ENDOCRINE INFLUENCES UPON HUMAN OLFACTORY FUNCTION

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INTRODUCTION

In non-human mammals, reproductive hormones influence the nature and deposition of biological secretions used in social communication. Furthermore, such hormones alter odor preferences and, in some cases, the ability to detect low concentrations of odorants. In humans, hormonal influences on chemosensory functioning are less clear, even though sex differences and menstrual-cycle related changes in odor perception are now well documented.

In this article I briefly review human studies which examine relationships between olfactory perception and reproductive hormones or associated factors. Since much of this literature has been reviewed in detail elsewhere (e.g., Doty, 1976; Doty, 1986), only the most salient points are considered.

SEX DIFFERENCES

With few exceptions (e.g., Bailey & Powell, 1885; Amoore and Venstrom, 1966; Venstrom and Amoore, 1968), most olfactory studies that have examined sex differences have noted that women, on the average, outperform men on tests of odor detection and identification. Sex differences have also been observed in odor preferences and in the magnitude of responses given to suprathreshold odorant concentrations.
In an early study, Toulouse and Vaschide (1899) found that women could detect camphor by smell at a concentration of 1 part per 100,000 (in water), whereas men required a concentration of 9 parts per 100,000 for such detection. A half century later, LeMagnen (1952) reported that women were more sensitive than men to the odor of the steroidal musk Exaltolide and to the steroid testosterone, but not to the odors of safrole, guiacol, amyl salicylate, and eucalyptus. This led LeMagnen to suggest that olfactory sex differences are likely specific to sex hormones and related substances. A number of more recent studies, however, have found women to be more sensitive than men to a wide variety of odorants, including citral, amyl acetate, phenyl ethyl alcohol, and m-xylene (Deems and Doty, 1987; Koelega and Köster, 1974; Schneider and Wolf, 1955).

In addition to reporting that women have greater sensitivity to camphor, Toulouse and Vaschide (1899) noted that women were superior to men in identifying a number of odorants, including orange flower water, cherry laurel water, rose water, artificial musk, citral, essence of mint, anethole, and camphor. Similar female superiority in odor identification performance has been subsequently observed by a number of workers (e.g. Cain, 1982; Doty et al., 1984; Kloek, 1961).

Examples of the odor detection and identification performances of men and women as a function of age are shown in Figures 1 and 2, respectively. The detection task was a single staircase, forced-choice threshold test using the rose-like odorant phenyl ethyl alcohol (a compound with comparatively little ability to stimulate intranasal trigeminal afferents; Doty et al., 1978). The odor identification task was a 40-item standardized forced-choice test incorporating microencapsulated odorants (the University of Pennsylvania Smell Identification Test; commercially termed the Smell Identification Test™, Sensonics, Inc., Haddonfield, NJ; Doty et al., 1984a,b). It is apparent from these two figures that age is a more important variable than gender in influencing these measures, and that women maintain their smell function to a greater age than do men. Interestingly, the sex difference in odor identification is quite general, as it has been found in all cultural groups tested to date, including Australians, British, Black Americans, Korean Americans, White Americans, and Japanese (e.g., Doty et al., 1985).
Fig. 1. Phenyl ethyl alcohol detection threshold scores as a function of age (decade) and gender in non-smoking men and women. Sample sizes indicated by data points. Reproduced with permission from Deems and Doty (1987).
There are a number of studies which suggest that, on the average, women rate suprathreshold concentrations of odorants as more intense than do men (for review, see Doty, 1986). This phenomenon has been noted in our laboratory for human vaginal odors (Doty et al., 1975), axillary odors (Doty et al., 1978), and breath odors (Doty et al., 1982). However, the degree to which this reflects a difference in perception or in response signification (i.e., modulus choice) requires further study.
MENSTRUAL CYCLE-RELATED INFLUENCES ON ODOR PERCEPTION

Although several investigators have noted heightened olfactory sensitivity during the ovulatory or preovulatory phases of the menstrual cycle (e.g., LeMagnen, 1952; Köster, 1965, 1968; Vierling and Rock, 1967; for review, see Doty, 1986), the exact nature of this phenomenon and its physiologic basis are poorly understood. In a comparatively extensive study, we used a signal detection paradigm to evaluate odor detection performance to furfural every other day across 17 menstrual cycles of women not taking oral contraceptives, 6 menstrual cycles of women taking oral contraceptives, and 6 equivalent time periods of three men (Doty et al., 1981). Measures of heart rate, blood pressure, body temperature, nasal airflow, and respiration rate were concomitantly taken, along with measures of plasma levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), estrone (E₁), estradiol (E₂), progesterone (P), and testosterone (T). In addition, responses to the Moos Menstrual Distress Questionnaire (MDQ; Moos, 1977) were collected. Following the combining of the data across cycles using a procedure which minimizes normalization problems (Doty, 1979), the data were subjected to analysis of variance. Sensitivity peaks were noted midcycle, midluteally, and during the second half of menses. Interestingly, similar peaks were noted in both women taking and not taking oral contraceptives, suggesting that gonadal hormones or hypophysal gonadotropins may not be the primary basis for the sensory changes.

The fluctuations in key variables of this study are presented for the normally cycling women in Figure 3. A comparison of the olfactory and endocrine data of the women taking and not taking contraceptives is shown in Figure 4.

To reduce, classify, and describe the relationships among the variables within the normally-cycling and oral contraceptive groups, we subjected the intercorrelations of the variables within each of these two groups to separate principle components factor analyses with varimax rotations. In both cases, the first five factors accounted for over 90% of the total variance; however, only the first two factors appeared to be logically interpretable.
Fig. 3. Mean (±SEM) changes in 13 variables as a function of menstrual cycle phase in normally cycling women. E₁ - estrone; E₂ - estradiol; FSH - follicle-stimulating hormone; LH - luteinizing hormone; MDQ - Moos Menstrual Distress Questionnaire; BBT - basal body temperature; M - menstrual phase; O - ovulatory phase (day of LH surge or day before); PO - preovulatory phase; L - luteal phase. Phase designations based upon normalization procedure of Doty (1979). The p values refer to the cycle phase factor of one-way analyses of variance. Reproduced with permission from Doty, Snyder, Huggins and Lowry (1981).
Fig. 4. Patterns of changes in signal detection measures of olfactory sensitivity and plasma levels of five reproductive hormones across cycle phases of women taking and women not taking oral contraceptives. Data are normalized and assigned to cycle phases using the Doty (1979) procedure. M = menstrual phase; PO = preovulatory phase; O = ovulatory phase (day of LH surge or day before in normally-cycling group, day 13 or 14 in oral contraceptive group, where day 1 = 1st day of menses); L = luteal phase. Reproduced with permission from Doty et al. (1982).
In the normally-cycling group, the first factor represented a "progesterone-cardiovascular" factor which relieved strong loadings from the variables of basal body temperature, heart rate, respiration rate, body temperature during testing, progesterone, nasal airflow, and the MDQ water retention symptom scale. FSH provided a negative loading. The second factor appeared to be an "estrogen-LH-olfactory sensitivity factor," receiving primary loadings from olfactory sensitivity (d'), E1, E2, FSH, and LH, likely reflecting the tendency of these variables to all peak around midcycle. The patterns of correlations along the variables loading heavily on factors 1 and 2 are presented in Figures 5 and 6, respectively.

Fig. 5. Cluster of intercorrelations (Pearson r's) greater than 0.60 among variables most strongly loaded on factor 1 of the factor analysis performed on the normally cycling group's data. Reproduced with permission from Doty (1986).
In the group taking oral contraceptives, factor 1 had a loading from FSH and positive loadings from body temperature during testing, systolic blood pressure, and heart rate (similar to the loadings noted in the normally-cycling group). However, progesterone, respiration rate, and the MDQ water retention symptom scale did not load strongly on this factor, possibly as result of the lack of cyclic progesterone in this group. In addition, nasal airflow loaded negatively on this factor. As in the non-pill group, olfactory sensitivity loaded strongly on factor 2, although no strong loadings were present from $E_1$, $E_2$, and LH. In addition, the MDQ symptom scales of concentration,
autonomic reactions, and control were positively loaded on this factor.

In a subsequent study of two menstrual cycles of a 24-year-old woman (Doty et al., 1982), we demonstrated that the sensitivity shifts observed during the pill cycles were present for the odorant phenyl ethyl alcohol. In addition, we found that similar fluctuations occurred in auditory brainstem evoked potentials and in pure-tone thresholds, as well as in measures of body temperature (Fig. 7). These data suggest that a close correspondence between the olfactory fluctuations and a number of these variables may be present, although slight differences in the times of their maxima and minima exist. Since these data are from only one subject and because each point represents a moving average (with equal weights attached to three adjacent time points), some of the lack of correspondence may reflect the multiple averaging of noise rather than the true underlying fluctuations. Most importantly, these data suggest that the menstrual-cycle related sensory alterations are not confined to the olfactory modality.

INFLUENCES OF CASTRATION AND/OR THE ADMINISTRATION OF GONADAL STEROIDS UPON OLFATORY SENSITIVITY

Surprisingly few studies have examined the possible influences of oophorectomy, orchidectomy, or gonadal hormonal replacement therapy on olfactory sensitivity. Unfortunately, these studies are limited in that they are based on very small sample sizes and have rarely incorporated double-blind procedures or control groups receiving placebo injections.

LeMagnen (1952) reported that the Exaltolide detection thresholds of seven ovariectomized women were approximately two log units higher than normal. The thresholds of five of these women were examined following the administration of estradiol. Two of these women evidenced a post-treatment drop in threshold greater than two log units, two evidenced a drop less than a log unit, and one evidenced no difference. The estrogen effect was not confined, however, to women; LeMagnen self-injected himself with estradiol and reported that his sensitivity to trimethylamine and pyridine increased, whereas his sensitivity to safrol decreased.
Fig. 7. Changes in nine variables across two consecutive menstrual cycles of a subject taking oral contraceptives. To diminish noise, a moving average with equal weights attached to three adjacent time points was applied to each series. Dark rectangles on the abscissa signify periods of menstrual bleeding, open rectangles days during which the oral contraceptives were taken. Testing took place from 9:30 AM to 12:00 PM on each test day. Pure-tone thresholds are averaged across a wide range of frequencies. Reproduced with permission from Doty et al., (1982).
The olfactory thresholds of two hypogonadal women (84 and 30 years of age) were tested by Schneider et al., (1958) once a week over 28- and 43-week periods using citral. The subjects received daily injections of either placebo or Equilin S04, Premarin, or estradiol interspersed in 1- to 2-week-long treatment intervals within the test period. The mean olfactory thresholds were reported as lower during the times of estrogen treatment than during the times of placebo administration, although the differences were small and considerable overlap was present in the distributions of threshold measures.

In a more recent study, Good et al., (1976) found, in a woman who was reportedly anosmic to Exaltolide, an increase in olfactory sensitivity following the administration of estrogen (dosage and type not indicated). The signal detection testing occurred on two days before and on each day after a 9-day series of hormone injections. The percentage of hits and false alarms were both zero on the two pretreatment days. The hit and false alarm rates rose to about the same level on the initial treatment days, whereas during the later ones the percentage of hits rose even higher and the false alarm rate dropped somewhat.

Unlike estrogen, testosterone has been suggested to decrease olfactory sensitivity in humans. In addition to a report by LeMagnen (1952) that self-injection of testosterone decreased his sensitivity to Exaltolide and several other odors, a study by Schneider et al. (1958) noted that testosterone decreased the olfactory sensitivity of a 69 year old woman to citral odor. This study, which was similar in design to their aforementioned estrogen study, noted that the average threshold was 0.10μg/L air during the testosterone treatment periods and 0.05μg/L of air during control periods.

CONCLUSIONS

It is apparent from this brief review that olfactory function is related to both gender and menstrual cycle stage. However, as indicated in detail elsewhere (Doty, 1986), the physiologic base(s) of such influences are poorly understood. Since the olfactory differences appear to be sexually-dimorphic and present before the age of puberty, early organizational effects of gonadal hormones upon brain
regions which influence olfactory perception are likely present. Concurrent influences of gonadal hormones on odor perception are not well established. Thus, cyclical fluctuations in odor perception occur in women taking oral contraceptives whose perturbations in gonadal hormone fluctuations have been mitigated. Furthermore, the studies in which gonadal hormones have been injected are not convincing. If, for example, under physiologic conditions testosterone has an adverse influence on olfactory sensitivity, then one might expect to see higher acuity in older than in younger males. This is clearly not the case.

Factors other than gonadal hormones which would be prime candidates for producing the menstrual cycle related alterations in olfactory function include luteinizing hormone releasing factor (LHRH) and selected central catecholamines (see Doty and Ferguson-Segall, 1987; Mair et al., 1986). The possibility that the brain mechanisms responsible for menstrual cycle related changes are associated with general arousal is suggested by observations that changes in several sensory systems occur across the phases of the menstrual cycle (e.g., Doty, 1978; Kenshalo, 1966; Millodot and Lamont, 1974; Procacci et al., 1972; Robinson and Short, 1977; Wynn, 1972). Additional research is obviously needed to ascertain whether this is, in fact, true.

REFERENCES

Doty RL (1978). Gender and reproductive state correlates of taste perception in humans. In McGill T, Dewsbury DA,


