-butanol, 1-hexanol, and 1-octanol were analytical grade reagents. Duplicate liquid dilution series were prepared in three-fold steps, starting from the undiluted chemical: 100 % v/v (dilution step 0), followed by 33.3 % v/v (dilution step 1), 11.1 % v/v (dilution step 2), 3.7 % v/v (dilution step 3), etc. Distilled water served as solvent and blank for 1-propanol, and mineral oil (light, U.S.P.) served as solvent and blank for the other alcohols.

Solutions (30 ml total volume) were kept in 270-ml, squeezable, polypropylene bottles. One type of cap was used to measure nasal thresholds and another to measure ocular thresholds. To measure odor and nasal pungency thresholds, the cap of the bottles had a pop-up spout that fits inside the tested nostril (each nostril was tested separately) (see [9]). To measure eye irritation thresholds, the cap of the bottles was adapted from the cap of variable volume dispensers, and had a short tube connecting the headspace of the bottle to a 25-ml, cylindrical, volumetric chamber, the rim of which fitted around the eye. A squeeze of the bottle forced an aliquot of the headspace into the chamber where the eye was exposed (each eye was tested separately) (see [5, 8]). To measure nasal localization thresholds, we used a motor-driven bottle squeezer. This apparatus can hold two bottles at a time, and they can be squeezed simultaneously by a moving arm. An aliquot of the headspace from one bottle was thereby sent to one nostril and an identical aliquot from the other bottle was sent simultaneously to the other nostril. Each stimulus traveled through a short length of teflon and glass tubing (of minimal dead volume) ending in a soft nosepiece placed in the subject's nostril. A buzzer sounded right before the squeezer began to compress the bottles, alerting the subject to inhale through the nose. The subject's head was kept in place by a chin rest and a forehead rest.

The headspace concentration of the stimulus on every bottle was measured by gas chromatography (GC) (flame ionization detector) using a gas sampling valve. The headspace of the bottle containing undiluted chemical was assumed to contain saturated vapor at room temperature ($\approx 23^\circ\text{C}$). GC readings from all other bottles were referred to the saturated vapor standard.

Subjects. A pool of six normosmics provided odor thresholds (measured with squeezing by hand and squeezing by the bottle-squeezer), localization thresholds, and eye irritation thresholds. One subject was female, the other five males. Their ages ranged from 22 to 41 years and all were nonsmokers. A minimum of eight thresholds and a maximum of twelve (half for the right nostril/eye, and half for the left nostril/eye) were measured for each chemical and sensory endpoint.

One anosmic — a 53 year-old, male, nonsmoker — provided nasal pungency and eye irritation thresholds. A total of six thresholds (half for the right and half for the left nostril/eye) were measured for each chemical and sensory endpoint.

Procedure. All thresholds were obtained by a two-alternative forced-choice procedure with an ascending concentration method of limits. Briefly, the participants had to choose, on each trial, which of two stimuli was stronger. One stimulus was a blank (distilled water or mineral oil), the other a dilution step of the tested chemical. The stimuli were presented starting with the lowest concentration (highest dilution step) and, as the subject made mistakes in the forced-choice, successively increasing to higher concentrations (lower dilution steps). This continued until the participant made five correct choices in a row for a particular step, in which case that step was taken as the threshold. As mentioned, each nostril and eye was tested separately.

In the case of nasal localization thresholds, the bottle-squeezer was used as follows: the first presentation of each pair entailed, for example, a blank to the right and the stimulus to the left, the second presentation entailed the opposite: blank to the left, stimulus to the right. If, for example, the right nostril was the one being tested, the participant was asked which presentation, first or second, was perceived in the right nostril. If the left nostril was being tested, the participant was asked which presentation was perceived in the left nostril. As with all other thresholds, an ascending concentration method of limits was used, with a criterion of five correct choices in a row for a particular step.

RESULTS

Figure 1 summarizes the overall results. As expected, all thresholds declined with carbon chain length [4], and odor thresholds were one or more orders of magnitude lower than all other thresholds (eye irritation, nasal pungency, and nostril localization) [8]. Odor thresholds measured through hand-squeeze of the bottles by the subjects themselves or through the bottle-squeezer did not differ significantly. Thresholds for eye irritation (in normosmics and anosmic), nasal localization (in normosmics) and nasal pungency (in anosmics) fell close together. 1-octanol failed to produce nasal pungency in the anosmic and, correspondingly, failed to be localized by the normosmics despite their perception of a clear odor sensation. Nevertheless, 1-octanol did evoke eye irritation in both the anosmic and the normosmics. Eye irritation thresholds in the anosmic were slightly above those in the normosmics across the whole series. The difference can be attributed to the small number of subjects but only further testing will resolve the issue.

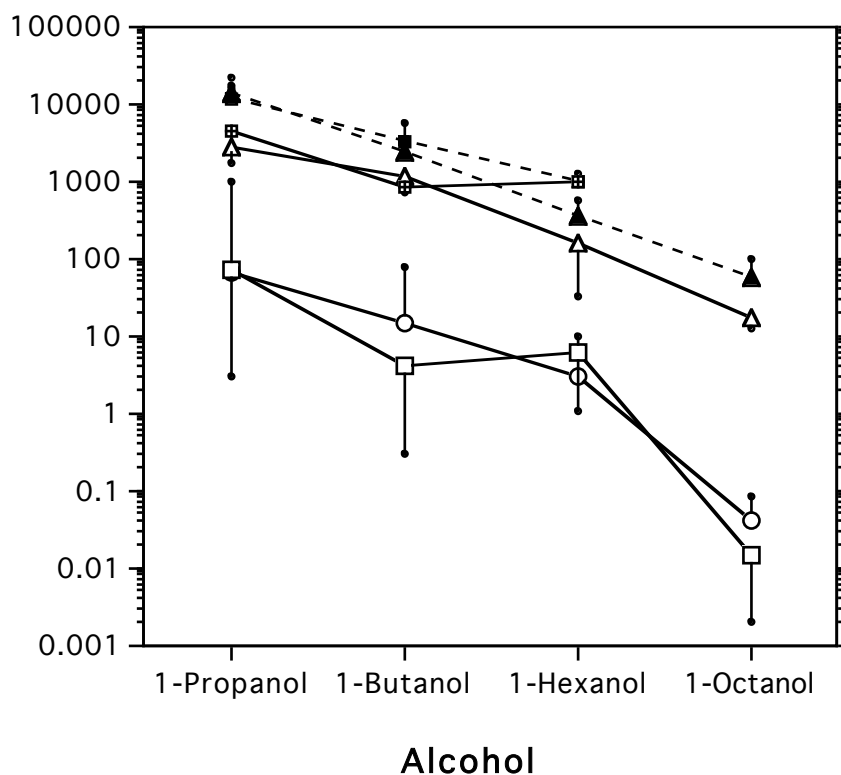


Figure 1. Average sensory thresholds (ppm \pm SD) for each of the four homologous n-alcohols. Odor thresholds obtained by hand-squeeze (empty squares); odor thresholds obtained by bottle-squeezer (empty circles); nasal localization thresholds in normosmics (squares with a cross); nasal pungency thresholds in the anosmic (filled squares); eye irritation thresholds in the normosmics (empty triangles); eye irritation thresholds in the anosmic (filled triangles).

DISCUSSION

Given that most odorants trigger both an odor and a pungent sensation, and given that, as a rule, the olfactory response is evoked at lower concentrations than the trigeminal response, measurements of nasal pungency thresholds in normosmics need to be done over an odorous background, in some cases quite strong. Differences among subjects in the criterion for calling a nasal sensation "pungent", as opposed to "strongly odorous", add difficulty to the task. For these reasons, in the past, we have estimated the potency of VOCs to elicit threshold nasal pungency by measuring nasal detection thresholds in subjects clinically diagnosed as anosmics. Since these subjects lack a functional sense of smell, their only remaining way of detecting nasally presented airborne compounds is through the CCS or chemesthesis, mediated by the trigeminal nerve. Nevertheless, the accessibility and number of anosmics available for testing is relatively limited.

The present outcome opens a new approach to explore the gap between the olfactory and the trigeminal stimulatory potency of airborne chemicals. Previous research uncovered evidence that localization to the right or left nostril of a nasal sensation produced by a vapor-phase compound necessarily relies on activation of the trigeminal nerve [12, 13]. If this is so, it would allow the use of normosmics subjects to explore the olfactory-trigeminal (i.e., odor-nasal pungency) threshold gap of substances. Instead of requiring the participants to report

when a nasal sensation becomes barely pungent (a question subject to biases and individual criterion variability, as already mentioned), participants will be tested for their ability to correctly identify the nostril receiving the stimulus as opposed to that receiving a simultaneous blank.

In order to confirm that such nasal localization thresholds in normosmics cannot be simply generated by olfactory cues we have compared them with: 1) odor thresholds in the same normosmics (obtained both through hand-squeeze of the sniff bottles by the subjects themselves, and through use of the bottle-squeezer by the experimenter), and 2) nasal pungency thresholds in a congenital anosmic. In the present study, as in previous ones, we have used members of an homologous chemical series, namely the n-alcohols, as stimuli. The strategy allows to relate the sensory outcome to physicochemical parameters that change gradually in such series.

Figure 1 shows that, indeed, nasal localization and nasal pungency thresholds fall into register well. A particularly revealing, additional, indication of their good correspondence is the fact that 1-octanol could not evoke nasal pungency in the anosmic and was also not able to be consistently localized by the normosmics despite evoking a clear, and strong, odor sensation. The outcome, preliminary due to the small number of subjects and the need to extend it to a wider array of VOCs, does support the notion of equivalence between nasal localization and nasal pungency thresholds. Interestingly, 1-octanol had also failed before to evoke nasal pungency consistently in some anosmics though not in all [4].

The study has also explored eye irritation thresholds for the same alcohols. Across the chemical series, besides a trend for the normosmics' eye irritation thresholds to be slightly lower than those of the anosmic, ocular thresholds fell into register with nasal thresholds for pungency and localization, except for 1-octanol. This compound did evoke eye irritation in **all** subjects despite its lack of ability to evoke nasal pungency in the anosmic or to be localized by normosmics. This raises the question of whether, as homologous series progress, the trigeminal response in the nose is lost earlier than that in the eye. Such an effect was also observed previously for homologous n-acetates, where nasal pungency began to be lost in some anosmics by the time the series reached octyl acetate, whereas eye irritation only began to fade in some subjects with decyl acetate [5].

Finally, we thought it illustrative to compare all thresholds obtained in the present investigation with those obtained before for the same substances, using a similar methodology (see Figure 2). The absolute values of our present odor and nasal pungency thresholds are slightly higher than the previous ones, and those of our present eye irritation thresholds slightly lower than the previous ones, but, nonetheless, the coincidence in trend and in relative threshold values within and across sensory modalities for the entire series speaks of the robustness of the data.

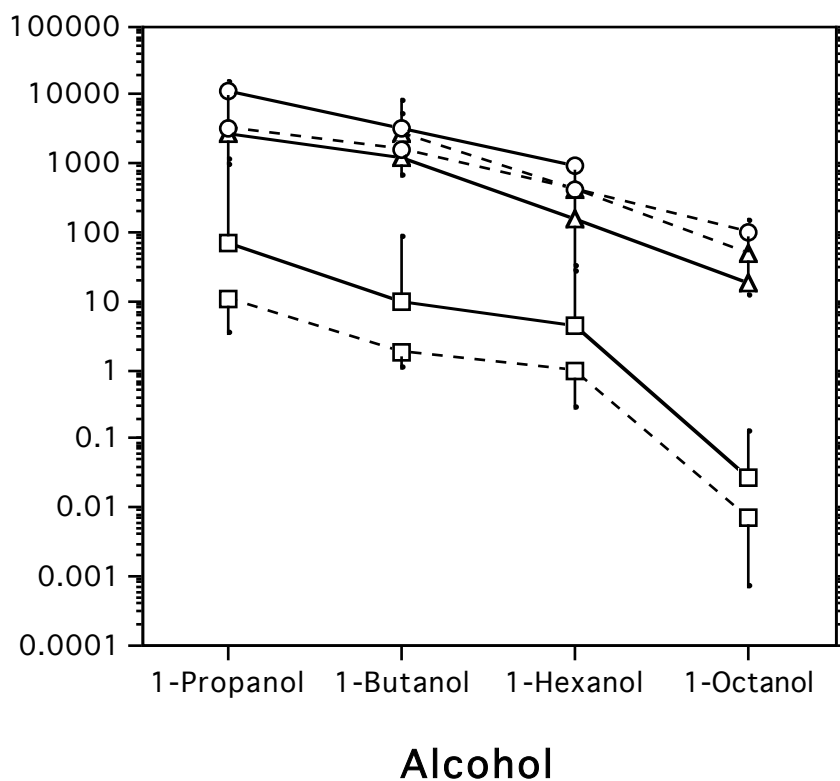


Figure 2. Comparison of present thresholds (continuous lines) with previous thresholds (broken lines) for odor (squares), nasal pungency (circles), and eye irritation (triangles). Vertical lines represent standard deviations. Previous thresholds taken from [4] and [8].

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