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TRIGEMINAL CHEMOSENSATION

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I. INTRODUCTION

During the early part of the 19th century, there was considerable debate regarding whether the sense of smell was mediated by the first cranial nerve (CN I, the olfactory nerve) or the fifth cranial nerve (CN V, the trigeminal nerve). Although Sir Charles Bell believed that olfaction was subserved by CN I (Bell, 1812), he erroneously thought that CN I and CN V fibers were united for a portion of their projection, as indicated in his 1811 classic *Idea of a New Anatomy of the Brain* (Bell, 1966). Francois Magendie, Bell's chief French rival and the primary proponent of the theory that CN V mediated olfaction, published his major arguments in 1824, along with a series of flawed physiological animal experiments that he touted as demonstrating his point (Magendie, 1824).

Magendie's conclusions received little confirmation from others, and reports soon appeared supporting Bell's contention that CN I mediates olfactory function. For example, in 1826 Eschricht noted that persons without olfactory nerves or with degenerate nerves were anosmic. Cruveilhier (1829) communicated a case to the Anatomical Society of Paris (of which he was President) in which a fungus of the dura matter had produced damage to the optic chiasm and had destroyed the olfactory nerves and sectors of the anterior cerebral lobes, but left the trigeminal nerves intact. This individual was both anosmic and blind. Vidal (1831) subsequently reported to the same society a case of an anosmic blind person who, at autopsy, had a tumor that destroyed the optic and olfactory nerves, but not the trigeminal ones. Two years later, Bishop (1833) reported on a patient with paralysis of the trigeminal nerve with normal ability to smell, and Shaw (1833) wrote a scathing critique of Magendie's earlier experiments, pointing out why they were invalid.[1]

[1] To place these observations in historical context, it should be noted that it was not until 1847 that Todd and Bowman reported that a sector of the epithelium on the upper turbinate differed in appearance from the rest of the nasal mucosa (Todd and Bowman, 1847). The different cell types within the olfactory epithelium were first described in 1855 (Eckhard, 1855; Ecker, 1855). The first

Today we know that the qualitative sensations of smell are mediated by CN I; however, we also know that most, if not all, odorous chemicals have the propensity to stimulate, directly or indirectly, free nerve endings of CN V located within the lining of the nasal vestibule and nasal chambers, producing such sensations as irritation, tickling, burning, warming, cooling, and stinging.[2] These sensations, which often serve to avert the organism away from harmful sources of stimulation, are classified by some as a component of the "common chemical sense", a term first used by Parker (1912) to describe the general chemical responsiveness of mucosal and epithelial tissue mediated via free nerve endings from a number of different nerves. This chemosensitivity is also known as "chemesthesis" (Green and Lawless, 1991; Green, Mason and Kare, 1990).

In addition to serving chemosensory functions, CN V fibers within the nasal vestibule mediate the tactile sensations of temperature and pressure, including the perception of nasal airflow during breathing (Burrow et al., 1983; Cauna and Hinderer, 1969). Importantly, CN V stimulation can reflexively influence cardiovascular responses (e.g., heart rate and blood pressure), respiration rate, nasal engorgement, epinephrine secretion, nasal secretion, and sneezing (A1arie, 1966; Allen, 1929; James and Daly, 1969, 1972; Kratschmer, 1870), and there is evidence that the trigeminal and olfactory systems interact centrally. For example, olfactory and trigeminal pathways converge on the same neural elements within the mediodorsal nucleus of the thalamus of the rat; blocking the trigeminal pathway enhances odor-induced activity in the nucleus (lnokuchi et al. , 1993). Lesioning or reversibly blocking the rabbit trigeminal ganglion inhibits olfactory bulb activity (Stone et al., 1968). Electrical stimulation of the trigeminal nerve decreases bulbar activity (Stone,

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descriptions and illustrations of true olfactory receptor cells and their cilia were published in 1856 (Schultz, 1856). An excellent review of these and other early studies is provided by Zippel (1993); see, also, the Introduction to this volume.

[2] There is some suggestion that the nasal mucosa may also receive some sensory fibers from the facial (CN VII), vagus (CN X), and upper thoracic spinal nerves, although their role, if any, in chemoreception is obscure. Eccles (1982) has speculated that these pathways may explain referred pain and headaches due to nasal disease.

1969), a phenomenon that has also been reported for electrical stimulation of the vagus nerve {Garcia-Diaz et al., 1984). Interestingly, CN V may also modulate the activity of olfactory receptor cells within the neuroepithelium via a local axon reflex associated with the release of substance P (SP) (Bouvet et al., 1987).

In this chapter, we (1) review basic aspects of the anatomy and physiology of the intranasal trigeminal system, with an emphasis on humans, (2) describe basic characteristics of human trigeminal chemosensory processing, and (3) present data from psychophysical studies related to potential CN V interactions with CN I-mediated chemoreception. The reader is referred elsewhere for more general reviews on this and related topics, including the complex relationships between the trigeminal system and autonomic processes in general (DeLong and Getchell, 1987; Eccles, 1990; Keverne et al., 1986; Tucker, 1963; Walker et al., 1990; Widdicombe, 1986).

II. ANATOMY AND PHYSIOLOGY OF THE CHEMOSENSORY TRIGEMINAL SYSTEM

In the human, sensory nerve endings from branches of the trigeminal nerve are found in the epithelia of the nose and sinuses, the oral cavity, the eyelids, and the cornea (Figure 1). The anterior and lateral portions of the nasal cavity are innervated by the lateral and medial nasal branches of the *ethmoidal* nerve, which is derived from the nasociliary branch of the ophthalmic division of CN V arising from the trigeminal ganglion (also called the Gasserian or semilunar ganglion). This nerve enters the nasal cavity via the anterior ethmoidal foramen near the lateral margin of the cribriform plate. The posterior portion of the nasal cavity is innervated by the nasopalatine nerve, one of the four nerves that branch from the sphenopalatine ganglion. This nerve contains parasympathetic postganglionic fibers from the sphenopalatine ganglion, sympathetic postgangli-

onic fibers from the sympathetic ganglia in the neck, and sensory fibers from the maxillary nerve

that traverse the sphenopalatine ganglion.

INSERT FIGURE 1 ABOUT HERE

Developmentally, the trigeminal nerve is well formed in utero (Gasser and Hendrickx, 1969; Hogg, 1941). Indeed, the perioral areas supplied by the mandibular and maxillary divisions are the first embryonic regions to respond to cutaneous stimulation (circa 7.5 weeks). The ophthalmic division can be observed at 4-5 gestational weeks and is presumed to be functional by 10.5 weeks (Brown, 1974; Humphrey, 1966; Streeter, 1908). Not surprisingly, trigeminal reactivity to chemical stimulation is present at birth. Thus, when the nares of newborn infants (ranging in age from 16 to 131 hr) were confronted with vials containing either cotton or ammonium hydrochloride, they turned away from the side of the ammonia on 64% of 304 trials (Rieser et al., 1976).

A number of fiber types are found within each of the branches of the trigeminal nerve. In the case of the infraorbital nerve of the rat, both myelinated and unmyelinated axons are present, with myelinated ones ranging from 0.8 to 14.9 μm in diameter and unmyelinated ones ranging from 0.3 to 1.5 μm in diameter (Jacquin et al., 1984). More unmyelinated than myelinated axons are found in the ethmoidal nerve, with the preponderance of fibers ranging from 2 to 6 μm in diameter (Biedenbach et al., 1975).

Immunocytochemical studies demonstrate that fine unmyelinated C-fibers that innervate the nasal cavities contain SP and, in many cases, associated calcitonin gene-related peptide (Finger et a1., 1990). Physiological studies suggest that unmyelinated C-fibers are responsible for irritative reactions in the nasal and respiratory passages, as well as in the body skin, although small myelinated A-delta fibers may also be involved (Jancso et aI., 1967; Lundblad et aI., 1983). Silver et aI. (1985) noted that chronic administration of capsaicin (which depletes, to a large degree SP from fine unmyelinated afferents) eliminated or severely reduced trigeminal nerve responses to chemicals in rats, suggesting that the small unmyelinated and possibly some myelinated fibers subserve trigeminal pain reactions. Other classes of peptidergic fibers (e.g., ones that contain

vasoactive intestinal peptide and luteinizing hormone releasing hormone) are also found within the nasal epithelium, although their role in chemosensory mediation is not defmed (Silver et al, 1985).

Although a few nonolfactory nerve fibers have been observed extending to the epithelial surface of the nasal epithelium (see, for example, Lundblad et aI., 1983), Finger et aI. (1990), using data from electron microscopy studies, report that the vast majority of CN V free nerve endings terminate within the lamina propria, at least in amphibia and rodents. Nevertheless, they observed a few trigeminal fibers that terminated within 1 μm of the epithelial surface, just below the tight junctions. Finger et al. point out that for volatile chemicals to stimulate these nerve endings, they must (1) pass into the nasal cavity, (2) partition into and diffuse through the mucus, and (3) cross the epithelial cell membranes and/or intercellular tight junctions. Since most trigeminal stimulants are lipid soluble, such transit is likely.

There is considerable evidence that trigeminal nerve endings express a number of specific receptors. Thus, vanilloid receptors, found in a subset of C-fibers, have a strong afinity for capsaicin, the pungent principle in hot peppers, as well as for closely related molecules (Szallasi, 1994). Interestingly, these receptors can also be activated by noxious heat (Caterina et al., 1997). Nicotinic acetylcholine receptors are also likely to be present on nasal trigeminal nerve endings (Alimohammadi and Silver, 2000). In fact, electrophysiological studies in rats (Walker et al., 1996), as well as psychophysical and electrophysiological studies in humans (Thürauf et al., 1999), suggest the existence of a dose-dependent stereoselective activation of the trigeminal sensory system by S(-) and R(+)-nicotine. In the case of reactive substances of varied structures, they could act directly on mucosal tissue, or indirectly by mucosal tissue damage (via chemical reaction) and subsequent release of endogenous chemicals which in turn, would act upon specific ion channels to produce the trigeminal response. Such endogenous compounds include ATP, H+, and bradykinin (Cesare and McNaughton, 1997; McCleskey and Gold, 1999).

Aside from the specific stimuli mentioned above, for which there seem to be finely-tuned receptors, the human trigeminal chemoreceptive system has been shown to respond to a myriad of relatively non-reactive volatile compounds possessing varied chemical functionalities such as alcohols, esters, ketones, carboxylic acids, aldehydes, and the like, including linear and branched, saturated and unsaturated, aliphatic and aromatic molecules. All of them capable of evoking trigeminal sensations, e.g., nasal pungency and eye irritation, when presented at high enough concentrations (see review in Cometto-Muñiz, 2001). In view of such diversity in chemical structures and functionalities, it is likely that the trigeminal impact of this broad range of substances rests heavily on general physicochemical parameters that govern stimulus transport from the vapor phase to the biophase, where trigeminal chemoreceptors lie. The success of a quantitative structure-activity relationship (QSAR) based on a solvation equation to describe and predict human thresholds for nasal pungency (Abraham et al., 1998a) and for eye irritation (Abraham et al., 1998b) lend support to this perspective (see section III. D. below).

III. CHEMOSENSORY TRIGEMINAL STIMULATION: HUMAN PSYCHOPHYSICAL AND PHYSIOLOGICAL STUDIES

Numerous studies have sought to determine the responses produced by volatile chemicals on the trigeminal system of humans. Such responses fall into three main categories: (1) changes in respiration, nasal secretion, and other physiological measures to chemosensory stimulation; (2) induction of perceptual qualities, such as cooling, burning, irritation, and pain; and (3) alterations in psychophysical measures of CN I-mediated odor perception. In this section, we review studies that examine the propensity of volatile chemicals, alone or in combination, to produce non-olfactory chemosensations and describe, among other things, the functional dissociation of the intranasal trigeminal and olfactory responses.

A. Trigeminal Stimulants and the Search for "Pure" Odorants

For many years investigators have sought to identify chemicals that produce "pure" olfactory

sensations, i.e., odorants uncontaminated by trigeminal activity. Such agents would be extremely useful in human olfactory research, since they would allow for the psychophysical investigation of CN I without potential confounding influences from CN V. In light of this quest, it is of interest that a number of early workers simply assumed that a rather clear distinction could be made between "pure" odorants and more "penetrating" ones, i.e., ones that produce tactile sensations. A case in point is Zwaardemaker (1925), who felt that the majority of essences, resins, and pitches fell into the "pure" odorant class.

Despite the attractiveness of this concept and the astute observations of many such workers, modern studies throw into question such a simple dichotomy of odorants, suggesting that even clean air can produce some intranasal trigeminal sensation, depending on its flow rate, temperature, and degree of humidification (Doty et al., 1978; Eccles, 1990). Nevertheless, as indicated in detail below, is clear that some chemicals produce much less trigeminal stimulation than others, and that at low concentrations and flow rates some agents likely produce little or no trigeminal activity (or at least no more trigeminal activity than that produced by inhalation of clean air).

Several major attempts to identify "pure" olfactory stimulants were made in the first third of this century. Thus, three years before Allen's (1928) classic ablation study that identified the nasociliary and maxillary nerves as the source of odor-induced respiratory and cardiovascular responses in dogs,[3] von Skramlik (1925) listed nearly 50 "pure" odorants, as inferred from the inability of five subjects to localize them to the side of the nose to which they were presented. Among these odorants were anethole, cadinene (juniper), eugenol, geraniol, indole, limonene, phenyl ethyl alcohol, pinene, skatol, and terpineol. Examples of "impure" odorants reported by von Skramlik were ones that produced smell + sweet sensations (bromoform, chloroform, ethyl chloride, iodoform, nitrobenzol), smell + sour sensations (acetic acid, butyric acid, propionic

[3] It is of interest that Allen reported that his study was a replication and expansion of observations made earlier by Kratschmer (1870) and Beyer (1901) on this topic.

acid, and valerianic acid), smell + cool sensations (camphor, eucalyptol, menthol, phenol, safrol), smell + warm sensations (ethanol, pentanol, propanol), and smell + painful or prickly sensations (acetone, acetic acid, ammonia, bromine, chlorine, formic acid, iodine, nicotine, pyridine, SO_2, thiophene, toluol, and xylol).

In 1929, Allen performed a series of human experiments to examine the influences of a number of volatile chemicals on cardiovascular responses. In one phase of this work, he described the responses of an anosmic college student to various inhaled chemicals. This student's anosmia resulted from a fall from a telephone pole, which produced a severe skull fracture and paralysis of the left rectus lateral eye muscle. Although the student reported being unable to smell any of the stimuli, he indicated that a number produced clear intranasal or intraoral sensations. As described by Allen (p. 625),

> Fresh cat's urine was not detected, but old decomposed cat's urine, possessing a trace of ammonia, was said to produce a different sensation than a strong concentration of ammonia. ...pyridin was described as a taste sensation coming from the back of the throat and tongue. Peppermint caused a cooling sensation in the nose and ether a disagreeable burning sensation appearing quickly. On the other hand, chloroform elicited a pleasant sensation in the nose. Formalin, described as a tickling sensation in the nose, was a long time in appearing. A weak concentration of acetic acid or ammonia produced a burning sensation in the nose and throat, which would have resulted in a movement of the head if inhalation had continued longer. Very singularly, the subject could inhale oil of mustard for a considerable length of time without any discomfort if the cone was held 4 or 5 cm. from the nostrils. In fact, the change in respiration appeared before the sensation was detected.

Importantly, menthol, eucalyptus, camphor, peppermint, ether, chloroform, and benzol, as well as weak concentrations of the strong irritants formalin, acetic acid, and ammonia, produced augmented inspirations without altering respiration rate per se. Inhalation of the oils of bergamot, cloves, orange, lavender, rose, and wintergreen, as well as asafetida, butyric acid, xylol, and fresh cat's urine, resulted in no such changes.

It is noteworthy that the stimuli reportedly detected by this anosmic student corresponded well to those classified by von Skramlik as being "impure" odorants (e.g., pyridine, chloroform, acetic acid, ammonia, menthol, peppermint, and formalin), providing at least rough validation of their non-olfactory effects. Similarly, a number of the chemicals that this study reported as not influencing respiration or being detected by the subject were the same as some of von Skramlik's "pure" olfactants [e.g., eugenol (cloves)].

Although in the years following these studies several other investigators commented on stimuli that reportedly produced no trigeminal stimulation (e.g., Elsberg et al., 1935), little psychophysical research was performed on this topic until 1975, when 14 anosmics were presented with 31chemicals in sniff bottles and asked if any intranasal sensations were detected (Doty , 1975). Eleven of the chemicals (35%) were reported by these subjects not to be detectable: anethole, benzyl acetate, eugenol, geraniol, heptane, heptyl alcohol, hexanoic acid, nonane, octane, 2-phenyl ethyl alcohol, and a-terpineol. Again, most of these chemicals fell within the set that von Skramlik reported as being "pure" olfactants.

In contrast to this finding, however, were the results of a subsequent and more extensive study of 47 chemicals [which included the 31 chemicals used in the Doty (1975) study] which incorporated a forced-choice detection paradigm (Doty et al., 1978). In this experiment, three groups of subjects (n = 15/group) were evaluated: (1) anosmics lacking CN I, but not CN V, nerve function; (2) normals asked to rate only intranasal CN V sensations (termed the trigeminal focus group); and (3) normals asked to rate their overall odor experience. During testing, each

subject was blindfolded and, on a given trial, was presented with two sniff bottles, one after the other in random order. One bottle contained a blank (propylene glycol) and the other an undiluted odorant. Each subject was asked to identify which of the two bottles seemed strongest. If reliable detection occurred, the subject was asked to rate the stimulus' intensity, pleasantness, coolness, warmth, and presumptive safety on a series of anchored rating scales.[4]

This study, unlike the previous one, found that nearly all (45/47, or 96%) of the chemicals were detected by at least some of the anosmics. Although differences in the rated intensities given to the stimuli were present among the three groups (e.g., the normal subjects consistently rated the stimuli as much stronger than did the other two groups), the relative rankings of the intensity responses were similar (r's ranging from 0.92 to 0.97). The pleasantness and presumed safety ratings were inversely related to the ratings of perceived intensity in all three groups. The major point of significance of this study was its conclusive demonstration that anosmics and normal subjects could detect nearly all the chemicals presented to them via non-olfactory means when the testing was performed in a forced-choice format, thereby throwing into question the conclusions of a number of previous psychophysical studies on this topic (where subjects were simply asked whether or not they smelled something).

The mean intensity ratings for each of the 47 chemicals provided by the anosmic, trigeminal focus, and normal subjects in the Doty et al. (1978) study are presented in Table 1, along with the proportion of subjects within each group who detected them. It is of interest that only one chemical, vanillin, was not detected by at least one subject from the anosmic or trigeminal focus groups, and

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[4]We also performed structure-activity studies to determine whether we could predict the degree of trigeminal stimulation of the chemicals. The use of 11-13 readily available and computer-derived molecular descriptors in linear learning machine pattern recognition analyses separated the stimuli correctly into four discrete intensity classes. A multiple linear regression equation based on such descriptors proved successful in predicting the trigeminal intensities of 12 chemical stimuli similar in structure to members of the original stimulus set ($r = 0.80$ between predicted and observed intensities).

that a number of chemicals reported to be "pure" odorants by von Skramlik and others (e.g., anethole, eugenole, geraniol, indole, limonene, phenyl ethyl alcohol, and turpineol) were detected (albeit as weak) by at least a few subjects from the anosmic and trigeminal focus groups.

INSERT TABLE 1 ABOUT HERE

An electrophysiological study by Silver and Moulton (1982) adds credence to the validity of these findings. Thus, these investigators found that the relative magnitude of whole-nerve recordings from the ethmoid branch of nine rats correlated very strongly ($r = 0.975$) with the intensity ratings from the Doty et al. study for the nine compounds they evaluated. The magnitude of this correlation is striking, particularly in light of the fact that responses of a quite different nature were being compared across species from different mammalian orders.

B. Functional Dissociation of Trigeminal and Olfactory Responses in the Nose

From the studies discussed in the previous section we conclude that most volatile organic compounds employed in olfactory studies are capable of stimulating both the olfactory and the trigeminal nerves. The issue of olfactory vs. trigeminal stimulation becomes, then, a matter of degree or dose, as a central concept in toxicology sustains. As a consequence, a more productive and practical approach to the problem consists in elucidating the gap between the two chemosensory responses rather than searching for “pure” odorants or “pure” irritants (both extremes, if indeed possible, no doubt being the exception rather than the rule).

Both human and animal studies support the general view that the olfactory system is more sensitive to chemicals than the trigeminal system (Doty, 1975, 1978; Henton, Smith, and Tucker, 1969; Walker and Jennings, 1991; Walker, Tucker, and Smith, 1979). Some attempts to separate odor responses from nasal pungency (i.e., irritant) responses entailed instructing subjects to focus on one type of sensation and ignore the other (e.g., Cometto-Muñiz, García-Medina, and Calviño, 1989; Cometto-Muñiz and Hernández, 1990). This strategy has merit for the study of suprathreshold sensations and finds validation in the aforementioned Doty et al. (1978) study,

where the responses of anosmics and the trigeminal-focus group show overall good agreement. Nevertheless, it cannot be easily applied to studies at the threshold level, more so if one decides to use a forced-choice detection paradigm to minimize response biases. In this case, the testing of anosmic subjects becomes crucial.

Assuming that, as a general rule, olfaction is more sensitive than the nasal trigeminal system, odor thresholds can be measured in normosmics, whereas nasal pungency thresholds (unbiased by odor sensations) can be measured in anosmics. Within this scheme, we can use the robust forced-choice procedure to measure both types of thresholds. Testing of anosmics represents an important tool in the functional separation of trigeminal and olfactory responses from the nose. We can, then, define, for any volatile odorant, the concentration below which the chemical would, on average, not be detected by smell, the concentration range in which the chemical will only evoke odor, and the concentration range above which it will evoke odor and concomitant nasal pungency. This way of expressing the chemosensory potency of a substance provides very relevant information, particularly for applied issues, e.g., perfumery, food, indoor air quality, that goes well beyond the simple classification of the stimulus as "olfactory" or "trigeminal".

Another strategy to probe into trigeminal chemoreception sensitivity without olfactory interference consists in testing the ocular mucosa. A number of physiological and psychophysical techniques have been developed for the evaluation of human eye irritation, either to single compounds (e.g., Hempel-Jørgensen et al., 1999a; Hempel-Jørgensen, Kjærgaard, and Mølhave, 1997; Kjærgaard, Pedersen, and Mølhave, 1992) or to mixtures (e.g., Hempel-Jørgensen, Kjærgaard, and Mølhave, 1998; Hempel-Jørgensen et al., 1999b; Kjaergaard and Pedersen, 1989). The eyes, also served by the trigeminal nerve, can be tested for eye irritation thresholds. These thresholds could represent a surrogate response to nasal pungency thresholds as measured in anosmics. Comparative studies of nasal and ocular trigeminal chemosensitivity have provided a picture of overall similarity (Cometto-Muñiz and Cain, 1991; Cometto-Muñiz and Cain, 1995;

Cometto-Muñiz and Cain, 1998; Cometto-Muñiz et al., 1999; Cometto-Muñiz et al., 1998). This does not rule out that for a certain chemical or under certain conditions, the trigeminal response in the eyes might turn to be more sensitive or less sensitive than that in the nose. The issue will be treated in more detail in the next section. The point to stress is that any difference in trigeminal chemosensitivity between the nose and the eyes dwarfs in comparison with the much higher sensitivity of the olfactory system (Cometto-Muñiz and Cain, 1995).

A third experimental approach to separate the trigeminal from the olfactory response of the nose to airborne stimulants is to measure nasal localization, or, perhaps more properly, nasal lateralization thresholds. An early investigation concluded that localization of a smell to the right or left nostril can occur based on differences in time or intensity of presentation to the two nostrils (von Bèkesy, 1964). The stimuli employed, however, likely had considerable trigeminal impact (benzol, eucalyptus, cloves, and lavender). A previous study (von Skramlik, 1925) and more recent work (Kobal, Van Toller, and Hummel, 1989; Schneider and Schmidt, 1967) presented robust data showing that localization to one or the other nostril is only possible via trigeminal and not olfactory activation. Thus, nasal localization thresholds can be measured in normosmics and in anosmics using a forced-choice procedure, and provide a mean to probe into nasal trigeminal sensitivity devoid of olfactory interference. As discussed in the next section, nasal localization thresholds in normosmics and anosmics fall close to each other.

C. Suprathreshold Responses to Nasal Irritants

Several lines of evidence suggest that the suprathreshold buildup in trigeminal sensation across increasing stimulus concentrations may be more rapid for the trigeminal than for the olfactory (or olfactory + trigeminal) nerve(s). For example, Doty (1975) found the average exponent of power functions fitted to magnitude estimation data from anosmic patients to be larger than those fitted to analogous data from normal subjects for both methyl ethyl ketone (0.35 vs. 0.30) and furfural (0.55 vs. 0.45), although these differences were not statistically significant. Cain

(1976) reported, for the odorant n-butanol, that the function relating perceived irritation to stimulus concentration is steeper than that relating perceived odor to stimulus concentration in normal subjects. Similarly, Murphy (1987) points out that the power function exponent for CO_2 (a strong irritant at high concentrations) is 1.2, a value much larger than those observed for odorants commonly used in olfactory research (e.g., Berglund et al., 1971; Doty,

D. Nasal Pungency, Eye Irritation, and Nasal Localization Thresholds Within Homologous Chemical Series

The above mentioned strategies provide useful tools to separate trigeminal from olfactory human nasal chemosensory responses. The other component of the stimulus-response interaction includes the myriad of diverse volatile agents that are capable of evoking odor and pungency. In order to expand our knowledge of the physicochemical basis for sensory potency of odorants and irritants, it is useful to resort to orderly arrays of stimuli for testing. Examples of such arrays can be found in homologous chemical series. Members of each of these series share a common chemical functional group (for example, a hydroxyl group, HO^-, in alcohols and a carboxylic group, -COOH, in organic acids) and differ from the next one in the addition or subtraction of one carbon atom (with its corresponding hydrogens, e.g., $-CH_2-$) to the carbon chain. One important feature within these series is that physicochemical properties (e.g., vapor pressure, solubility) change systematically across members. This allows one to correlate these orderly physicochemical changes with corresponding changes in chemosensory potency, as measured, for example, by detection threshold procedures. Carbon chain length constitutes, then, a convenient "unit of change" in reporting the results.[5]

Employing the dual strategy of testing anosmics to separate nasal trigeminal from olfactory detection, and of employing homologous chemical series to create a continuum of physicochemical

properties, Cometto-Muñiz and colleagues measured odor and nasal pungency thresholds for homologous n-alcohols (Cometto-Muñiz and Cain, 1990), acetate esters (Cometto-Muñiz and Cain, 1991), secondary and tertiary alcohols and acetates (Cometto-Muñiz and Cain, 1993), ketones (Cometto-Muñiz and Cain, 1993), alkylbenzenes (Cometto-Muñiz and Cain, 1994), aliphatic aldehydes and carboxylic acids (Cometto-Muñiz, Cain, and Abraham, 1998), and for selected terpenes (Cometto-Muñiz et al., 1998). Figure 2 shows how odor and nasal pungency thresholds change across homologous alcohols, acetates (including some secondary, tertiary, and branched members in both series), ketones, and alkylbenzenes. Figure 3 shows analogous data for homologous aldehydes and carboxylic acids, as well as for selected terpenes.

INSERT FIGURES 2 AND 3 ABOUT HERE

It is apparent from these figures that, for all of the stimuli tested, nasal pungency thresholds lie between one and five orders of magnitude above odor thresholds along the concentration axis (log ppm by volume). Within the various homologous series, both nasal thresholds decline with carbon chain length, albeit at a faster rate for odor than for pungency (at least for the first few members of each series). In various series odor thresholds tend to reach a plateau, whereas pungency thresholds show a "cut-off" effect. This means that, from a certain member on, a nasal pungency threshold cannot be reached with certainty in all repetitions of testing or in all the anosmics tested (even when presenting the stimulus at full vapor saturation). For the different series, the cut-off occurs, approximately, at the level of 1-octanol, octyl acetate, propyl benzene, octanal and hexanoic acid (dashed lines on Figures 2 and 3). Two mechanisms have been proposed to explain the appearance of such cut-offs in homologous series (Franks and Lieb, 1990): a physical one whereby the series reaches a member whose maximum available quantity in the vapor phase falls below the threshold for the effect, and a biological one whereby the series reaches a member

[5] It should be noted, however, that numerous physicochemical properties co-vary (e.g., molecular weight with chain length), making it difficult to ascertain the specific element responsible for any

lacking a key property, e.g., becomes too big to fit a binding pocket or to interact with a receptor site. A systematic exploration of the extent and generality of cut-offs for nasal pungency thresholds along homologous series (e.g., Cometto-Muñiz, Cain, and Abraham, 1998) will provide a better understanding of the physicochemical basis for this chemosensory response.

As mentioned above, measuring eye irritation thresholds constitutes an alternative experimental approach to probe into the trigeminal impact of volatile chemicals. As a general rule, eye irritation and nasal pungency thresholds fall well into register (Figure 4) (Cometto-Muñiz and Cain, 1991; Cometto-Muñiz and Cain, 1995). Nevertheless, there are cases where it is possible to measure a robust eye irritation threshold for an homolog that extends just beyond the cut-off point for nasal pungency (e.g., 1-octanol, octyl acetate) or for certain chemical family member for which no nasal pungency threshold can be firmly measured (e.g., geraniol among the terpenes) (see Figure 4). Also, measurement of continuous psychometric detectability functions for eye irritation (as opposed to measurement of a discrete threshold value) has indicated slightly higher eye than nasal trigeminal sensitivity for 1-butanol but no difference for 2-heptanone (Cometto-Muñiz et al., 1999). The implications and generality of these preliminary findings have not yet been investigated.

INSERT FIGURE 4 ABOUT HERE

Another alternative to assess trigeminal nasal chemosensitivity consists in measuring nasal localization (i.e., lateralization) thresholds. These thresholds tend to overlap or fall slightly above nasal pungency thresholds (Figure 5). Interestingly, roughly the same substances that occasionally or systematically fail to evoke a nasal pungency threshold (cut-off effect) also fail to produce a nasal localization threshold (Cometto-Muñiz and Cain, 1998; Cometto-Muñiz et al., 1998).

INSERT FIGURE 5 ABOUT HERE

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psychophysical change.

When anosmics began to be systematically tested in search of nasal pungency thresholds devoid of odor biases, the question arose of whether their trigeminal sensitivity was comparable to that of normosmics. Normosmics sometimes report considerable pungency at, or even below, the anosmics' thresholds (Cometto-Muñiz and Cain, 1990; Gudziol, Schubert and Hummel, 2001; Kendal-Reed et al., 1998) and such reports tend to show high variability (Kendal-Reed, Walker and Morgan, 2001). Without an experimental design that controls for response biases, this observation could reflect confusion in normosmics between strong odor and pungency or it could reflect different trigeminal sensitivity between anosmics and normosmics. A study of chemo-somatosensory event-related potentials using the strongly trigeminal stimulus carbon dioxide found normosmics to produce a marginally (but significantly) larger peak-to-peak amplitude in the early P1N1 wave than did persons with olfactory impairment (Hummel et al., 1996). In contrast, psychophysical measurements employing forced-choice detection paradigms to minimize response biases have not observed significant differences between anosmics and normosmics in trigeminal chemoreception. For example, eye irritation thresholds measured in normosmics and anosmics employing homologous n-alcohols (Cometto-Muñiz and Cain, 1998) and a group of terpenes (Cometto-Muñiz et al., 1998) are similar in both groups. Detectability functions (which cover the range from chance detection to virtually perfect detection) for eye irritation evoked by 2-heptanone, 1-butanol, butyl acetate, and toluene are also similar in normosmics and anosmics (Cometto-Muñiz et al., 1999; Cometto-Muñiz et al. 2001a). Nasal localization thresholds measured in normosmics and anosmics for n-alcohols (Cometto-Muñiz and Cain, 1998) and terpenes (Cometto-Muñiz et al., 1998) gave a picture of comparable nasal trigeminal sensitivity in both groups since a small advantage for normosmics failed to reach significance. Overall, such data suggest that any difference in trigeminal sensitivity between normosmics and anosmics, if in fact real, is likely small. Along these lines, a study of irritation-induced reflex changes in respiration in mice revealed no effect of anosmia on sensitivity to nasal irritation (Hansen et al., 1994).

E. Quantitative Structure-Activity Relationships (QSARs) for Human Trigeminal Chemosensory Responses

An important feature of the thresholds presented in Figures 2 through 5 is that they were all obtained with a uniform methodology. This included: (1) a two-alternative, forced-choice method with presentation of increasing concentrations (e.g., see Cometto-Muñiz and Cain, 1998), (2) a common criterion for threshold (five correct choices in a row), (3) the same stimulus-delivery technique (the commonly used "squeeze bottle" technique, a form of static olfactometry (Cain, Cometto-Muñiz, and de Wijk, 1992; Doty, 2000), and (4) calibration and direct measurement of the chemical stimulus in the vapor phase via gas chromatography. These characteristics provide the database with a robust intrinsic consistency, essential for comparative studies of quantitative structure-activity relationships. Also of value in such studies is the selection of compounds from diverse chemical families (i.e., homologous series, terpenes) whose properties cover a wide range of values and varied systematically.

1. The Linear Solvation Model

A number of descriptors have been used to correlate sensory irritation. Among them we can mention normal boiling point (Doty et al., 1984; Muller and Greff, 1984), adjusted boiling point (Roberts, 1986), saturated vapor pressure (Nielsen, Thomsen, and Alarie, 1990), the Ostwald solubility coefficient of the irritant (that is, log L where L = concentration in solvent/concentration in gas phase) (Nielsen, Hansen, and Alarie, 1992), and partition coefficients (specifically, water-air and octanol-water) (Doty et al., 1984; Hau, Connell, and Richardson, 1999). Interestingly, all these descriptors are physicochemical parameters and do not involve the precise chemical structures of the compounds. Attempts have also been made to correlate olfactory potency (Anker and Jurs, 1990; Chastrette, 1997; Dravnieks, 1977; Egolf and Jurs, 1993; Hau and Connelll, 1998; Rossiter, 1996; Schnabel, Belitz, and von Ranson, 1988; Shvets and Dimoglo, 1998). For the most part these relationships are difficult to interpret either chemically or mechanistically (Abraham, 1996).

More recently, a linear solvation model was developed that not only provides strong statistical fit but that also conveys chemically and mechanistically meaningful information on both the stimulus (i.e., the chemical irritant) and the receptor biophase responsible for the sensory response. This model was developed by Abraham and has been successfully applied to a number of physicochemical and biochemical processes (Abraham, 1993a; Abraham, 1993b; Abraham, 1996). The approach involves modeling, through a solvation equation, the transfer of the stimulus (i.e., the irritant) from the vapor phase (i.e., the air entering the nose) to a condensed (bio)phase (i.e., the nasal epithelium) and being distributed among various biophases, including the one where reception takes place (i.e., the free nerve endings of the trigeminal nerve). The equation takes the following general form:

$$\log SP = c + r \,.\, R_2 + s \,.\, \pi_2^H + a \,.\, \sum\alpha_2^H + b \,.\, \sum\beta_2^H + l \,.\, \log L^{16} \qquad (1)$$

Here, log SP is the dependent variable, where SP, in our case, is a sensory property: either the reciprocal of the nasal irritation or pungency threshold (1/NPT) or the reciprocal of the eye irritation threshold (1/EIT). We use the reciprocals simply because the larger the quantity, the more potent is the irritant. The independent variables are: excess molar refraction (R_2), dipolarity/polarizability (π_2^H), overall or effective hydrogen-bond acidity ($\sum\alpha_2^H$), overall or effective hydrogen-bond basicity ($\sum\beta_2^H$), and gas-liquid partition coefficient on hexadecane at 298K (L^{16}). The coefficients c, r, s, a, b, and l are found by multiple linear regression analysis. However, these are not simply fitted coefficients since they reflect the complementary properties of the biophase that must be receptive to the chemosensory stimulus. In this way, the independent variables provide a physicochemical characterization of the stimulus, whereas the coefficients provide a physicochemical characterization of the receptive biophase that will interact with that stimulus. The r-coefficient gives the tendency of the biophase to interact with the gaseous volatile through polarizability-type interactions, mostly via electron pairs. The s-coefficient is the measure

of the biophase dipolarity/polarizability (because a dipolar stimulus will interact with a dipolar biophase and a polarizable stimulus will interact with a polarizable biophase). The a-coefficient represents the complementary property to the chemical stimulus hydrogen-bond acidity and thus is a measure of the biophase hydrogen-bond basicity (because a stimulus that is a hydrogen-bond acid will interact with a basic biophase). Similarly, the b-coefficient is a measure of the biophase hydrogen-bond acidity (because a stimulus that is a hydrogen-bond base will interact with an acidic biophase). The l-coefficient is a measure of the biophase lipophilicity.

2. Nasal Irritation or Pungency Thresholds

The values of nasal irritation or pungency thresholds depicted in Figure 2 served to develop the first version of a solvation equation specific for that sensory modality (Abraham et al., 1996). Later on, this equation proved successful not only to describe experimentally-obtained nasal pungency thresholds, but, also, to predict nasal pungency thresholds for volatile organic compounds (VOCs) that were not employed to develop it (i.e., new VOCs not included in the 34 used to build the equation) (Cometto-Muñiz, Cain, and Abraham, 1998). These additional VOCs were the carboxylic acids and aliphatic aldehydes whose measured NPTs, shown in Figure 3, could be accurately predicted (with the exception of acetic acid). In turn, the incorporation of these additional NPTs allowed a refinement of the equation that reads as follows (Abraham et al., 1998a):

$$\log (1/NPT) = - 8.519 + 2.154\ \pi_2^H + 3.522\ \sum\alpha_2^H + 1.397\ \sum\beta_2^H + 0.860 \log L^{16} \qquad (2)$$

Here, NPT stands for nasal pungency threshold in ppm by volume. The number of data points (i.e., VOCs) used in the calculation of this equation was 43, the goodness of fit (r^2) was 0.955, the overall SD in log (1/NPT) was 0.27, with an F statistic = 201. The respective standard deviations for each of the five coefficients were 0.274, 0.343, 0.215, 0.355, and 0.034. The t-test showed all listed coefficients (s, a, b, l) to be significant at or below p = 0.001. In contrast, the r . R2 term of

equation (1) failed to show significance and was discarded. In turn, equation (2) satisfactorily predicted NPTs for selected terpenes (Abraham et al., 1998d; Cometto-Muñiz et al., 1998)

3. Eye Irritation Thresholds

The number of VOCs for which human eye irritation thresholds had been measured with a uniform methodology (Cometto-Muñiz and Cain, 1991; Cometto-Muñiz and Cain, 1995; Cometto-Muñiz, Cain, and Hudnell, 1997) was considerably lower than that for nasal pungency thresholds. This situation hampered the development of a comparable solvation equation for the ocular trigeminal response. Nevertheless, a considerable body of data is available in terms of Draize eye scores in rabbits. Apart form the difference in species tested, the Draize test relies on testing the eyes with pure liquids, not vapors. A recent investigation described a straightforward calculation to convert Draize eye scores for pure organic liquids into scores for the corresponding vapors (Abraham et al., 1998c). With this tool at hand, it was shown, in a follow-up study, that Draize eye scores and eye irritation thresholds in humans can be combined into one QSAR (Abraham et al., 1998b), giving rise to the following equation:

$$\log (1/EIT) = - 7.918 - 0.482\ R_2 + 1.420\ \pi_2^H + 4.025\ \sum\alpha_2^H + 1.219\ \sum\beta_2^H + 0.853\ \log L^{16} \qquad (3)$$

Here, EIT stands for eye irritation threshold in ppm by volume. The number of data points (i.e., VOCs) used in the calculation of this equation was 54, the goodness of fit (r^2) was 0.928, the overall SD in log (1/EIT) was 0.36, and the F statistic = 124. The respective standard deviations for each of the six coefficients were 0.211, 0.307, 0.376, 0.404, 0.455 and 0.048.

4. Applicability of the Solvation Equations

The equations that we have presented above for human nasal and ocular trigeminal chemoreception apply to what can be called “transport” processes. That is, those processes where the key step is either the distribution of a stimulus between biophases or the rate of transfer of the stimulus from one biophase to another. The equations would not apply to stimuli that acted mainly

through exact geometrical or conformational states since changes of that sort in molecular structure would change the above mentioned physicochemical parameters only slightly (if at all), whereas, when relevant, stereochemical differences could change potency dramatically.

Also, the described equations would underestimate the potency of chemically reactive substances (Abraham et al., 1990), i.e., those substances that can directly react with tissue via various mechanisms such as breaking of disulfide bonds, chemical reaction with a nucleophilic group, oxidation, etc. (Nielsen, 1991). In summary, the success of equations (2) and (3) in correlating, and even predicting, human nasal pungency and eye irritation thresholds evoked by relatively nonreactive VOCs suggests that, indeed, the key step in the production of these chemosensory responses is the passive transport of the stimulus to a receptive biophase.

F. Trigeminal Reponses to Mixtures of Chemicals

In situations of everyday life, the chemical senses are stimulated by complex mixtures of substances, and the trigeminal system is certainly no exception. Despite this fact, little is known about how the trigeminal system, in particular, processes stimulation with chemical mixtures (for a discussion of chemical mixtures in olfaction, see Chapter 10). The topic can be addressed at the level of clearly-suprathreshold stimulation and at the level of peri-threshold stimulation. Again, separation of the trigeminal from the olfactory response becomes difficult to accomplish, particularly at the suprathreshold level, since almost all VOCs can stimulate both chemosensory channels. Early investigations with the pungent odorants formaldehyde and ammonia presented in binary mixtures have shown that at low, medium, and high concentrations of the components, the total nasal perceived intensity of the mixtures shifts from hypoadditivity to simple additivity and, finally, to hyperadditivity (Cometto-Muñiz, García-Medina, and Calviño, 1989). In other words, as the concentration of both compounds increased, the intensity of the corresponding mixtures turned out significantly lower than, equal to, and, finally, greater than the sum of its components. The outcome was interpreted to reflect a progressive trigeminal involvement, at the expense of olfactory

involvement, in the overall response. A follow-up study with identical substances and mixtures, where subjects were asked to assess the olfactory (odor) and trigeminal (pungency) attributes of the evoked sensations, confirmed this interpretation since odor was always hypoadditive in mixtures whereas pungency was, mainly, additive, and even suggested hyperadditivity (Cometto-Muñiz and Hernández, 1990).

The approach of testing homologous chemical series for olfactory and trigeminal thresholds served as the basis for an investigation comparing odor, nasal pungency, and eye irritation thresholds for five chemical mixtures against the same thresholds for the individual components of the mixtures (Cometto-Muñiz, Cain, and Hudnell, 1997). The five mixtures tested included: two three-component mixtures, two six-component mixtures, and one nine-component mixture. Given the significant role that lipophilicity of the stimulus plays on both olfactory and trigeminal stimulation, the constituents of the mixtures were selected such that one of the three-component mixtures and one of the six-component mixtures contained relatively low molecular weight, low lipophilicity homologs, whereas the remainding three- and six-component mixtures contained relatively high molecular weight, high lipophilicity homologs. The nine-component mixture contained both types of compounds. The outcome revealed various degrees of stimulus agonism (i.e., additive effects) for the olfactory modality and for the two trigeminal modalities. Degree of agonism increased with number of components and with the lipophilicity of such components, particularly for the trigeminal responses. In fact, synergistic stimulus agonism characterized the eye irritation response to the most complex (the nine-component) and the most lipophilic (one of the six-component) mixtures.

Instead of measuring a threshold according to a fixed criterion of response, a recent study focused on measuring complete detectability (i.e., psychometric) functions for 1-butanol and 2-heptanone singly and in binary mixtures of varying proportions (Cometto-Muñiz et al., 1999). Again, the chemosensory responses comprised odor, nasal pungency, and eye irritation. Knowledge

of the detectability function for each individual substance allowed the calculation of sensory equivalent concentrations, that is, concentrations of the two chemicals that produced the same percentage of detectability. In turn, this allowed to express all stimuli, single and mixtures, in concentration units of one (or the other) compound. The outcome showed that a single function could fit these combined data for each sensory endpoint, lending support, as a first approximation, to the notion of chemosensory agonism (in the sense of dose additivity) between the members of binary mixtures presented at perithreshold levels (Figure 6). Very recent studies on the nasal pungency and eye irritation detectability of mixtures of butyl acetate and toluene have confirmed the outcome of complete sensory agonism in mixtures of relatively low detectability (but still above chance detection) and have indicated a partial loss of sensory agonism in mixtures of relatively high detectability (but still below perfect detection) (Cometto-Muñiz et al., 2001b).

INSERT FIGURE 6 ABOUT HERE

G. Psychophysical Interactions between the Olfactory and Trigeminal Systems

In light of the physiological interactions between the olfactory and trigeminal systems that were mentioned earlier, one might expect that stimulation of CN V might alter sensations derived from stimulation of CN I. There is some mention of this in the early literature. Thus, as noted by Cain and Murphy (1980), it was reported by Alexander Bain in 1868 that "if a current of carbonic acid accompanies an odour, the effect (odour) is arrested." In 1930, Katz and Talbert reported that the irritation property of some odorants with both odor and irritative properties predominates at high concentrations, suggesting that CN V stimulation is masking CN I-mediated perception.

More recent support for this concept comes from a study by Cain and Murphy (1980). These investigators had eight subjects judge the perceived magnitude (i.e., intensity) of four concentrations of n-amyl butyrate, four concentrations of carbon dioxide, and all 16 combinations of these mixtures. The stimuli were presented to one nostril only, and magnitude estimates were made using the method of magnitude estimation (where subjects assign numbers relative to

the perceived magnitude of the stimuli; see Chapter 10). The subjects first judged the magnitude of the overall sensory experience, and then of the odor and irritative components. A similar experiment, in which the CO_2 was presented to one nostril and the odorant to the other, was also performed using 10 subjects. Overall, the perceived magnitude of the n-amyl butyrate appeared to be suppressed by the CO_2, and vice versa (i.e. , the magnitude of irritation was depressed by some concentrations of n-amyl butyrate), even when the odorant and irritative stimuli were presented to separate nares. This suggested to these authors that the locus of interaction was in the central nervous system.

H. Environmental Applications of Psychophysical Measurements

Separation of trigeminal from olfactory chemosensory responses evoked by airborne chemicals constitutes a central aspect to many environmental areas. Two of the most relevant areas involve occupational or industrial exposures and non-industrial (including residential) exposures. Regarding industrial exposures, it has been estimated that about 40% of the Threshold Limit Values (TLV's) established by the American Conference of Governmental Industrial Hygienists (ACGIH) (American Conference of Governmental Industrial Hygienists, 1994) for industrial and occupational exposures are based on sensory irritation (Alarie, 1981). This includes, primarily, irritation of the eyes, nose, and throat. In these environments the substance (or group of substances) that could be responsible for symptoms of sensory irritation is (are) typically known from the materials and processes used in that particular setting. The critical information consists in establishing the concentrations at which these compounds singly or in mixture begin to evoke irritative responses, as well as noticeable odors. Once such levels are established, TLV's can be chosen that avoid untoward symptoms. An animal bioassay based on the respiratory frequency depression of mice exposed to irritants (Alarie, 1966; Alarie, 1973) has been used to extrapolate probable human irritation responses (Alarie, 1981), but the suitability of the test has been questioned (Bos et al., 1992). The strategies described in this chapter to separate olfactory from

trigeminal responses provide the means to assess directly in humans the irritative properties of airborne chemicals, at least for those whose health effects of concern at environmentally realistic concentrations rest on sensory irritation.

Regarding non-industrial exposures, there is growing concern about the high incidence of occurrence of certain health and toxicological effects in indoor environments such as office buildings, schools, and even residential buildings. A percentage of occupants of these indoor spaces report such symptoms as headache, difficulty in concentration, drowsiness, and lassitude, with symptoms of sensory irritation of eyes, nose, and throat figuring prominently (Cometto-Muñiz and Cain, 1992). This wide array of symptoms has been referred to as the "sick building syndrome" (Apter et al., 1994). It is likely that a number of chemical and physical agents might be involved in the production of these symptoms but it is recognized that VOCs play an important role (Hodgson, Levin, and Wolkoff, 1994; Kostiainen, 1995; Rothweiler and Schlatter, 1993). Given the prevalence of trigeminally-mediated responses in problematic indoor environments, studies of this chemoreceptor system can contribute substantially to the understanding, prevention, and control of their appearance. Among the most relevant issues are (1) understanding the physicochemical basis for the production of sensory irritation by VOCs so that better and less offending materials can be employed within buildings (e.g., those used in furnishings, carpets, paints, etc.) and (2) knowledge of how individual members of complex mixtures produce their combined trigeminal impact, allowing for the translation of chemical measurements into corresponding irritative sensory responses.

It should be pointed out that the trigeminal and olfactory thresholds cited here have been measured with the "squeeze bottles" (Amoore and Ollman, 1983; Cain, 1989; Doty, 2000). As shown above, this simple and convenient delivery system produced a robust picture of relative chemosensory potency within and across homologous series and chemical families. Nevertheless, the thresholds obtained might not be, in absolute terms, the values produced under environmentally

realistic conditions such as whole-body exposures. A very recent investigation of nasal pungency thresholds in homologous alcohols, acetates, and ketones has found that an improved delivery system (based on glass vessels) produced thresholds uniformly lower than those produced via the plastic squeeze bottles by a factor of 4.6, although the relative potency of the homologs remained essentially unaltered (Cometto-Muñiz et al., 2000). Additional studies should provide insight into the relationship between chemosensory thresholds measured via various delivery systems and those obtained in whole-body exposures.

IV. SUMMARY

In this chapter, basic aspects of the anatomy, physiology, and chemical responsiveness of the human trigeminal system were reviewed. Additionally, studies demonstrating that ocular trigeminal sensitivity may be similar to intranasal trigeminal sensitivity were reviewed. Among other topics addressed were the functional dissociation of CN I and CN V responses, the application of modern structure-activity studies in predicting irritative responses of volatiles, and an assessment of potential functional interactions between CN I and CN V. It is apparent from the material reviewed in this chapter that the trigeminal system is generally less sensitive to volatile agents than the olfactory system, and very few, if any, odorants fail to stimulate CN V at high enough concentrations. It is pointed out that knowledge of the factors responsible for nasal and ocular irritation is not only of theoretical interest, but of practical interest as well, particularly in relation to environmental concerns.

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Figure Legends

Figure 1. Primary branches of the trigeminal nerve that innervate the nasal and oral cavities. (Reprinted with permission from Silver, 1987).

Figure 2. Thresholds for nasal pungency (filled circles) and odor (empty circles) along homologous series of alcohols, acetates, ketones, and alkylbenzenes. Only primary and unbranched homologs are joined by a line. Stretches of dotted lines on nasal pungency thresholds show those members for which pungency begins to fade or cut-off (see text). Bars, sometimes hidden by the symbol, indicate standard deviations.

Figure 3. Thresholds for nasal pungency (filled circles) and odor (empty circles) along homologous series of aliphatic aldehydes and carboxylic acids, as well as along selected terpenes. Stretches of dotted lines on nasal pungency thresholds show those members for which pungency begins to fade or cut-off (see text). For six terpenes a threshold for nasal pungency could not be evoked. Only two of the remaining six terpenes (carene and cineole) evoked nasal pungency in all repetitions and all anosmics (Cometto-Muñiz et al., 1998). Bars, sometimes hidden by the symbol, indicate standard deviations.

Figure 4. Thresholds for nasal pungency (in anosmics) (filled squares, continuous lines) and for eye irritation (in normosmics) (empty triangles, dotted lines) along homologous alcohols, acetates, ketones, and alkylbenzenes, and along selected terpenes. Bars, sometimes hidden by the symbol, indicate standard deviations.

Figure 5. Comparison of thresholds for odor (empty squares), nasal pungency (filled squares), and nasal localization (circles) along homologous n-alcohols and selected terpenes.

Figure 6. Showing how a single detectability function for odor (upper panel), nasal pungency (middle panel) and eye irritation (lower panel) fits the detection data for two single chemicals (2-heptanone: filled circles, and 1-butanol: filled squares) and their various binary mixtures (all other symbols) when all stimuli are expressed in concentrations units of one chemical (here, 2-heptanone) via the concept of sensory equivalent concentrations (see text). The equation that best fits the experimental data for each sensory modality is shown on each graph.

Table 1. Mean Intensity Rating Scale Values (± SD) of Anosmic, Trigeminal-Focus, and Normal Experimental Groups of Doty et al. (1978) Study. Maximum Possible Rating = 9.

Compound	Anosmic group		Trigeminal-focus group		Normal group
	Proportion Detecting	Intensity	Proportion Detecting	Intensity	Intensity
Decanoic acid	00/15	0.00(0.00)	01/15	0.13(0.05)	4.07(2.14)
Vanillin	00/15	0.00(0.00)	00/15	0.00(0.00)	4.20(1.68)
Phenyethanol	01/15	0.13(0.50)	04/15	0.80(1.51)	4.40(1.96)
Eugenol	01/15	0.13(0.50)	02/15	0.67(1.85)	5.20(1.56)
Coumarin	02/15	0.13(0.34)	02/15	0.20(0.54)	4.60(1.36)
Nonane	03/15	0.27(0.57)	05/15	1.07(2.02)	4.53(2.25)
Octane	03/15	0.27(0.57)	04/15	1.13(1.86)	4.33(1.96)
Indole	03/15	0.53(1.20)	05/15	1.13(1.86)	4.60(1.99)
α-Terpineol	05/15	0.53(1.02)	07/15	1.20(1.47)	5.60(1.78)
Geranoil	02/15	0.60(1.54)	04/15	0.87(1.71)	5.13(1.31)
Heptanoic acid	05/15	0.87(1.45)	03/15	0.33(0.70)	4.80(2.01)
Limonene	06/15	0.93(1.44)	08/15	1.60(1.96)	5.40(1.86)
Hexanoic acid	07/15	0.93(1.39)	04/15	1.07(2.21)	5.33(1.78)
Heptane	05/15	1.00(1.86)	04/15	1.13(2.22)	4.67(2.15)
Benzyl acetate	07/15	1.40(2.12)	08/15	1.80(2.34)	4.87(2.03)
Methyl salicylate	09/15	1.60(1.86)	10/15	2.46(2.25)	6.27(1.88)
β-Ionone	09/15	1.93(2.21)	10/15	2.47(2.28)	4.47(2.31)
Anethole	08/15	2.73(2.86	07/15	1.47(2.16)	5.93(1.06)
Heptyl alcohol	13/15	2.80(1.80)	09/15	1.93(1.88)	5.13(1.67)
Guaiacol	13/15	2.80(1.87)	09/15	2.73(2.77)	5.93(1.34)
Citral	12/15	2.87(2.25)	07/15	1.73(2.35)	5.53(1.75)
Camphor	14/15	3.53(2.09)	12/15	3.87(2.90)	6.00(1.51)
4-Methylvaleric acid	09/15	3.93(3.68)	06/15	1.07(1.84)	6.20(2.43)
Linalool	13/15	4.00(2.37)	09/15	2.53(2.47)	6.00(1.82)
n-Butyl ether	13/15	4.00(2.10)	12/15	3.73(2.70)	6.53(1.41)
Valeric acid	15/15	5.00(2.16)	14/15	3.80(2.66)	6.00(2.22)
2,4-Pentanedione	15/15	5.57(1.29)	14/15	5.27(2.65)	7.13(1.20)
Furfural	15/15	6.07(1.24)	14/15	5.33(2.55)	6.00(1.93)
Menthol	15/15	6.14(0.92)	14/15	5.80(2.20)	6.60(1.41)
iso-Amyl acetate	15/15	6.67(1.19)	13/15	5.73(3.02)	6.67(1.81)
n-Butyl alcohol	15/15	6.67(1.30)	14/15	5.87(3.01)	6.13(1.54)
Acetaldoxime	15/15	6.71(0.80)	14/15	5.93(2.32)	7.00(1.41)
2-Heptanone	15/15	6.73(1.00)	15/15	6.80(2.34)	7.53(1.02)
iso-Valeric acid	15/15	6.73(1.24)	14/15	6.27(2.32)	7.47(1.26)
Ethyl benzene	15/15	6.87(2.00)	14/15	6.60(3.34)	6.73(1.24)
n-Butyl acetate	15/15	7.33(1.08)	13/15	5.93(2.93)	6/93(1.48)
Ethyl acetate	15/15	7.53(1.02)	15/15	7.40(1.93)	7.60(0.95)
Methanol	15/15	7.67(1.14)	15/15	6.80(2.23)	6.93(1.29)
Benzaldehyde	15/15	7.73(0.93)	15/15	7.87(1.36)	7.33(1.08)

Cyclohexanone	15/15	7.80(1.38)	14/15	6.27(2.54)	7.40(1.25)
Toluene	15/15	7.87(1.09)	14/15	7.13(2.60)	6.80(1.51)
Butyric acid	15/15	7.87(0.96)	15/15	7.00(2.42)	7.93(1.34)
Acetal	15/15	8.13(1.15)	14/15	7.87(2.28)	7.93(1.12)
Ethyl methyl ketone	15/15	8.40(0.61)	14/15	7.33(2.09)	8.40(0.71)
pyridine	15/15	8.47(0.72)	15/15	8.13(2.00)	8.13(1.31)
Acetone	15/15	8.53(0.88)	15/15	8.13(1.41)	7.93(1.73)
Propionic acid	15/15	8.73(0.57)	15/15	8.27(1.73)	8.47(0.88)

See text for details.

FIGURE 1

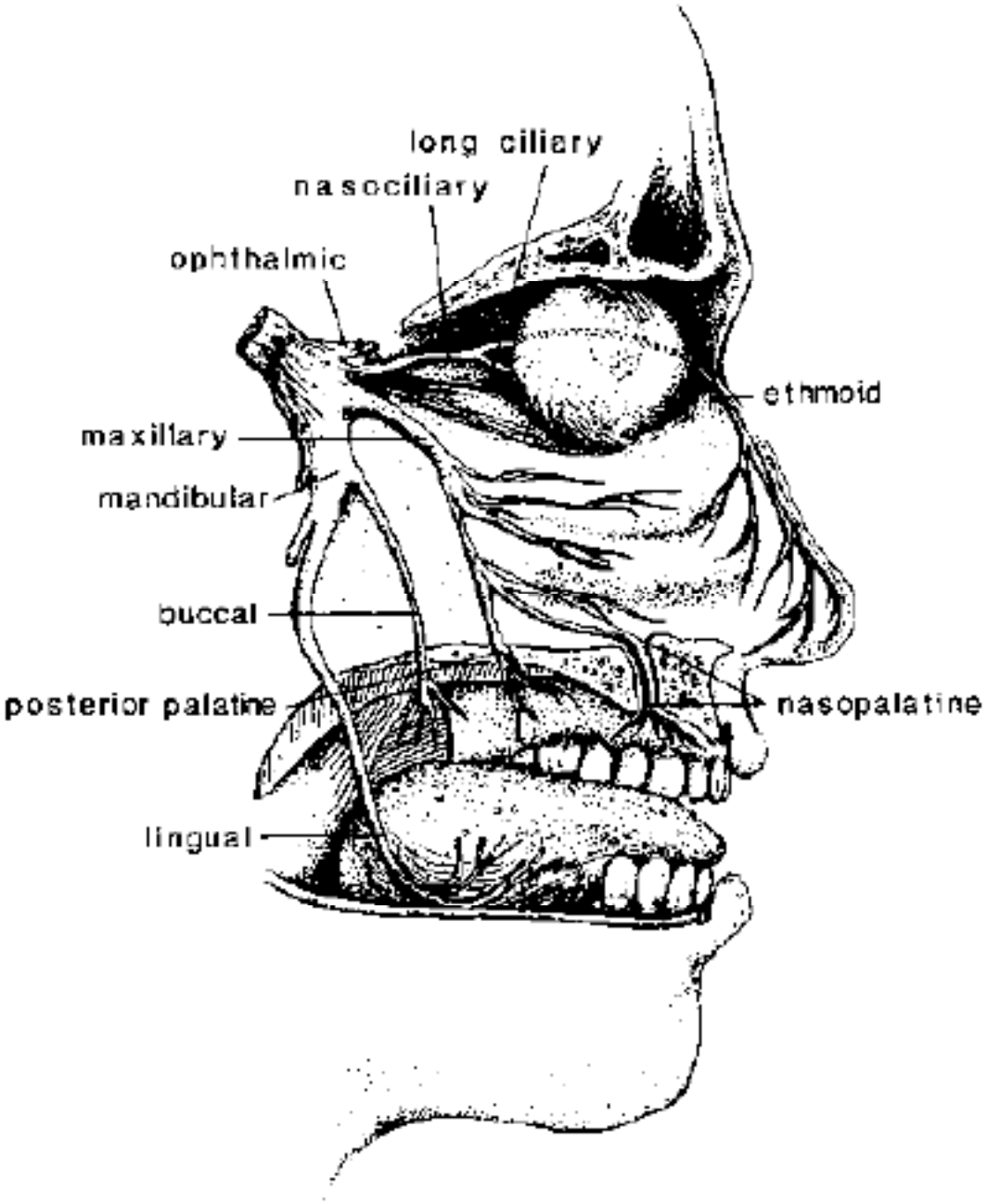

long ciliary
nasociliary
ophthalmic
ethmoid
maxillary
mandibular
buccal
posterior palatine
nasopalatine
lingual

FIGURE 2

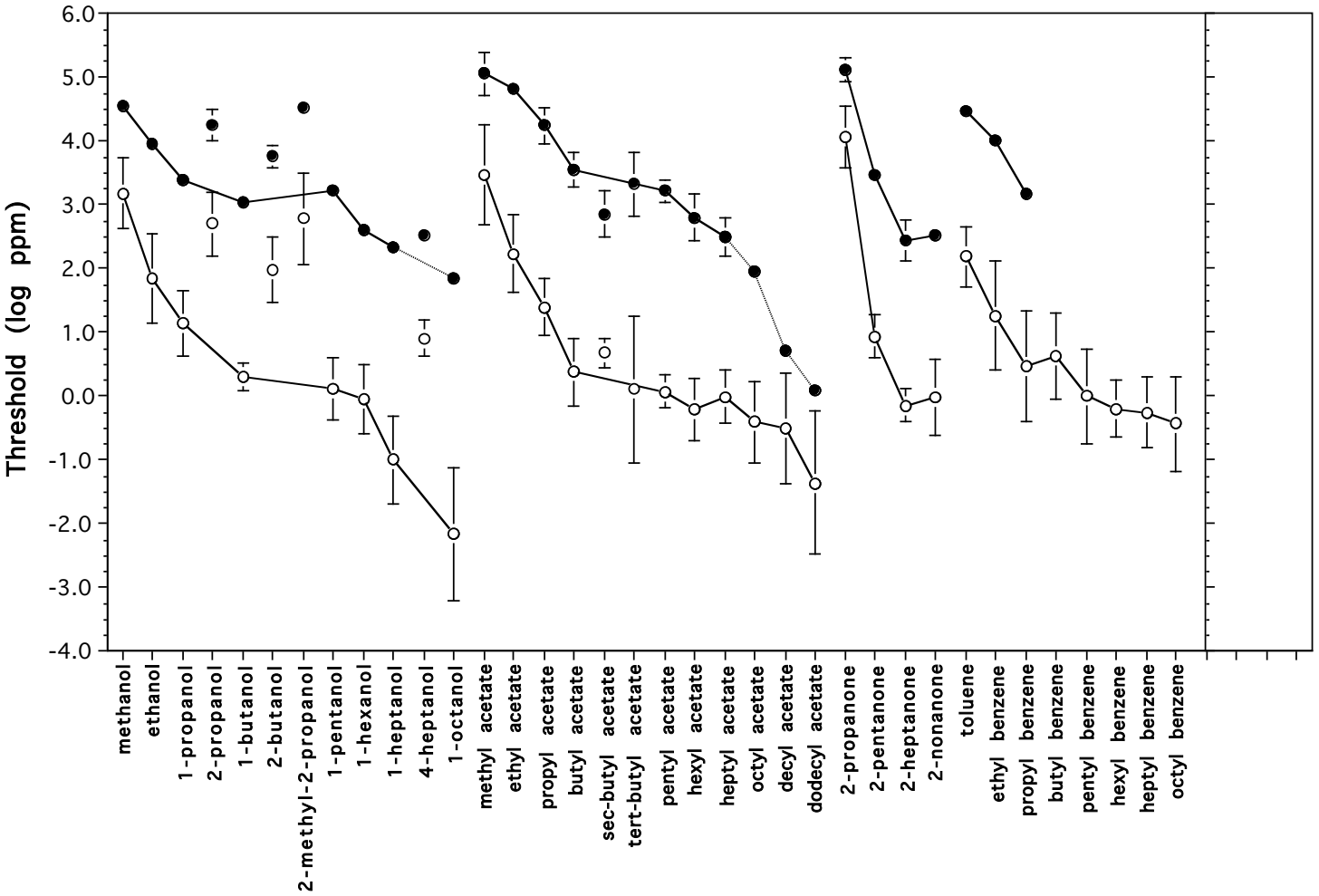

Threshold (log ppm)
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
-4.0
methanol
ethanol
1-propanol
2-propanol
1-butanol
2-butanol
2-methyl-2-propanol
1-pentanol
1-hexanol
1-heptanol
4-heptanol
1-octanol
methyl acetate
ethyl acetate
propyl acetate
butyl acetate
sec-butyl acetate
tert-butyl acetate
pentyl acetate
hexyl acetate
heptyl acetate
octyl acetate
decyl acetate
dodecyl acetate
2-propanone
2-pentanone
2-heptanone
2-nonanone
toluene
ethyl benzene
propyl benzene
butyl benzene
pentyl benzene
hexyl benzene
heptyl benzene
octyl benzene

FIGURE 3

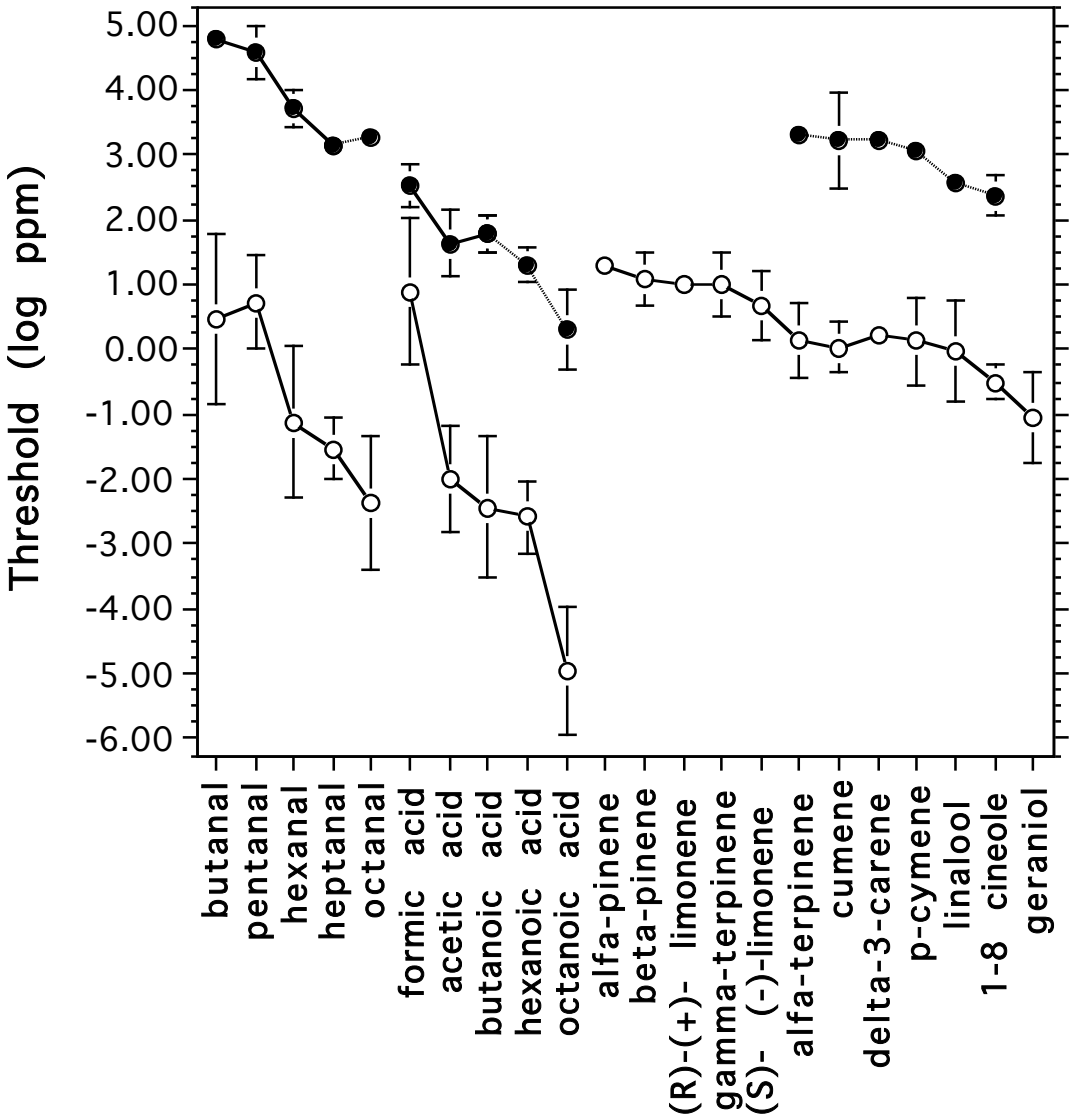

Threshold (log ppm)
5.00
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00
butanal
pentanal
hexanal
heptanal
octanal
formic acid
acetic acid
butanoic acid
hexanoic acid
octanoic acid
alfa-pinene
beta-pinene
(R)-(+)- limonene
gamma-terpinene
(S)- (-)-limonene
alfa-terpinene
cumene
delta-3-carene
p-cymene
linalool
1-8 cineole
geraniol

FIGURE 4

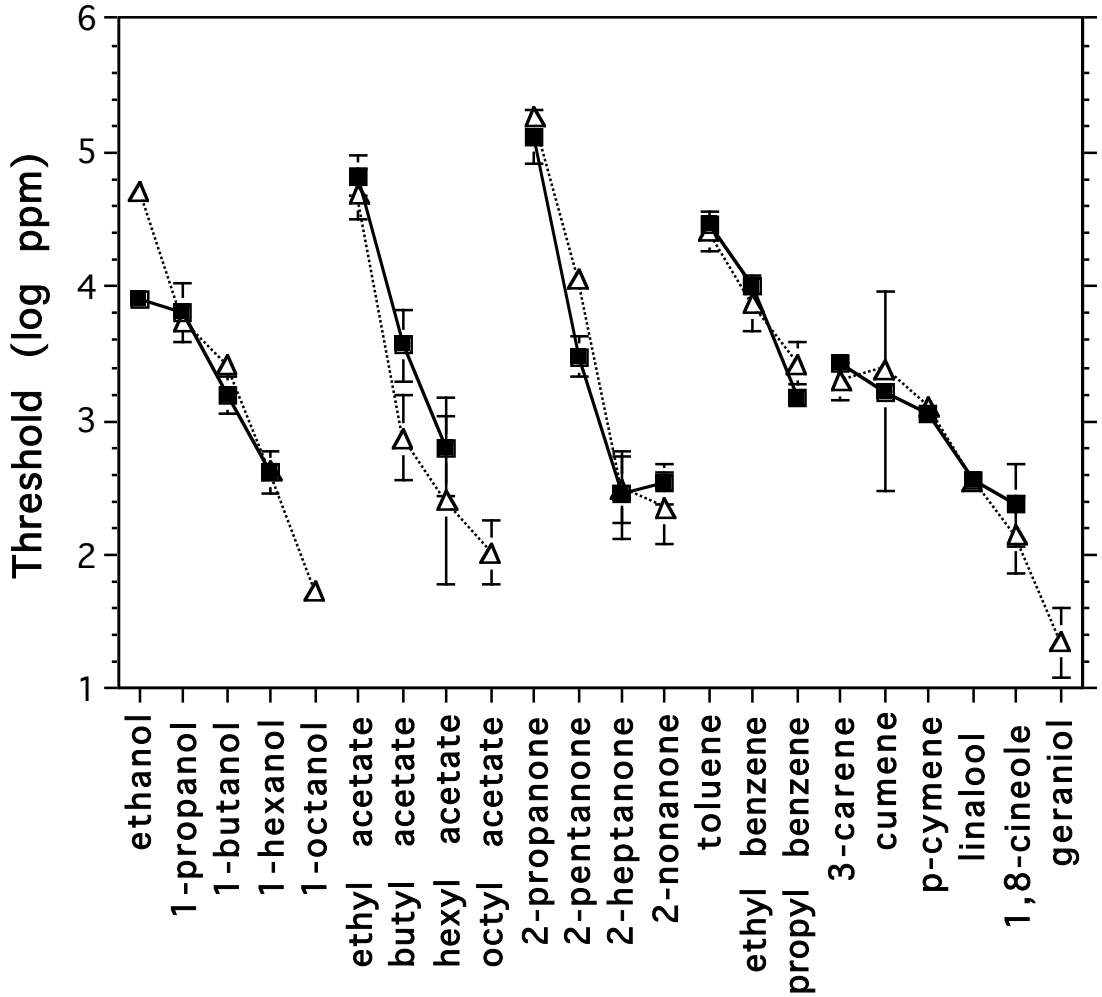

Threshold (log ppm)
6
5
4
3
2
1
ethanol
1-propanol
1-butanol
1-hexanol
1-octanol
ethyl acetate
butyl acetate
hexyl acetate
octyl acetate
2-propanone
2-pentanone
2-heptanone
2-nonanone
toluene
ethyl benzene
propyl benzene
3-carene
cumene
p-cymene
linalool
1,8-cineole
geraniol

FIGURE 5

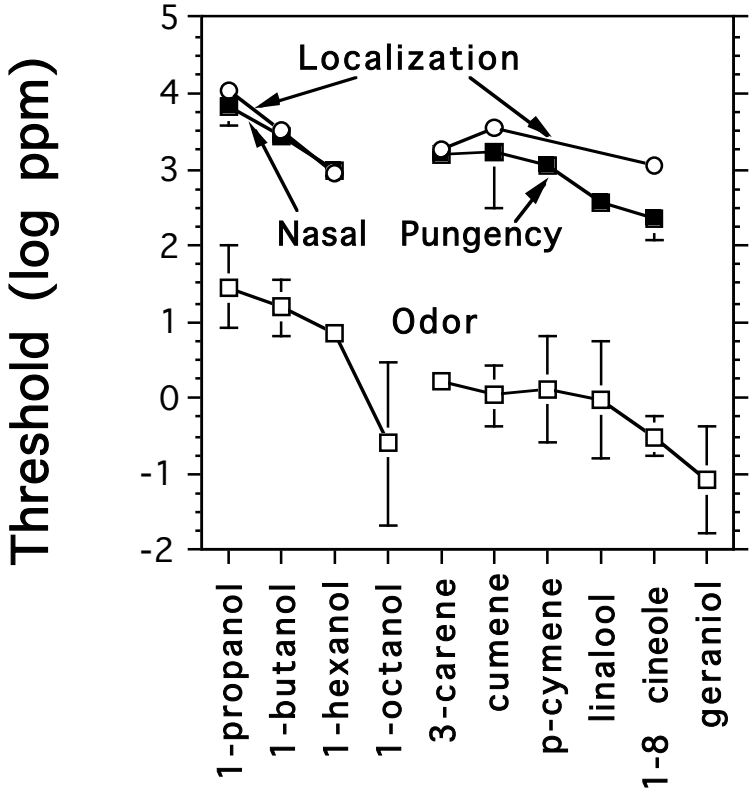
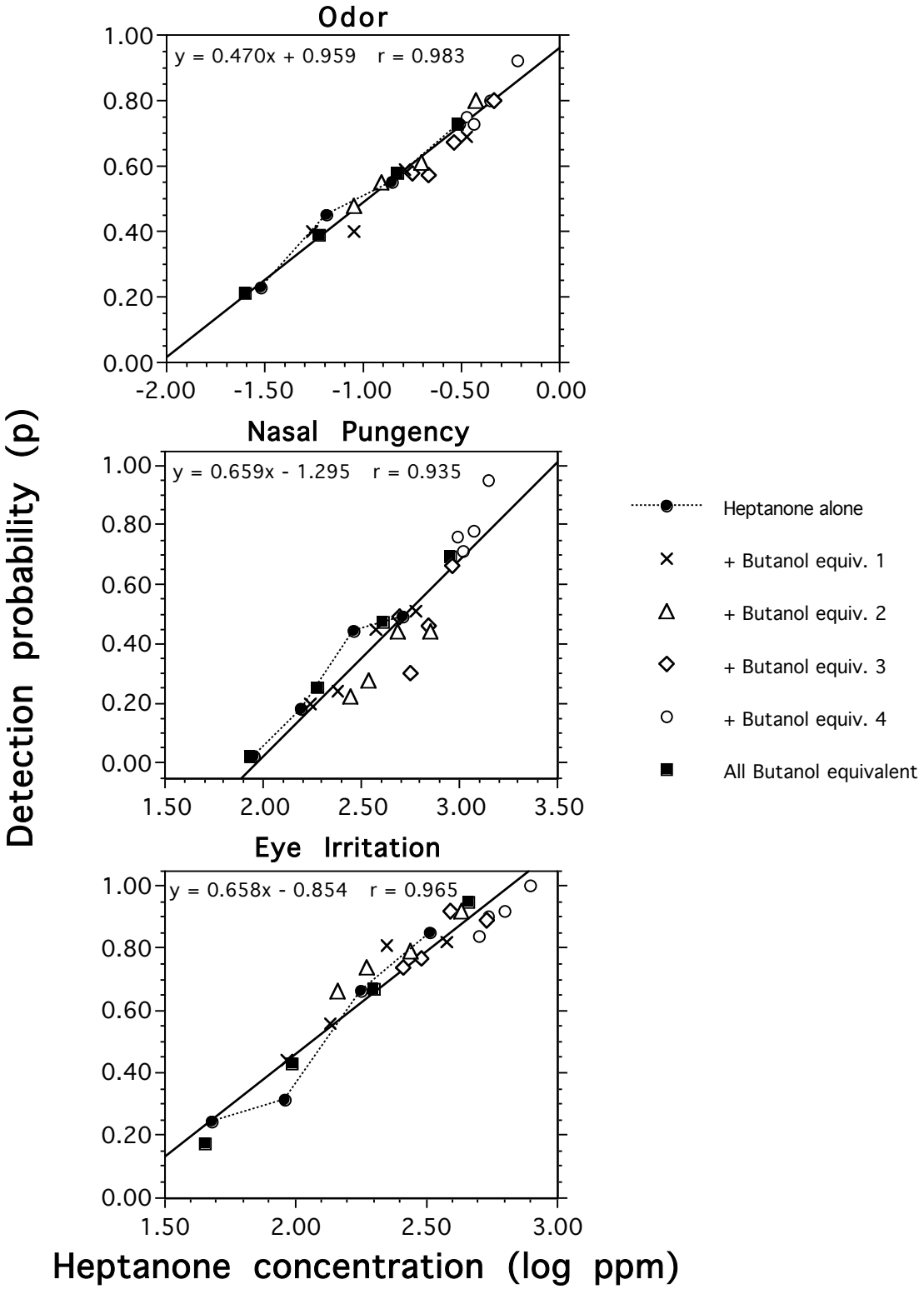

Threshold (log ppm)
5
4
3
2
1
0
-1
-2
Localization
Nasal
Pungency
Odor
1-propanol
1-butanol
1-hexanol
1-octanol
3-carene
cumene
p-cymene
linalool
1-8 cineole
geraniol

FIGURE 6


Odor
y = 0.470x + 0.959 r = 0.983
Nasal Pungency
y = 0.659x - 1.295 r = 0.935
Eye Irritation
y = 0.658x - 0.854 r = 0.965
Detection probability (p)
Heptanone concentration (log ppm)
Heptanone alone
+ Butanol equiv. 1
+ Butanol equiv. 2
+ Butanol equiv. 3
+ Butanol equiv. 4
All Butanol equivalent