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Nasal Pungency, Odor, and Eye Irritation Thresholds for Homologous Acetates

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COMETTO-MUÑIZ, J. E. AND W. S. CAIN. *Nasal pungency, odor, and eye irritation thresholds for homologous acetates.* PHARMACOL BIOCHEM BEHAV **39**(4) 983–989, 1991.—We measured detection thresholds for nasal pungency (in anosmics), odor (in normosmics) and eye irritation employing a homologous series of acetates: methyl through octyl acetate, decyl and dodecyl acetate. All anosmics reliably detected the series up to heptyl acetate. Only the anosmics without smell since birth (congenital) reliably detected octyl acetate, and only one congenital anosmic detected decyl and dodecyl acetate. Anosmics who lost smell from head trauma proved to be selectively less sensitive. As expected, odor thresholds lay well below pungency thresholds. Eye irritation thresholds for selected acetates came close to nasal pungency thresholds. All three types of thresholds decreased logarithmically with carbon chain length, as previously seen with homologous alcohols and as seen in narcotic and toxic phenomena. Results imply that nasal pungency for these stimuli rests upon a physical, rather than chemical, interaction with susceptible mucosal structures. When expressed as thermodynamic activity, nasal pungency thresholds remain remarkably constant within and across the homologous series of acetates and alcohols.

Olfaction Common chemical sense Odors Nasal pungency Nasal irritation Eye irritation
Thresholds Thermodynamic activity Anosmia Homologous acetates Muscosal chemoreception

OUR understanding of the molecular basis of the odor of airborne substances remains surprisingly poor. Various investigators have propounded "odor theories" to explain why some chemicals are potent odorants, whereas others are not, and what governs the particular odor quality of a substance. In these theories, odor qualities have been associated with stereochemical properties (2), diffusion through bilipid membranes (25), and molecular vibration and energy absorption in the far infrared range (52). Other investigators approached the issue somewhat more empirically by trying to uncover the pharmacological (5) and physicochemical (30,40) bases of the olfactory response.

Olfaction is not the only chemical sense present in the human nose. There is also the so-called common chemical sense (CCS). Whereas the olfactory sense relies on specialized olfactory neurons to detect airborne odorants, the CCS lacks such morphologically specialized receptor structures. Common chemical sensations from any region of the face are mediated by the endings of the trigeminal nerve (cranial nerve V), whereas odor sensations are mediated by the olfactory nerve (cranial nerve I). Stimulation of the CCS gives rise to sensations like stinging, prickling, irritation, tingling, burning, piquancy, freshness, and the like which can be generically called pungent sensations. These are not restricted to the nose, like olfaction, or the oral cavity, like taste, but are characteristic of all mucosae. That includes the conjunctiva, i.e., the ocular mucosa, when referring to the face.

Olfaction and the CCS function by different rules and have different vulnerabilities (11,12). For example, previous investigations reported a decreased nasal common chemical sensitivity in smokers (31), probably larger than the decrease in olfactory sensitivity (18). It was suggested that a higher degree of impairment of the CCS with smoking could arise from different pharmacological responsiveness between olfaction and the CCS towards the active constituents of tobacco smoke.

Many airborne substances have the ability to stimulate both olfaction and the CCS. One approach to the study of nasal pungency of such substances has entailed asking subjects to discriminate and assess odor and pungency separately [e.g., (11, 19, 22, 23)]. This approach does not provide a control for differences among participants in the criterion used for extracting the odorous and pungent components of an overall sensation. To add to the complication, olfaction and the CCS show mutual inhibitory interaction such that stimulation of one can mask stimulation of the other (17). The availability of subjects with unilateral destruction of the trigeminal nerve (9) and those lacking olfactory function, i.e., anosmics (27,28), has offered another, and perhaps better, way to study olfaction or the CCS devoid of the influence of the other. With the establishment of taste and smell clinics during the last decade [e.g., (16,29)], patients with documented anosmia have become more readily available.

Only a modest amount is known about the molecular basis of nasal pungency. Alarie (1) describes some features of pungent

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(irritant) stimuli and provides examples. Many such stimuli are highly reactive, even corrosive, e.g., sulfur dioxide, acrolein, chloroacetophenone, benzalmalononitriles, chlorine. But, as Alarie noted, many CCS stimuli fail to exhibit such properties and were classified in a different category. These are generally considered, at most, mild irritants according to classical toxicological criteria. Nevertheless, their pungency emerges clearly from experiments with human anosmics (28).

Certain functional differences between olfaction and the CCS can be learned by using, on the one hand, homologous series of nonreactive chemicals whose physicochemical properties change uniformly and systematically and, on the other hand, both anosmic and normosmic (normal smell) participants. We sought to measure detection thresholds in these two groups. An understanding of the absolute sensitivity of the human CCS and of the physicochemical basis of pungency could help elucidate the mechanism of human common chemical stimulation by nonreactive substances.

In order to expand the results from a previous study (20) where we employed a homologous series of alcohols, from methanol to 1-octanol, we included in this study a homologous series of esters, from methyl to dodecyl acetate. It was realistic to expect the threshold for the normosmics to fall below that of the anosmics and to reflect olfactory detection of these commonly employed odorants. This is so since anosmics are classified as such by their extremely impoverished olfactory ability, as measured by standard clinical tests, e.g., (13, 15, 16), including measurements of nasal detection thresholds.

Since chemical sensitivity of the conjunctival mucosa is also provided by the trigeminal nerve, it is of special interest to know how the eyes compare to the nose in the ability to register the presence of airborne chemicals. A second group of normosmic subjects participated in an experiment that measured ocular detection thresholds for the even acetates from ethyl to decyl acetate.

METHOD

Stimuli

Nasal detection. The 10 acetates employed, methyl through octyl acetate, decyl, and dodecyl acetate, were analytical grade reagents. Mineral oil served as solvent for all substances.

The strongest stimulus for every acetate was the pure chemical (100% v/v), labeled dilution step 1. For all acetates, except methyl acetate, the following dilution steps (No. 2 through No. 15) were all successive ⅓ dilutions of the immediately previous step. For methyl acetate, due to its limited solubility in mineral oil, the second step (No. 2) was a ¼ dilution of the pure substance, but all successive steps (No. 3 through No. 15) were ⅓ dilutions of the immediately previous step, as with the rest of the acetates.

Stimuli were presented in 250 ml capacity, squeezable, polypropylene bottles, containing 30 ml of the stimulus. The bottle closure had a pop-up spout that allowed testing of each nostril separately (4, 13, 16). As the data shown in the results will illustrate, the method led to highly reliable thresholds in both groups of subjects.

The concentration of the acetate in the headspace of a bottle was measured, via a gas sampling valve, by a Hewlett-Packard 5890A Gas Chromatograph (PID detector). As a rule, these were four GC measurements taken from each concentration step, the outcome showing close agreement. The dilution series for methyl acetate and the even acetates were measured again by GC after three to four months and resulted in comparable values to those obtained previously.

Ocular detection. Five members of the acetate series were selected to study thresholds of ocular irritation: ethyl, butyl, hexyl, octyl, and decyl acetate. The same dilution steps used before for each of these chemicals served in this experiment.

Stimuli were presented from the same squeezable bottles as before. In this case, however, the top of the bottle contained a 25 ml roughly conical measuring chamber the rim of which could be placed around the eye. The chamber was fed by a tube that sat in the headspace above the liquid stimulus. A squeeze of the bottle with the chamber in place delivered a puff of vapor directly to the eye. The open end of this chamber is 2.8 cm in diameter. A polyethylene dust cover closed the open end of the measuring chamber when the bottle was not in use.

Subjects

Nasal detection. Four subjects (three males and one female) that tested normosmic on the CCCRC olfactory test (see [16]) comprised the normosmic group. The males were 40, 48 and 67 years old, the female was 60. The anosmic group also comprised four subjects (two males, two females). The males were 40 and 64 years old, the females were 35 and 59. One normosmic male, the 40-year-old, was a current smoker.

Within the anosmic group, one male (40 years old) and one female (59 years old) were congenital anosmics, whereas the other male (64 years old) and female (35 years old) were head trauma anosmics. The anosmics had undergone clinical evaluation for their chemosensory condition [see (13, 15, 16)] at either the Connecticut Chemosensory Clinical Research Center, University of Connecticut or at Yale-New Haven Hospital. None of the anosmics had cognitive impairment, and all four were in good general health.

Ocular detection. Four normosmic subjects (two males and two females) served in this experiment. Their ages ranged from 22 to 36 years old, average: 29. One male was a smoker.

Procedure

Nasal detection. Subjects placed the pop-up spout inside the nostril and squeezed the bottle as they sniffed. Using this procedure, participants sought on each trial to choose the stronger of two stimuli: One was a blank (solvent) and the other a dilution step of the substance being tested. Subjects were asked to squeeze and sniff with the same strength on every trial.

Each participant started by using one nostril to compare the intensity of the lowest concentration of a stimulus to a blank and deciding which one was stronger. An incorrect choice triggered the presentation of the next dilution step (a concentration three times higher) also paired with a blank. A correct choice entailed the presentation of that same concentration (from a duplicate set) paired with a blank, until either an error was made or five correct choices in a row were made, in which case that concentration was taken as the threshold. Hence, errors triggered increments in concentration, whereas correct choices led to another presentation of the same concentration (from another bottle). Once the threshold was measured for that nostril, the same procedure was followed, using the same substance, with the other nostril. After that, testing began with another substance in an identical manner.

This ascending concentration approach to measure the threshold, and the alternate use of each nostril, minimize the effects of adaptation, a phenomenon commonly found in olfactory investigations (8, 10, 11, 38).

Sessions lasted between two and four hours and were re-

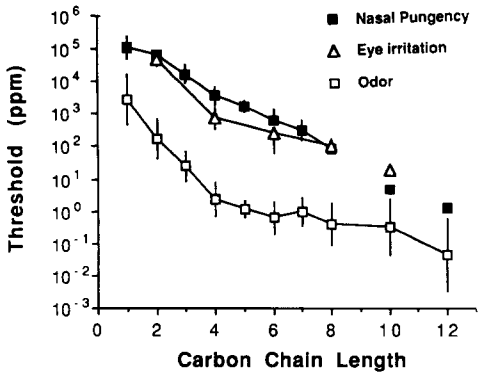

FIG. 1. Average (±SD) nasal pungency thresholds obtained from anosmics (filled squares), average (±SD) odor thresholds obtained from normosmics (empty squares), and average (±SD) eye irritation thresholds obtained from normosmics (triangles) as a function of carbon chain length for the acetates (1 = methyl acetate through 12 = dodecyl acetate). Thresholds are expressed as the headspace concentration of the stimulus. Nasal pungency threshold values for decyl and dodecyl acetate are not connected to the rest by lines since they represent the result from only one anosmic; the other three anosmics did not reliably detect these two stimuli. Eye irritation threshold for decyl acetate is not connected to the rest since it represents the result from the only subject who reliably detected it.

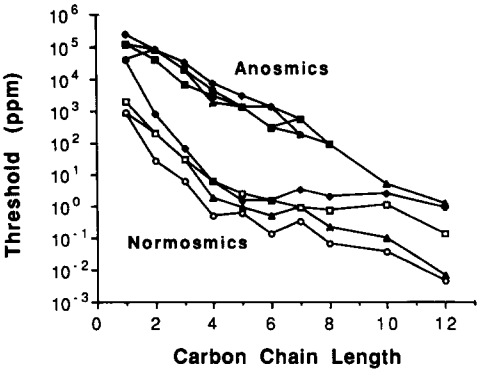

FIG. 2. Individual nasal pungency thresholds, measured in anosmics, and individual odor thresholds, measured in normosmics, as a function of carbon chain length for the acetates. Each symbol represents the median of 12 thresholds measured in that subject. Out of a total of four anosmics, two were unresponsive to octyl acetate and those same two, plus a third, proved unresponsive to decyl and dodecyl acetate.

peated until 12 thresholds (6 for each nostril) per subject were obtained for each stimulus. This equalled a total of 120 thresholds per subject and 48 thresholds per substance in each group (anosmic or normosmic). The order of presentation of the chemicals differed from subject to subject. The number of times that the right or left nostril was tested first for a certain substance was counterbalanced for each subject.

Ocular detection. The subjects had to lift a dust cover from the measuring chamber atop a bottle and then placed the measuring chamber over the eye. Then, the subject squeezed the bottle while keeping the tested eye open and assessed the sensation experienced. The same was done with the second bottle of each presented pair (as before, one bottle was a blank). Finally, the subject had to decide which one produced the stronger ocular sensation. Participants were instructed to squeeze with the same strength on every trial.

Exactly the same forced-choice, ascending concentration procedure described for odor and pungency threshold measurements was employed for eye irritation. Sessions lasted between 15 and 45 min and were repeated until 6 thresholds (three for each eye) per subject were obtained for each stimulus. This represents a total of 30 thresholds per subject and 24 per substance. The order of presentation of the chemicals differed from subject to subject. The number of times that the right or left eye was tested first for a certain substance was counterbalanced for each subject.

Data Analysis

The median served to summarize a subject's 12 (nasal) or 6 (ocular) thresholds per substance. Given that thresholds show a log normal distribution (3, 7, 14), the geometric mean served to summarize the results across subjects. In those cases where a subject did not reliably detect even the pure substance (dilution, step 1, i.e., 100% v/v), the threshold was entered as dilution step 0 in order to calculate the median.

RESULTS

Figure 1 depicts the odor, nasal pungency, and eye irritation thresholds for the acetates. As seen before (20), and not surprisingly, normosmics outperformed anosmics at detection of all stimuli.

Within the anosmic group, the threshold criterion was achieved in 100% of instances for methyl through heptyl acetate. Two anosmics, interestingly the head trauma anosmics, did not reliably detect octyl acetate, so the threshold shown for that chemical in this and subsequent figures represents the result from only the other two (congenital) anosmics. Finally, three anosmics, both head trauma and one of the congenital ones, failed to detect decyl and dodecyl acetate reliably, so the thresholds shown for these chemicals represent the outcome from the remaining congenital anosmic. This anosmic did not achieve the criterion threshold in 2 out of 12 instances (~17%) for decyl acetate and in 4 out of 12 instances (~33%) for dodecyl acetate, but her median response was above dilution step 1 for both chemicals.

Ocular irritation thresholds fell very close to those for nasal pungency and considerably above the odor thresholds. Only one of the four participants in this experiment achieved a reliable eye irritation threshold for decyl acetate.

Figure 2 presents the individual thresholds for nasal pungency and odor, showing the clear separation between normosmics and anosmics. One of the two cases of partial overlap between the groups occurred for methyl acetate, where the threshold for the 67-year-old normosmic male was coincident with that of the 35-year-old anosmic female. The threshold for the anosmic who was age and sex matched to that normosmic, the 64-year-old male anosmic (filled diamonds), was considerably higher. This outcome falls into register with previous findings showing females to be more sensitive than males to nasal pungency (24, 31, 34), and showing decreasing sensitivity with age for nasal pungency and odor (49,50).

The other case of overlap occurred for dodecyl acetate, the substance at the other end of the homologous series. Here, the only anosmic able to detect it, the 59-year-old female congenital anosmic, showed a threshold only slightly higher than that of the 64-year-old male control, but it should be pointed out that the normosmic reached the criterion threshold 100% of the instances, whereas the anosmic did so in only 67% of instances.

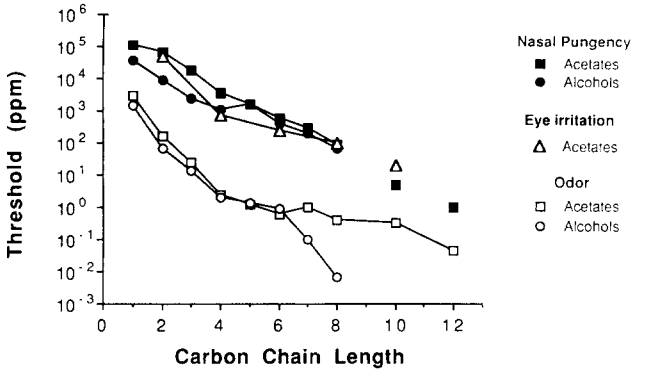

FIG. 3. Comparison between two homologous series: a) normal aliphatic alcohols from 1 = methanol to 8 = 1-octanol and b) acetates from 1 = methyl acetate to 12 = dodecyl acetate in terms of their ability to provoke threshold nasal pungency and threshold odor. Eye irritation thresholds are also shown for selected acetates. Thresholds for the alcohols are from Cometto-Muñiz and Cain (20).

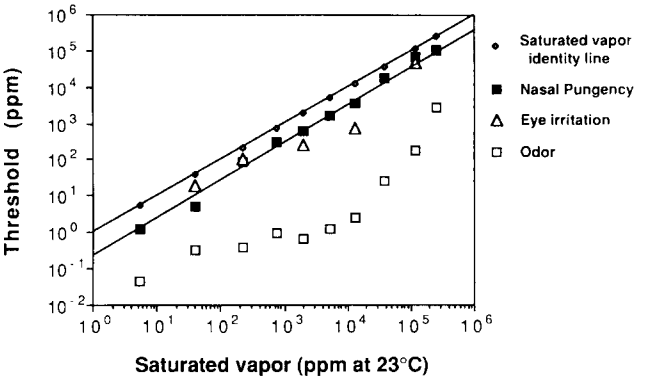

FIG. 4. Average odor and nasal pungency thresholds as a function of saturated vapor concentration of the acetates. Also presented are average eye irritation thresholds. The function describing nasal pungency and eye irritation thresholds has a slope of 1.03 and a correlation coefficient (r) of .98. The saturated vapor identity line for the acetates (slope = 1.00, r = 1.00) is shown for comparison.

It is interesting to compare these thresholds for homologous acetates with those previously obtained for homologous alcohols (Fig. 3) (20). The similarity in tendency, and even in absolute values, is striking.

DISCUSSION

Anosmics reliably detected all acetates up to heptyl acetate. Only congenital anosmics could reliably detect octyl acetate. This raises the question of whether congenital vs. head trauma anosmics differ in their ability to detect certain airborne chemicals. We believe that the issue merits further research.

It was possible to evoke eye irritation in all subjects with all but one of the test stimuli: decyl acetate. For this substance only one participant (a female) detected eye irritation, and did so at near vapor saturation.

Regarding the ability of these nonreactive substances to evoke nasal pungency, it might be worthwhile to distinguish between absolute and relative efficiency. An example might clarify this difference. We could say that 1-octanol is more efficient in absolute terms than methanol given that its pungency threshold, measured as external vapor phase concentration, is about two and a half orders of magnitude below that of methanol (see Fig. 3). For analogous reasons (see Fig. 1), octyl acetate is more efficient than methyl acetate.

Nevertheless, methanol could be seen as more efficient, relative to its odor threshold, than 1-octanol given that the pungency threshold is achieved not much above the methanol odor threshold, measured as external vapor phase concentration (see Fig. 3). For 1-octanol, on the other hand, the threshold for pungency lies well above its odor threshold. The same holds for the acetates, at least up to hexyl acetate, where the thresholds for anosmics and normosmics seem to stop diverging (see Fig. 1).

Data reflecting the absolute efficiency of pungent chemicals find direct application in problems related to indoor air pollution (21). Information on the relative efficiency of the same stimuli on both sensory systems is important in modeling the comparative reception processes in olfaction and the CCS, including perireceptor events (35,36).

Spontaneous comments and reactions from the anosmics suggest that when the pungency threshold is reached for the lower members of both homologous series, even one dilution step above it could be overwhelmingly pungent, whereas for the higher members the pungency at threshold is not so effective or clear, so the concentration could be increased by one, two or even three dilution steps above the threshold and no such overwhelming effect is observed. This characteristic is typical of the highest members of both series (1-octanol and octyl, decyl and dodecyl acetate).

The odor of the acetates also becomes less sharp as chain length increases, giving rise to a less precise threshold value. This is reflected by the higher spread of individual odor thresholds (see Fig. 2) observed for the higher members of the series. A similar trend toward higher spread among higher members of the series was noted for odor detection of the acetates in the behaving rat (45). A recent study also uncovered a tendency for an inverse relationship between the absolute threshold for odor and variance of the threshold distribution (14).

Even ocular irritation changes to a duller type of sensation when the acetate series reaches octyl acetate, and by the time

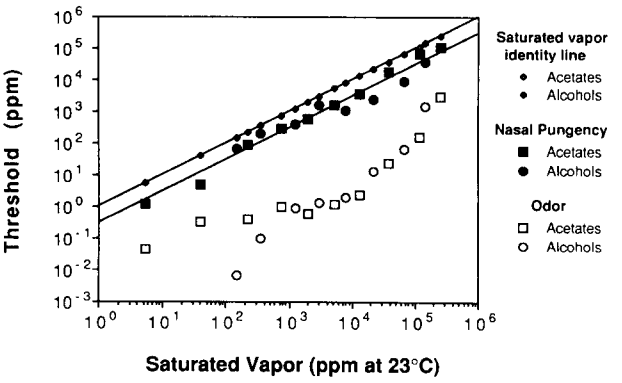

FIG. 5. Analogous to Fig. 4 but including, for comparison purposes, aliphatic alcohols from methanol to 1-octanol. The function describing nasal pungency thresholds for acetates and alcohols has a slope of 1.00 and an r = .98. The alcohol thresholds are from Cometto-Muñiz and Cain (20).

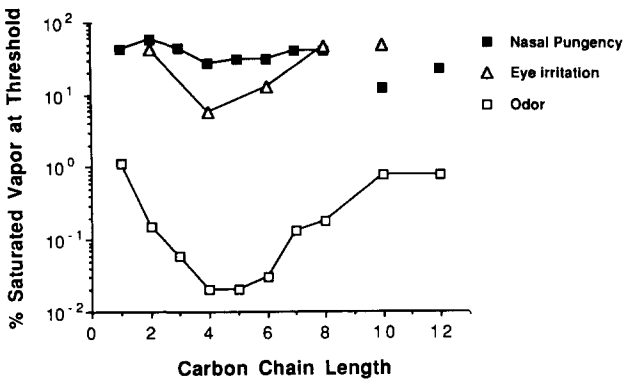

FIG. 6. Thermodynamic activity at threshold odor, at threshold nasal pungency, and at threshold eye irritation for the acetates. Thermodynamic activity was calculated as the ratio between vapor concentration at threshold odor, nasal pungency, or eye irritation, over saturated vapor concentration, multiplied by 100. Nasal pungency thresholds for decyl and dodecyl acetate are not connected to the rest by lines sinces they represent the result from only one anosmic; the other three anosmics did not reliably detect these two stimuli. Eye irritation threshold for decyl acetate is not connected to the rest since it represents the result from the only subject who reliably detected it.

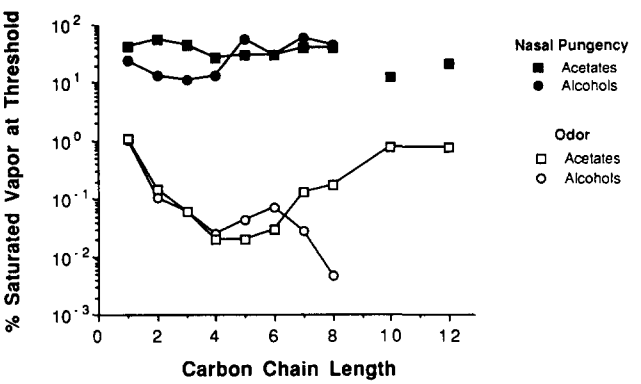

FIG. 7. Same as in Fig. 6 but including, for comparison, data from aliphatic alcohols (from 1 = methanol to 8 = 1-octanol). The alcohol thresholds are from Cometto-Muñiz and Cain (20).

we get to decyl acetate, three of the four subjects failed to experience eye irritation, even at vapor saturation.

Maybe the best way to describe the higher relative (reference odor) efficiency of the lower alcohols and esters in stimulating the CCS is to say that they are more intrinsically pungent than their higher counterparts. This result could very feasibly rest upon the higher chemical reactivity typical of the lower members of these homologous series.

Our previous investigation employing homologous alcohols (20) showed that anosmics, as a group, were unresponsive in 8% of instances to 1-heptanol and in 25% of instances to 1-octanol. Here, as pointed out, the two head trauma anosmics did not reliably detect octyl acetate, and only one of the two congenital anosmics continued to detect decyl and dodecyl acetate reliably, being unresponsive in 17% and 33% of instances, respectively. The other three anosmics did not detect decyl and dodecyl acetate at all. The results indicate that a point is reached in the series where the substances elicit barely detectable pungency, whether nasal or ocular, even at vapor saturation.

The two congenital anosmics had different etiologies underlying their inability to smell. One had a focal area of encephalomalacia in the region of the olfactory bulb. This was detected recently at the Connecticut Chemosensory Clinical Research Center by Magnetic Resonance Imaging (MRI) scan. The other congenital anosmic, the one who could reliably detect even decyl and dodecyl acetate in most instances, did not have any clear cause for her deficit. There was, however, a family history of smell deficits. She recalled that her grandmother could not smell, nor can one of her three children. It is possible that her anosmia is genetic with no other apparent manifestation, as opposed to other well-described genetic anosmias [e.g., Kallmann's syndrome, see (42)].

When nasal pungency and eye irritation thresholds are plotted as a function of the saturated vapor of the acetates at room temperature (Fig. 4), a close to linear relationship resulted. Odor thresholds seem to depart from linearity in a systematic fashion. Furthermore, the function describing nasal pungency and eye irritation thresholds parallel the saturated vapor identity line, strongly suggesting that both thresholds are reached when approximately the same fixed percentage of saturated vapor is achieved, irrespective of the particular acetate. This suggests that simple physical properties could predict the levels at which nonreactive airborne chemicals start to elicit a response from the CCS.

It is quite striking that when we incorporate into Fig. 4 data from the previous study on odor and nasal pungency thresholds for the alcohols, the outcome is so uniform and regular that it would appear that we are dealing with only one series of chemicals (Fig. 5). The regularity holds for nasal pungency throughout both series. The regularity holds for odor only up to molecules of six carbon atoms.

Various physical properties whose constants represent expression of a distribution between heterogeneous phases, e.g., water solubility, surface activity, vapor pressure, and partition coefficients (32), show logarithmic changes with carbon chain length. It has been pointed out that a relationship of this sort indicates the existence of an equilibrium between different phases (43).

Thresholds for narcosis (6,33) and for a number of toxic phenomena (41,47), as well as odor and pungency thresholds for alcohols (20) and, now, for acetates, also follow logarithmic changes in homologous series. Given that the first two phenomena, narcosis and toxicity, are basically determined by a distribution equilibrium between an external phase, where the concentration is measured, and an internal biophase or biophases, our data suggest that odor and pungency of these relatively unreactive chemicals could also be determined by such an equilibrium. If this is so, our data points to a primary action of a physical nature.

In those equilibrium conditions, the thermodynamic activity of the stimulus would be the same in all phases involved, air, aqueous mucus and lipid membrane, while its concentration could be vastly different depending on the relative solubility of the particular substance on each phase. The thermodynamic activity of a stimulus in the gas phase, assuming ideal gas behavior, can be calculated by the ratio between vapor pressure at a threshold effect (whether narcosis, pungency, toxicity or odor) over saturated vapor pressure at that temperature. This value reflects the activity of the substance at the site of biological action wherever this site might be.

Figure 6 depicts thermodynamic activity (expressed as percent of saturated vapor) at threshold odor, nasal pungency, and eye irritation for each acetate. For odor, activity declines with chain length up to butyl acetate, then rises from pentyl up to

decyl acetate. A strikingly similar relationship between odor thresholds, expressed as activity, and carbon chain length was observed in the behaving rat, though in this study heptyl acetate was the highest member tested (45). The variation in odor threshold across the acetates reduces from more than four orders of magnitude, when the thresholds are expressed as external vapor phase concentration, to less than two, when they are expressed as percent of saturated vapor.

Much more impressive, though, is the reduction in the variation of nasal pungency thresholds. It falls from three orders of magnitude, when pungency is expressed as external vapor phase concentration, to about half an order of magnitude, when pungency is expressed as activity. If one does not count decyl and dodecyl acetate, detected by only one out of the four anosmics, the reduction is even more impressive: it falls to a third of an order of magnitude.

Eye irritation thresholds, expressed as a percent of saturated vapor, fall somewhat in the middle between the other two sensations, albeit closer to nasal pungency. In terms of shape of the function, eye irritation thresholds resemble odor since they first decline up to butyl acetate, and then they rise up to octyl acetate. Nevertheless, in terms of absolute values eye irritation thresholds lie much closer to those for nasal pungency.

Figure 7 allows comparison of odor and nasal pungency thresholds for the acetates, expressed as thermodynamic activity, with those obtained for the alcohols (20). Nasal pungency thresholds for the two homologous series are again (as in Fig. 3) roughly coincident, depicting a remarkable constancy in activity between the series. Odor thresholds, expressed as activity, are coincident between acetates and alcohols, except for the last members of the series. For odor, the variation in activity at threshold across the series is considerably lower than in external ppm at threshold (see Fig. 3). Nevertheless, the odor thresholds lack the constancy of nasal pungency thresholds when expressed as activity.

The production of nasal pungency by these relatively nonreactive chemicals is achieved at a fairly constant percentage of saturated vapor, regardless of the size or functional group of the molecule. This suggests that the production of nasal pungency by these substances is the result of a nonspecific, physical interaction between the stimuli and susceptible mucosal target sites, most probably within the lipid membrane of free nerve endings from the trigeminal nerve.

Our results on eye irritation, expressed as percent of saturated vapor (Fig. 6), indicate increased sensitivity of the eyes vs. the nose towards the middle acetates, butyl and hexyl, but no difference towards the extreme acetates, ethyl on the one hand and octyl on the other. Results from decyl and dodecyl acetate, where only one normosmic and one anosmic reached threshold eye irritation and nasal pungency respectively, cannot allow us to draw conclusions. Further research with a high number of participants could unveil the true proportion of a target population being sensitive or insensitive to these chemicals.

Differences in relative sensitivity between ocular and nasal mucosae could most probably be ascribed to physicochemical differences in the fluid layers covering them (26, 37, 44, 46), to specific responses and susceptibilities of their respective cell types, or to the accessibility and proximity of free nerve endings. These issues have been addressed principally in animals, where the techniques allow separation of olfactory from CCS functioning (39,48). The availability of anosmic humans similarly offers an opportunity to study in vivo human trigeminal chemoreception without olfactory interference. The issue of the relative sensitivity of eyes and nose to irritation and pungency [e.g., (51)] has also relevance both to the physicochemical basis for CCS stimulation and to practical issues in environmental toxicology (e.g., indoor air pollution).

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