OLFACTION AND MULTIPLE CHEMICAL SENSITIVITY

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In this paper, a description of olfactory anatomy is presented, followed by a brief review of modern procedures for testing olfactory function. Information from the sole study which has quantitatively examined olfactory function in patients with apparent multiple chemical sensitivity (MCS) is presented. In essence, this study suggests that MCS is associated with increased nasal airflow resistance, respiration rate, heart rate, and scores on the Beck Depression Inventory, but not with significant changes in odor detection threshold sensitivity to phenyl ethyl alcohol and methyl ethyl ketone, the two target stimuli evaluated. Whether MCS patients evidence hypersensitivity to other chemicals is unknown.

INTRODUCTION

The human sense of smell determines to a large degree the flavor of foods and beverages, and is responsible for a wide variety of aesthetic experiences. Losses or distortions of this sense significantly alter the quality of life, including the appreciation of fine wine, perfumes, and fresh spring air. Importantly, abnormalities in the ability to smell can lead to death or severe injury, as when persons with limited mobility, such as the aged, are unable to detect the smell of fire, leaking natural gas, fireplace effluence, automobile exhaust fumes, or smoke. In a recent study of 750 consecutive patients presenting to the University of Pennsylvania Smell and Taste Center with complaints of disordered chemosensation, 68% viewed their dysfunction as effecting their quality of life, 56% indicated that the problem altered their daily living and/or psychological well being, and 46% reported that the problem changed either their body weight or appetite (Deems et al., 1991).

Decreased ability to smell is quite common. For example, approximately half of individuals between the ages of 65 and 80 years of age have major difficulty in smelling odors (Doty et al., 1984b). In contrast, increased ability to smell is rare, and its prevalence in the general

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population is unknown. Despite the fact that there are reports of heightened olfactory sensitivity in patients with adrenal cortical insufficiency (Henken and Bartter, 1966) and cystic fibrosis (Henken and Powell, 1962), such hypersensitivity has not been confirmed by others. Indeed, in the case of cystic fibrosis, decreased, not increased, sensitivity has been reported. Thus, Hertz et al. (1975) found that cystic fibrosis patients exhibit decreased sensitivity to the odor of n-butanol. A similar decrease in threshold sensitivity to the odorant phenylethylmethylethylcarbinol, as well as in odor identification ability, was noted by Weiffenbach and McCarthy (1984) in such patients. Importantly, only a small subgroup of the 20 patients examined in this study evidenced marked olfactory dysfuction, with most being either normal or only minimally different from controls.

To our knowledge, only one study has examined the olfactory sensitivity and nasal resistance of individuals reporting symptoms consistent with the diagnosis of multiple chemical hypersensitivity (MCS)(Doty et al., 1988b). Although this study, which is described in detail later in this chapter, found no evidence of MCS-related heightened olfactory sensitivity to the two odorants studied, phenyl ethyl alcohol and methyl ethyl ketone, it did find that MCS patients had more resistance to nasal airflow than did matched normal controls.

The purpose of this chapter is to briefly describe (a) the anatomy of the olfactory system, (b) basic psychophysical procedures for assessing its function, and (c) the olfactory function of patients with presumed multiple chemical hypersensitivity. The reader is referred elsewhere for more detailed reviews of the first two of these topics (e.g., Getchell et al., 1991; Serby and Chober, 1992; Doty, 1995).

BRIEF DESCRIPTION OF THE ANATOMY OF THE OLFATORY SYSTEM

Volatile chemicals enter the nose where they may, depending upon a number of physicochemical factors, activate cells of the olfactory nerve (CN I) and/or free nerve endings from the ophthalmic and maxillary divisions of the trigeminal nerve (CN V). The latter nerve filaments are distributed throughout the nasal mucosa, including the olfactory neuroepithelium (Figure 1). Some inhaled chemicals also stimulate free nerve endings within the oral pharynx and cavity, such as those from the glossopharyngeal (CN IX) and vagus (CN X) nerves. However, qualitative sensations commonly termed odor are mediated solely by the olfactory nerves (CN I); the sensations mediated by CN V, IX, and X are largely somatosensory in nature, such as warmth/coolness, irritation, and pungency (Silver, 1987).

Although olfactory receptor cells have the propensity to replenish themselves at regular intervals, replacement does not always occur, particularly when marked damage to the olfactory membrane has taken place (e.g., Hurtt et al., 1988). Furthermore, the regenerative process is influenced by a number of factors, including the quality of the air, metabolic factors associated with age or health, and hormonal status (see Matulionis, 1982; Hinds et al., 1984; Breipohl et al. 1986; Rehn et al., 1986).
The unmyelinated axons of the olfactory receptor cells collect into bundles and course through the foramina of the cribriform plate into the olfactory bulb. Synapses with second order neurons are then made in the bulb within round structures termed glomeruli, which receive many more incoming axons than outgoing dendrites from the second order cells. The major second order neurons (mitral and tufted cells) project to higher brain centers within the primary olfactory cortex, which includes the anterior olfactory nucleus, the olfactory tubercle, the piriform cortex, the lateral entorhinal cortex, and the periamygdaloid cortex. Interbulbar communication occurs via the anterior commissure, and complex intrabulbar connections are present between interglomerular cells, periglomerular cells, granule cells, and numerous collateral projections from the mitral and tufted cells. The olfactory bulb receives centrifugal fibers from various parts of the brain, including most of those to which it projects. Many of these fibers arrive via the ipsilateral lateral olfactory tract and typically synapse within the external plexiform and granule cell layers of the bulb. However, terminations are found in all layers of the bulb, with the exception of the olfactory nerve fiber layer (Powell and Cowan, 1963; Powell et al., 1965). Centrifugal fibers also project from the contralateral side, but are small in number and rarely extend beyond the mitral cell layer (Powell et al., 1965; for recent reviews of olfactory anatomy, see Scott and Harrison, 1986; Price, 1987; Greer, 1991; Moran et al., 1991; Shipley and Reyes, 1991).

The entorhinal cortex, in addition to receiving direct projections from the bulb, also receives projections from the prepiriform and periamygdaloid cortices (Powell et al., 1965). Although there is no direct pathway between the olfactory bulb and the hippocampus, connections are present between the entorhinal cortex and the hippocampus, reportedly giving the olfactory system the most direct access of all sensory systems to the latter structure (Shipley and Reyes,
The hypothalamus receives projections from both the olfactory bulbs and the amygdala (Powell et al., 1965). Importantly, the orbitofrontal cortex receives direct projections from the primary olfactory cortex, as well as indirect projections from the entorhinal cortex via a relay in the dorsomedial nucleus of the thalamus (Powell et al., 1965).

MODERN STIMULUS PRESENTATION AND PSYCHOPHYSICAL PROCEDURES FOR ASSESSING OLFACTORY FUNCTION

A wide variety of procedures have been developed for presenting odorants to subjects (see Doty and Kobal, 1995, for review). With the exception of the measurement of event-related electrical responses (where precise timing of stimulus presentation is required), meaningful assessment of olfactory function can be made using rather simple stimulus presentation equipment. Thus, for most purposes, it is not necessary to know the number of molecules which enter the nose in order for an olfactory test to be valid. The key issues are whether a test procedure is sensitive and reliable, and whether normative data are available to establish whether a subject's performance on the test is normal or not. Among the most popular means of presenting odors to subjects are (i) glass sniff bottles (e.g., Cheesman and Townsend, 1956; Doty et al., 1986), (ii) glass rods, wooden sticks, or strips of blotter paper dipped into odorants (e.g., Toyota et al., 1978), (iii) plastic squeeze bottles (e.g., Amoore and Ollman, 1983; Cain et al., 1988) and (iv) microencapsulated "scratch and sniff" odorized strips (Doty et al., 1984a). Because tests based upon electrical responses are presently (i) largely experimental, (ii) not widely available, (iii) applicable to only some subjects, and (iv) comparatively expensive, they are not discussed here. The reader is referred elsewhere for such a discussion (Doty and Kobal, 1995).

A common psychophysical means for assessing chemosensory function is to establish, operationally, the lowest concentration of a stimulus that can be discerned, i.e., the absolute threshold. Since the olfactory system is dynamic and olfactory sensitivity fluctuates from moment to moment, such a measure is only an estimate of basal sensitivity. At very low odorant concentrations qualitative odor sensations (e.g., "banana-like") are rarely perceived, as only a faint presence of something is noted. In most modern olfactory detection threshold tests, a subject is asked to indicate, on a given trial, which of two or more stimuli (e.g., an odorant and one or more blanks) smells strongest, rather than to report whether an odor is perceived or not. Such "forced-choice" tests are less susceptible than non-forced choice tests to contamination by response biases (i.e., the conservatism or liberalism in reporting the presence of an odor under uncertain conditions) and are more reliable and sensitive (Blackwell, 1953; Doty et al., 1994a).

Two types of threshold procedures which have received wide use in the clinic are the ascending method of limits and the single staircase procedures. In the ascending method of limits procedure, odorants are presented sequentially from low to high concentrations and the point of transition between detection and no detection is estimated. In the single staircase method (a variant of the method of limits technique; see Cornsweet, 1962; Deems and Doty,
1987), the concentration of the stimulus is increased following trials on which a subject fails to detect the stimulus, and decreased following trials where correct detection occurs.

An alternative and equally sensitive approach for assessing olfactory function derives from test measurement theory and focuses on the comparative ability of subjects to identify a number of odorants at the suprathreshold level. The most popular test using this approach — the University of Pennsylvania Smell Identification Test (UPSIT; commercially available as the Smell Identification Test,™ Sensonics, Inc., Haddon Heights, NJ) — has been administered in over 2500 clinics in North America. The number of correct items out of 40 (presented in a forced-choice multiple alternative format) serves as the test measure. This value is compared to normative data and a percentile rank is determined, depending upon the age and gender of the patient (Doty, 1983). The UPSIT has several unique features, including amenability to self administration, a means for detecting malingering, and lack of dependence upon complex equipment or cumbersome sniff bottles. Importantly, this test is very reliable (test-retest reliability $r > 0.90$) and sensitive to even subtle olfactory deficits present in a number of diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Kallmann's syndrome, Korsakoff's psychosis, Parkinson's disease, and schizophrenia (e.g., Deems et al., 1991; Doty, 1991, 1992; Doty et al., 1988).

It should be noted that test scores from most nominally distinct psychophysical tests of olfactory function (e.g., tests of odor identification, detection, discrimination, and memory) are intercorrelated and likely measure, at least in normal subjects spanning a wide age range, a common source of variance (Doty et al., 1994b). Since, however, different tests have different degrees of reliability, they can be differentially sensitive to olfactory deficits, a problem which is particularly critical when small groups of subjects are tested. Thus, when an olfactory deficit is found by one type of test but not by another, the discrepant findings must be cautiously interpreted, as the test which does not detect a deficit may simply be less sensitive or reliable than the one that does. The lack of independence among nominally distinct tests can also lead to problems in the interpretation of test results. For example, while a patient may do poorly on a test of "odor memory," such performance could reflect an inability to detect or recognize odorants, rather than a deficit in odor memory, per se.

OLFACTORY FUNCTION IN PATIENTS WITH APPARENT MULTIPLE CHEMICAL SENSITIVITY

A common complaint of persons with symptoms of multiple chemical sensitivity (MCS) is heightened ability to smell (Randolph and Moss, 1980). Therefore, it was of interest to us whether olfactory thresholds are altered in persons complaining of somatic hypersensitivity to environmental chemicals (Doty et al., 1988b). We hypothesized that odor detection thresholds for phenyl ethyl alcohol (a major component of rose oil) and methyl ethyl ketone (a common solvent) would be lower in MCS patients than in normal controls. Since no common underlying physiologic basis for MCS has been identified and there is lack of consensus regarding the specific factors necessary for a primary diagnosis of MCS, we operationally
defined MCS on the basis of the following: (i) historical evidence of adverse effects to environmental chemicals; (ii) the achievement of a high score on a quantified version of Randolph's Environmental Questionnaire (REQ), an index of somatic reactions to a variety of chemicals and household products (Randolph and Moss, 1980); and (iii) a careful evaluation of the patient's medical history to determine whether factors other than exposure to chemicals might explain the symptoms. The section of the REQ used to help establish the MCS classification consisted of 91 items to which subjects made the responses of "like," "neutral," "dislike," or "made sick from." These categories were assigned the respective values of 0, 1, 2, and 4.

Control subjects were matched to the 18 MCS subjects on the basis of age, gender, ethnic background, and smoking habits, and received equivalent testing, as described below. To ensure that the control group did not include persons with MCS, a prerequisite for inclusion in the study was an REQ item average score of less than 1.86 (a value that fell 2.5 SDs below the mean of an independent group of 72 persons who were asked to complete the questionnaire in a pilot study). Compared to the mean (± SD) MCS patient item score of 2.38 (± 0.54), the mean item score of the controls was 1.38 (± 0.24). All experimental and control subjects completed the Beck Depression Inventory before participation (Beck, 1967).

The design of the study was straightforward. Each subject participated in two test sessions separated from one another by 15 to 30 minutes. In the first session, blood pressure, heart rate, respiration rate, and nasal airflow resistance in each nasal chamber (as determined by anterior rhinomanometry) were determined, followed by bilateral detection threshold sensitivity to phenyl ethyl alcohol (PEA) (Doty et al., 1984a, 1986). Following this testing, measures of blood pressure, heart rate, respiration rate, and nasal airflow resistance were again obtained. In the second session, the same sequence of testing was performed, with the exception that unilateral detection thresholds for ethyl methyl ketone, rather than bilateral thresholds for phenyl ethyl alcohol, were measured.

The PEA detection threshold was established using a single-staircase procedure. On a given trial, two glass sniff bottles were presented to the subject in rapid succession. Each bottle was immediately opened and held over the nose in a standardized manner (see Doty et al., 1978). One bottle contained 20 ml of a given concentration of odorant dissolved in propylene glycol, whereas the other contained propylene glycol alone. The task of the subject was to report which of the two bottles produced the strongest sensation. If no sensation was discernable from the bottles or if the sensations appeared equivalent, the subject was required to guess which bottle contained the strongest stimulus (i.e., the test was forced-choice). No feedback as to the correctness of a subject's responses was provided. The initial trial was begun at the -6.00 log concentration step of a half-log step dilution series extending from -7.50 to -1.00 log concentrations. If an incorrect response occurred on this trial, a concentration one log step higher was presented. If an incorrect response occurred on this trial, a stimulus one log step higher was again presented. When four consecutive correct trials occurred at a given concentration, the subsequent stimulus was presented one half-log concentration step lower.
From this point on, sampling of the concentrations occurred at half-log steps, with one or two trials occurring at each step (i.e., if the first trial was missed, the second one was not given, and the next highest concentration was presented; if both were responded to correctly, the next lowest concentration was presented). The geometric mean of the last four of seven reversal points served as the threshold value.

The MEK thresholds were established in a similar manner, although separate threshold values were determined for each side of the nose and the stimuli were presented using an air-dilution olfactometer. Ten stimulus concentrations (0.6, 1.0, 1.8, 3.2, 5.6, 10.0, 17.8, 31.6, 56.2, and 100 ppm) were shunted, along with blank air, to 1.5-L stimulus delivery flasks arranged around the circumference of a rotating stimulus sampling table. The contents of each flask were sampled from small glass nozzles. The side of the nose to be tested was determined randomly from trial to trial. To eliminate knowledge as to which stimulus was presented, the subject was required to wear opaque goggles during testing. Odorant concentrations were determined empirically using a photoionization detector (Analytical Instruments, Avondale, PA, model 910). The olfactometer was calibrated before each session using a 250-ppm butadiene span gas and calibration factors provided by the manufacturer.

PEA was tested prior to MEK in all cases, since MEK has a greater propensity to stimulate intranasal trigeminal afferents and thereby alter mucus secretion and nasal tubinate engorgement. All tests were performed in a 290 m³ stainless-steel environmental chamber specifically designed for olfactory testing (Environmental Growth Chambers, Chagrin Falls, OH). The ambient air temperature within this 3.25 m W x 3.35 m D structure was 23 ± 0.3 C. The chamber's air was reconditioned through the plenum every 45 seconds and was completely replenished with filtered outside air every eight minutes.

No evidence was found to support the view that patients with MCS were more sensitive to the two target stimuli than were matched controls. Thus, for the MCS group, the mean (SD) male and female PEA threshold values, respectively, were -4.56 (1.67) and -4.96 (1.67), compared to analogous control group values of -4.27 (1.50) and -4.46 (1.05) (all values log vol/vol). The mean (SD) male and female MEK threshold values (in ppm) were 5.69 (5.40) and 7.63 (8.41) respectively, compared to analogous control values of 8.25 (4.46) and 8.10 (13.37). A group by gender analysis of variance demonstrated no significant group, gender, or interaction effects for these data. Also, within the MCS group no correlation was present between the degree of self-reported hypersensitivity and the PEA or MEK olfactory thresholds (respective Pearson r values = -0.01 and -0.13, ps > 0.20).

In the case of nasal airflow measurement, the MCS group evidenced higher nasal resistance on both inhalation and exhalation than did the controls both before and after the two test sessions (see Doty et al., 1988, for specific values). In addition, the MCS group had a higher average respiratory rate than that of the controls in both test sessions. While Beck Depression Inventory scores were significantly higher in the MCS than in the control subjects, heart rate and blood pressure did not differ between the two groups.
In conclusion, these data suggest that, on average, patients with complaints of MCS do not evidence higher olfactory threshold sensitivity than do matched normal controls. Our finding of increased nasal resistance in MCS individuals is in accord with previous suggestions that such patients have increased nasal congestion (Cullen, 1987; Meggs and Cleveland, 1993). This observation, along with the finding of increased respiration and heart rates in such patients, suggests that MCS patients may have labored breathing, which might explain some of their somatic complaints. It is well documented that the nasal airway represents the single largest component of total airway resistance and can influence tidal volume, respiratory function, and expiratory time (Swift and Proctor, 1977; Cole, 1982). Thus, understanding the basis of such problems may shed considerable light on the MCS syndrome.

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REFERENCES


