

AXILLARY ODOR: DETERMINATION, FORMATION AND CONTROL

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I. INTRODUCTION

Research on the formation and control of axillary 'malodors' has led to the identification of specific steroids and acids which represent this unique body odor. The characterization of secretions of the underarm as well as the skin bacteria which are involved in odor formation have resulted in a complete picture of the microcosm of the underarm. Standard odor control mechanisms such as use of antiperspirant salts to reduce bacterial action or substantive fragrances to mask odors are still the commercial methods for reducing an individuals' body odor. However, there is the potential for using the understanding of the body's chemistry to develop new methods of odor control. In addition the normal axillary odorants may be involved in human olfactory communication by affecting the physiological states of others. These topics will be explored in this chapter.

Research on the origin and characterization of axillary odors has been primarily from two laboratories, the Monell Chemical Senses Center [Philadelphia, PA] and the laboratories of Dr. D. B. Gower, currently of King's College London, which focused on the metabolism of androst-16-enes. Extensive reviews have been published on studies from these laboratories (1-7).

II. AXILLARY SECRETIONS

Significant variations in both the total number of bacteria and the composition of the bacterial flora exist for different body regions reflecting differences in the amount of water and nutrients available to support bacterial growth (8). The human axilla provides an ideal combination of ecological factors for bacterial growth. The anatomy of the axilla produces a semi-occluded environment that minimizes evaporation of water needed for bacterial growth. The rich supply of eccrine sweat glands, which provide water, amino acids, electrolytes and minerals, apocrine sweat glands, which secrete a substance rich in protein and lipid, and sebaceous glands, which produce a mixture of lipids, contribute substrates which support bacterial proliferation.

The apoeccrine gland has been characterized in the axilla and shown to develop from the eccrine gland. This gland as well as the apocrine gland develops at puberty, responds to both cholinergic and adrenergic stimulation. It is as numerous as the eccrine and apocrine glands and is capable of sustained fluid secretion greater than the eccrine gland and may contribute substantial moisture to the axillary environment (9).

Of additional interest is the presence of steroid components of the apocrine secretions which serve as possible precursors for formation of malodors. Two androgen steroid sulfates, dehydroepiandrosterone (DHA) and androsterone sulfates, have been characterized in the secretion as well as steroid conjugates, such as androstenol sulfate and glycosides, which serve as bacterial substrates (10,11). Proteins are present in the secretion and several enzyme activities have been

detected in excised apocrine glands including: V-glucuronidase, 3- α -hydroxy-steroid dehydrogenase, 4-ene-5 α -reductase and esterases which can metabolize steroid precursors. Protein/acid complexes have also been identified which on dissociation release characteristic 'sweaty axillary malodorants'. [see below]

III. Bacteriology

The bacterial flora of human skin is a relatively simple one, consisting of aerobic cocci of the Micrococcaceae family, aerobic diphtheroids, primarily *Corynebacterium* species, anaerobic diphtheroids of the genus *Propionibacterium*, yeast from the genus *Pityrosporum*, and occasional Gram-negative species. The axilla supports one of the highest densities of bacteria on human skin and, because of the semi-occluded anatomy, is relatively less prone to environmental contamination. Organisms recovered from the axilla are therefore representative of the indigenous flora of skin. Quantitative and qualitative changes in the bacterial flora, specifically the aerobic cocci and diphtheroids, have been correlated with differences in the quality of axillary odor [see below].

In a study of 205 subjects, employing quantitative techniques, the axillary flora was found to consist of a stable population of aerobic and anaerobic organisms with the total number ranging from 5×10^5 to 10^6 organisms/cm² (12). The day-to-day variation was minimal, with a coefficient of variation of 13%. Axillary hairs were found to have extremely low numbers of bacteria and were not viewed as a significant aspect of axillary bacteria. Comparison of the axillary flora in terms of right- and left-handedness did not reveal any significant differences, nor did a comparison of the right versus the left axillary flora within subjects. Males and females had similar numbers of bacteria; significant compositional differences (described below) were found.

In a classical study, *Staphylococcus aureus*, *S. epidermidis*, coryneforms, *M. juteus*, and Gram-negative bacteria were isolated from cultures made from a small number of subjects (n = 20). When these organisms were incubated with apocrine sweat, malodor was produced only with the Gram-positive organisms (13). Coagulase-negative cocci and coryneforms were the dominant organisms recovered in another group (n = 29) (14). In a study designed to determine the effects of topical antibacterial agents on the flora of the axilla and the production of odor, aerobic coagulase-negative cocci and coryneform bacteria were found to be the most abundant organisms (15). The number of bacteria recovered from the axilla was of the order of 10^6 organisms/cm².

Two distinct types of axillary flora have been described - a flora dominated by lipophilic diphtheroids [85% of the flora] and a flora dominated by coagulase-negative cocci (16). In experimental manipulation of the cutaneous flora, excessive hydration favors proliferation of coryneform bacteria, and for this reason a major factor determining the composition of the axillary flora may be a difference in eccrine sweating (17). Another report found 70% of the axillary flora to be coryneforms and concluded that these organisms were predominantly *Corynebacterium* species (18). Aly and Maibach (16) found the axillary flora to be dominated by coryneforms but concluded that the majority (78%) were nonlipophilic in nature. In a comprehensive study involving 163 males and 122 females, Jackman (17) also found that the axillary flora was dominated by aerobic cocci or by coryneforms. In his series, 64% of the males had an axillary flora dominated by coryneforms and 27% had a coccal flora. This ratio was reversed in the females. The predominant genus found in the axillary coryneforms was *Corynebacterium* (83%), with 5% *Brevibacterium* and 12% other coryneforms. In those with a coryneform-dominated flora a mean of

106 coryneforms/cm³ was recovered, compared to a fivefold lower density in those with a coccal-dominated flora.

Studies in our laboratories showed that all subjects had Micrococcaceae recovered from the axillae. The most frequently recovered was *Staphylococcus epidermidis* species (51%); *Staphylococcus saprophyticus* was recovered from 29%, while *S. aureus* was found in only 10% (12). Differences in other studies may be explained by population and /or climate differences. Aerobic diphtheroids or coryneforms were frequently recovered. They are classified as aerobic diphtheroids belonging to two genera-*Corynebacterium* and *Brevibacterium*. The aerobic diphtheroids that do not require lipid (large colony diphtheroids) have not been as well characterized, but those recovered from the axilla also appear to belong to *Corynebacterium* (21). Significant differences in the carriage rate of lipophilic diphtheroids (*Corynebacterium lipophilicus* is the proposed name for this species) were found in males and females. Males had a carriage rate of 85%, compared to 66% for females (12). However, the mean number of these organisms, when present, was the same for males and females. The non-lipid-requiring diphtheroids (large colony diphtheroids) were found in 26 and 25% of males and females and the mean number of these bacteria when present was the same for both sexes. Higher numbers of diphtheroids, i.e. 10⁶ to 10⁷/cm² have been found (19).

The association of odor with bacteria in vivo has been confirmed in a more extensive study involving a European population where odor-positive Coryneforms were all species of *C. xerosis* (22,23). Further studies also showed that the axillary pH of 6.0 was the optimum pH for the Coryneforms. Axillary extracts from low odor formers gave strong axillary odor on incubation with Coryneforms suggesting that odor differences may not be in quality of apocrine secretion but in the makeup of the bacterial population. However, in other studies with a North American population, the lipophilic diphtheroid strains identified in the axillae were found to be distinctly different from both *C. bovis* and *C. xerosis*, though the latter has been found in populations of elderly in institutional settings and those with poor hygiene (21)..

IV. AXILLARY STEROIDS

A. CHARACTERIZATION OF AXILLARY STEROIDS

Studies directed at the elucidation of axillary secretions and their odors have focused on determining the type, abundance and origin of the androst-16-enes. These studies have paralleled work in the analysis of the same compounds in boar saliva and boar fat, where it was necessary to quantitate the off-odor, i.e. “boar taint odor”, due to a combination of androstenone and skatole. In 1945, Prelog et.al. commented on the intense urine /perspiration-like odor of the androst-16-ene ketones, particularly 5 α -androst-16-en-3-one (androstenone) (24). These initial organoleptic observations coupled with the identification of these volatile steroids in the axillary region have prompted many investigators to assume that volatile steroids were the predominant odorants in the axillae.

Initially it was necessary to use the techniques such as isotope dilution mass spectroscopy using deuterated steroids and radioimmunoassay (RIA) because of the low levels and low odor thresholds of the d-16-androstenes. Using mass spectrometry, Gower was the first to detect androstenone in the axilla and later with RIA could show significant differences between males (range 12-1134 pmol/24h or 3-310 ng) and females (13-39 pmol/24h or 3.5-11ng) (25). There was

some variation among individuals on a retest over a 2 to 3 day period; however, there were no differences with handedness and no relationship with age among adults (26).

Androstenol was also detected on axillary pads as indicated earlier as well as in urine along with androstadienol as glucuronide derivatives (27). In a 1976 study, the ratio of androstenone to testosterone in the plasma was reported as 1:1.4, while in the axilla it is 10:1 (28). This is suggestive of selective excretion of at least a close precursor of androstenone in apocrine secretion. Androstenone has also been detected in samples of human saliva and adipose tissue. Androstenone was detected in axillary hair (0.1-100ng/mg) while androstadienone was at a higher concentration than androstenone in all subjects (29). Subsequent studies have also detected all five androstenes in apocrine secretion (30).

In another study, axillary secretions were collected on cotton pads worn overnight in the underarm. Following extraction and then removal of steroid sulfates, analysis by gas chromatography-mass spectrometry using multiple ion monitoring was sensitive enough to detect all the androstene steroids including: androstenone (molecular ion =272), androstadienone (270), β -androstenol, α -androstenol (274) and androstadienol (272) (1). The results of an analysis of 10 male subjects showed the levels of androstadienone are higher than androstenone and both steroids are present in those individuals with higher odor ratings.

B. METABOLISM OF ANDROSTENES: URINOUS/MUSK ODORS

Androst-16-enes can be formed from pregnenolone using enzyme preparations from the boar testes, adrenals or sow ovaries. Subsequent studies show this also occurs in human testis (31). The steroid sequence involves the formation of androstadienol and its subsequent modification to androstadienone, androstenone and further reduction to α - or β -androstenol. Initial experiments involving lipophilic diphtheroids and selected steroid substrates showed the hydrolysis and oxidation of 3β -sulfates and the oxidation of 3α -sulfates. Thus, the sulfates of androstadienol, pregnenolone and DHA, all with β -geometry, are converted to the corresponding 3-keto derivatives. 3α -androstenol, but not its sulfate, is converted to androstenone (1).

Further reports have examined steroid transformations by axillary Coryneforms and *C. xerosis* in particular (22,23,31,32). Odor positive aerobic Coryneform species converted both androstadienone and androstadienol to androstenone and 3α -androstenol. The odor negative and *Micrococcus* species could only bring about the latter reaction. In all cases, no androst-16-enes were observed to be formed from testosterone, pregnenolone, DHA or any non androst-16-ene precursor (33). Subsequent to this report it has been determined that androsterone sulphate [AS] is converted into androsta-4,16-dien-3-one and androst-16-enyl-3-sulfate into androstenone, both odorous steroids, with an axillary Coryneform isolate (32). AS metabolism also led to formation of androst-16-en-3-ols. The above studies confirm the previously proposed scheme (**FIGURE 1**). This involves the initial and necessary secretion of a conjugate of androstadienol [or androsterone or other non-X-16-androstene] to begin the metabolic sequence. All subsequent enzyme reactions are available from the odor positive bacteria or extracellular enzymes in apocrine secretion. Further studies supporting this scheme, based on enzyme inhibitors, are described in the section on odor control.

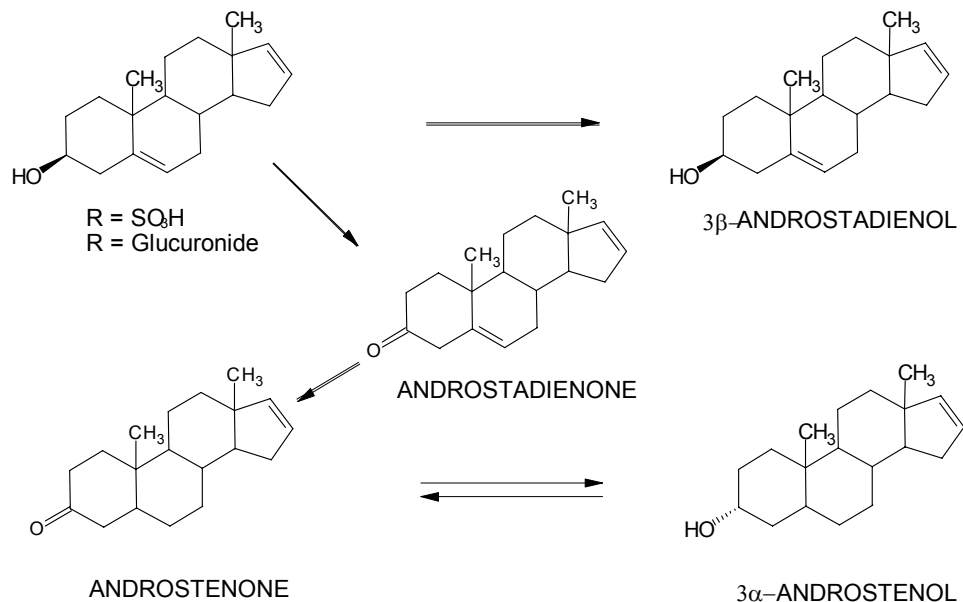


FIGURE 1 Formation of Odorous Steroids from conjugates of Androstadienol

V. AXILLARY ACIDS

A. CHARACTERIZATION OF AXILLARY ACIDS

The descriptors used for axillary odors include sweaty, acid, musty-damp and/or hircine (goat-like). Previous analyses had shown the presence of isovaleric acid and similar short-chain acids in axillary secretions (1). Subsequent studies, which sought the compound responsible for the characteristic axillary odor, employed both an odor panel and "smell chromatography" (33). Olfactory comparison of the chromatographically separated odors from six male subjects with the original concentrated extracts identified a region in the chromatogram which had characteristic axillary odor. This region did not correspond to either volatile steroids or short-chain acids in retention time. Analysis of these components by GC/MS showed an array of C-6 to C-11 straight chain, branched chain and unsaturated acids. The largest was (E)-3-methylhexenoic acid [TABLE 1].

Confirmation of the structure of the major characteristic odor component, (E)-3-methyl-2-hexenoic acid (TMHA), was based on mass spectral, infrared and NMR data as well as synthesis. It was distinguished from the (Z)-cis isomer which is also present as a minor component in the axillary extracts (33). In terms of relative abundance, the C6 -C11 organic acids, particularly E3M2H are present in far greater concentrations than androstenone: ~ 357 ng/ul extract of E3M2H vs. ~ 0.5 ng/ul extract of androstenone. Combined female axillary extracts have also been examined (34). In female samples, the straight-chain acids were present in greater relative abundance than E3M2H; further, no androstenone was seen in female extracts. Androstenol was present, albeit in far lower concentration than E3M2H or the other acids: ~ 150 ng/ul extract of E3M2H vs. ~ 3.5 ng/ul extract androstenol (33). The Z-isomer of TMHA is also present in each gender, however in different relative abundance: 10:1 (E:Z) in males, 16:1 (E:Z) in females.

TABLE 1 ACIDS CHARACTERIZED IN AXILLARY SECRETIONS

STRAIGHT-CHAIN	METHYL-BRANCHED	ETHYL-BRANCHED
Hexanoic	2-Methyl Hexanoic	2-Ethyl Hexanoic
Heptanoic	<i>3-Methyl Hexenoic</i>	4-Ethyl Pentanoic
Octanoic	3-Methyl Hexanoic	<i>4-Ethyl Heptanoic</i>
Octenoic	2-Methyl Heptanoic	4-Ethyl Octanoic
Nonanoic	2-Methyl Octanoic	4-Ethyl Nonanoic
Nonenoic	2-Methyl Nonanoic	4-Ethyl Decanoic
Decanoic	2-Methyl Decanoic	
Undecanoic		

In addition, 7-octenoic acid is also present and represents a compound with a high odor impact. The "goat acid", 4-ethyl-heptanoic acid, was also identified as one of the acids. This had been previously characterized as a doe attractant and the main odor constituent of the sebaceous gland secretion of the mature male goat during breeding season (35). This compound also shows a mixed reaction to men while being disagreeable to women; a specific anosmia exists in humans as well as a low odor threshold [TABLE 2] (36).

TABLE 2 SPECIFIC ANOSMIAS RELATED TO BODY ODORS

Odor Source	Odorant	Primary Odor	Anosmia(%)	[Threshold]
Axilla	Androstenone	Urinous	46-50	[0.18ppb]
	Androstenol	Musky	12	[6.2ppb]
	E-3-Methylhex-2-enoic	Sweaty	11	[14ppb]
	4-Ethylheptanoic	Hircine	16	[1.8ppb]
Axilla/Foot	Isovaleric Acid	Sweaty	3	[1ppm]
Uremic Breath	Trimethylamine	Fishy	6	
Semen	1-Pyrroline	Spermous	16	

E3M2H was once thought to characterize the odor of patients suffering from schizophrenia, since it was first identified in their whole body sweat, but was later found in normal individuals (37,38). E3M2H has an odor which is characteristic of human axillary sweat. Although E3M2H is a major analytical component of the characteristic axillary odor in males, a number of components are necessary for the complete axillary "bouquet". In addition, studies from both our laboratory and another documented both the presence of a specific anosmia for both isomers of 3M2H, and an olfactory threshold for the E-isomer that is of the same order or magnitude as that for androstenone (39,40). Consequently, the strength and quality of the odor produced in the axillae appears to be related to the axillary bacterial populations and perhaps the concentrations of E3M2H present, but further, rigorous organoleptic studies must confirm this.

B. METABOLIC FORMATION OF AXILLARY ACID ODORANTS

Early studies on the role of bacteria in generating axillary odor demonstrated that apocrine sweat was sterile and odorless and that odor was produced by axillary microorganisms acting in apocrine sweat (13). Sterile eccrine sweat produced no odor when incubated with bacteria. Numerous studies now demonstrate that a decrease in axillary odor correlates with a decrease in axillary coryneforms (12,41).

In studies comparing the axillary flora of those with a strong disagreeable axillary odor [similar to androstenone] to those with a "sweaty" odor, significant quantitative and qualitative differences were found. Those with a strong unpleasant odor had a significantly higher number of bacteria, 106/cm² compared to 105/cm² (12). More striking, however, were the marked differences in the composition of the flora. Every subject with a strong axillary odor had lipophilic diphtheroids present in high numbers. The geometric mean count was 810,000 compared to a 55% prevalence with a mean of 53,000 in those with a sweaty odor. These results suggested that lipophilic diphtheroids (*C. lipophilicus*) were responsible for generating the most offensive notes. In further studies, sterile odorless apocrine sweat was placed on the forearms of volunteers and subsequently incubated with aerobic cocci, coryneform bacteria, and Gram negative organisms. Typical strong axillary odors were produced only when lipophilic and large colony Corynebacteria were incubated with apocrine sweat. A sweaty, isovaleric acid type of odor was produced by micrococci and gram-negative bacteria.

Recent studies have demonstrated that the water soluble components of apocrine secretion contain TMHA and other constituents of the characteristic axillary odor bouquet bound to non-volatile molecules (42). These odorants can be released by base hydrolysis (5% NaOH) or by incubation with axillary bacteria. Separation and hydrolysis (by NaOH or enzymes) of the proteins found in apocrine secretions have demonstrated that E3M2H is carried to the skin surface bound to two proteins which have been designated as Apocrine Secretion Odor Binding proteins 1 and 2 (ASOB1 and 2). ASOB1 and ASOB2 have apparent molecular weights of 45 and 26 kDa, respectively, by sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE; 43,44). Antisera to each of these proteins were prepared using purified proteins pooled from several male donors. The antisera were employed to probe, by Western blotting, the proteins from male and female apocrine secretions as well as a variety of other body fluids (e.g. tears, forehead and areaolar sweat, submaxillary and parotid saliva, urine, ear wax, serum and nasal secretions) from males. All except urine showed the presence of these proteins. The male and female apocrine secretion proteins were qualitatively similar (45). Structure determination of ASOB2 showed that the primary amino acid sequence of ASOB2 is identical to that of apolipoprotein D (apoD) and in situ hybridization demonstrated that the site of expression for the apoD is the apocrine gland.

ApoD is a member of the a-2u microglobulin superfamily of proteins (also known as lipo calins). The role of plasma apoD is not known, nor is its ligand(s). E3M2H is the first in vivo ligand identified for apoD, as it appears in apocrine secretion. There is a 2:1 molar ratio of E3M2H to apocrine apoD.

VI. ODOR COMMUNICATION

A. AXILLA AS SOURCE OF PRIMER PHEROMONES

Studies with rodents have demonstrated that reproductive behavior is modulated by odors. The effects of female odors on males include puberty acceleration, hormonal surge and odor production while male odors can induce estrus or block pregnancy. Female odors can advance or delay the cycle of competing females thus inducing estrus synchrony (46). These are examples of primer pheromonal effects which result in internal metabolic responses and differ from releaser effects which result in overt immediate behavioral changes and have been reviewed elsewhere (3,47). Although the popular press has romanticized the involvement of releaser effects in human sexual interactions, these effects are inherently more difficult to demonstrate because the responses to odor are confounded by other sensory inputs and by the context in which the odor is presented. No releaser pheromone effects have been demonstrated in humans.

There is evidence that the human axilla is a source of 'odorants' which act as primer pheromones. This conjecture is based on the physiology and anatomy of the axillae and its similarity to other mammalian systems which produce 'odorants' that induce a physiological change. Indirectly, both the sebaceous and apocrine glands are secondary sexual characteristics and fully develop during puberty. This results in a distinct change in body odors particularly in the axillary and scalp region. At puberty it is possible to discriminate between the sexes based on axillary odor. The apocrine glands, androgen target organs, are analogous to the apocrine/sebaceous glands in other mammals and could be considered as the human scent gland (2,3).

B. EFFECTS ON MENSTRUAL SYNCHRONY

The anecdotal observations of synchrony among women living in college dormitories has been confirmed in several experiments (for review see 2,48). Though there has been some controversy surrounding these results, it is generally accepted that synchrony, though not occurring in all cases, is a real phenomenon and represents a potential human pheromonal effect (49,50). In an initial investigation of this phenomenon, Russell demonstrated that axillary odors could effect menstrual synchrony (51). In a more extensive double-blind study, axillary odors were collected from throughout the cycle of four donor women and were combined into 10 extracts each representing 3 day periods of a "synthetic" 30 day menstrual cycle. The extracts from the appropriate phase were placed on the upper lips of female recipients for three consecutive menstrual cycles. Their cycles were found to approach the cycle of the donor after the third menses (52).

A similar protocol of axillary extract application was used in an experiment when male axillary secretions were placed on women, who had a history of unusually long or short cycles. These recipients showed a statistically significant change in their cycle length toward the normal length (29.5 + 3 days) after 12 weeks exposure to male extracts (53). In each case, it is possible to have an objective measurement, change in cycle length, rather than the subjective measures, e.g., "attraction", "arousal", "submissive", used to define the releaser effects. Recent results suggest that females who received axillary secretions from donor females collected during the follicular phase experienced a shortening of their menstrual cycles. There was a lengthening of the cycle for females who received secretions collected during the ovulatory phase (54).

The above studies present compelling evidence that human axillary extracts contain components which act as primer pheromones which alter menstrual cycle length and timing. When considered together with the chemical studies described, which demonstrate that a major axillary odorant is carried to the skin surface by apoprotein D, these results suggest a remarkable similarity between the human axilla and non-human mammalian odor sources used in chemical signaling. In the hamster, house mouse, and possibly the pig, chemical signals which modify in endocrinology and behavior are carried by lipocalin proteins (3).

These results also suggest that an analytical examination of axillary extracts from females during the menstrual cycle might reveal marked differences in axillary constituents. In one analysis of the steroid content of the extracts, it could be demonstrated that androstenol concentrations varied over the cycle and peaked at the mid-follicular phase (55). Several of the acidic components, which constitute the characteristic axillary odors, have been isolated and analyzed by GC/MS from the follicular and ovulatory phases of the menstrual cycle. High levels of n-C7, C8 and C10 acids as well as subnanogram levels of E3M2H are found in the follicular phase. E3M2H levels increased significantly and concentrations of normal acids remained constant or decreased in the ovulatory phase (56).

Quantification of donor's axillary flora indicated no difference in the number of micrococci (*Staphylococcus epidermidis* and *S. saprophyticus*) in either cycle phase. However, differences were found in the population of LDs with significantly greater amounts of LDs found in the ovulatory phase. The increased levels of E3M2H in the ovulatory phase extracts may be due to changes in the number of LD bacteria, which are associated with stronger smelling axillary secretions.

C. INVOLVEMENT OF VOMERONASAL ORGAN

In many animals, the sensory receptors for some pheromones are a specialized group of neurons located in the vomeronasal organ (VNO) or "Jacobson's organ" which is in the nose. Numerous recent reports have suggested that humans possess a functioning VNO and that activation of the organ is possible with certain chemosensory cues or "vomeroferins" (57,58). Openings to this putative structure are on either side of the nasal septum, about 1 cm from the opening of the nasal cavity. "Vomeroferines" are steroidal in structure and are alleged to be isolated from human skin or are synthetic analogs of skin-derived steroids; several of these steroids resemble androstenol and androstenone in structure. In addition, two naturally occurring "vomeroferins" are reported to be androsta-4,16-diene-3-one (androstadienone, from males is identical to one of the axillary steroids and "excites" female VNO) and estra-1,3,5(10),16-tetra en-3-o1 (estratetraneol, from females, "excites" male VNO) (59). Vomeroferines, in "proportions that are trade secrets" have been incorporated in Realm fragrances.

Vomeroferins are alleged to be human pheromones because they "stimulate" the human VNO. People did not report smelling anything during administration of vomeroferins, suggesting that olfactory receptors were not stimulated. Electrical responses, equivalent to generator potentials, were recorded from the putative VNO of humans (58,60). These responses differed with the type of chemical cue used and the gender of the subject. One should be cautious in interpreting the origin of these responses since explanations other than activation of "pheromone receptors" are possible. Further, many of the steroid compounds being employed as "synthetic vomeroferins" in these experiments closely resemble naturally occurring estrogen, androgen and progesterin hormones. Thus, since actual steroid hormones have not been used in control studies, one can

speculate that metabolic enzyme systems in the nose altered the "vomeroherin" structures to become an active steroid hormone (47,61).

VII. OLFACTORY PERCEPTION

A. BODY ODORS AND SPECIFIC ANOSMIA

In psychological experiments dealing with odor perception, the absolute threshold (the lowest concentration perceived can be used to determine the relative sensitivity of individuals. For most odorants, i.e. floral, a bell-shaped distribution is observed for individual thresholds. However, for many odorants associated with the human body there is a bimodal distribution with individuals being either sensitive or insensitive to the odor. This phenomenon is known as "specific anosmia" and such anosmias have been characterized for odors representing fishy, sweaty, spermous, urinous and musky (62,63). These represent 5 of the more than 30 suggested anosmias some of which relate to specific fragrance classifications (64).

TABLE 2 shows the odor sources, a representative chemical and the percentage of the population which show the specific anosmias which are directly related to human odors. Though there are other anosmias, i.e. carvone, the urinous and sweaty odors from the above list represent some of the highest percentages which are found. These data show that in many situations individuals do not perceive, and thus may not be able to interpret human odors in the same manner (62,65). This has implications for the interpretation of any studies on malodor masking by odor panels if the panel has not been prescreened for the relevant anosmias. The association of human body odors with the odors of both natural and synthetic fragrance components has been detailed in the publications of Jellinek (66).

B. PERCEPTION OF ANDROSTENONE AND E3M2H

Other interesting olfactory effects include the induction of odor perception with androstenone and cross-adaptation with both androstenone and E3M2H. Two of the laboratories studying the olfactory properties of androstenone have reported incidences of the investigators who were originally anosmic to this material to have acquired the ability to detect it. A controlled study showed that individuals exposed to androstenone three times per day over a six week period became osmic to it with a substantial increase in threshold for 10 of 20 subjects (4,67). Several compounds similar in structure and/or odor to axillary malodorants have been tested for their ability to modify their perception (68-71). The ethyl esters of E3M2H were tested for their potential to reduce perception of E3M2H malodor. The protocol involved the alternate presentation of ester and malodor and an odor intensity assessment of E3M2H. If an individual is first adapted to the ethyl esters, the perception of E3M2H is reduced (68).

Androstenone has been reported to have both a urinous and musk component to its odor with the latter experienced by those who are less sensitive. Interestingly there is a third group which does not detect this material at any concentration (63). Attempts to use a musk compound, galaxolide, to adapt and therefore reduce the odor intensity of androstenone were unsuccessful. This is in accord with the lack of correlation of galaxolide and androstenone anosmics in men or with threshold data although women anosmics to both were more than four times as frequent as expected (65). Exposure over time (twice a week for 8 weeks) to a compound with different structure but similar odor, same anosmia profile and stereochemistry, *cis*-4-(4'-*t*-butylcyclohexyl)-

4-methyl-2-pentanone (pemenone), produced a reduction in threshold to androstenone (69) [see reference 2 for discussion of androstenone analogs]. Another alicyclic compound, 4-(4',4'-dimethylcyclo-hexyl)-2-methylcyclohexanone, also cross-adapted androstenone (70). In other experiments androstanone cross-adapted androstenone and a significant but weaker cross adaptation was found for an odorless analog, 3-methylidene-androstane, to androstanone but not androstenone (71). All of these molecules share the urinous-sweaty odor note. These approaches offer some rational for designing molecules for specific malodors but require a better understanding of this phenomenon.

VIII. ODOR CONTROL

The various methods for axillary odor control have been reviewed in a previous edition and only additional approaches will be described here. There are several basic approaches for odor control all of which take advantage of the knowledge of the compounds responsible for the malodor and the mechanism of odor formation. These include anti-bacterials and antiperspirants to control bacterial growth, fragrances created specifically to blend/mask with the malodors and methods to extend fragrance delivery through encapsulation or fragrance precursors [profragrances] which can utilize either pH changes on skin or bacterial enzymes for prolonged fragrance delivery.

A. ANTIBACTERIAL

The primary method for odor control has been the reduction of moisture by antiperspirants usually aluminum salts, i.e. aluminum chlorhydrate, which are known to physically penetrate and block the sweat pores. This reduces the presence of moisture and nutrients provided by glandular secretions which control bacterial growth and ultimately the bacterial metabolism of the bodies secretions. Al salts can also act as antibacterials and can reduce the pH below the optimum for bacterial metabolism. The properties of aluminum salts have been extensively reviewed (73).

At present, the antibacterials, triclosan and trichlorocarbanilide, which are stable, substantive to the skin and safe, are used in deodorants and deodorant soap (72). The latter are believed to act through interaction with cell membranes and interference with the uptake of cell nutrients. Triclosan was shown to be effective in specifically reducing axillary bacteria during a 6 month usage study. Specific components of fragrance oils have shown some antibacterial activity but are 100 to 1000x less effective than the antibacterials used in deodorant soaps. The drawbacks of the above approaches are individual sensitivity, the reduction in effectiveness of antimicrobials which sometimes occurs because of the delivery system, the indiscriminate effects on all bacteria and in the case of antiperspirants, the prevention of sweating which is in itself effective in odor removal. The use of the aluminum salts and chloroantibacterials also have some negative effects in the context of environmental and personal safety that may lead to their replacement as was the case for hexachlorophene. Alternative approaches involving fragrance delivery or enzyme inhibition offer future opportunities.

B. ODOR NEUTRALIZING/MASKING

NaHCO₃ is still a popular active ingredient in deodorants and can be formulated into all delivery forms including aerosols. It is effective in neutralizing the acidic components such as E3M2H once

formed. However, the bicarbonate might be expected to keep the axilla basic and actually facilitate the enzyme reactions.

Fragrance has been used to counter malodorants either by overpowering the malodorants or by odor masking (74,75). The use of selected compounds tested against the acid and steroid malodorants can result in effective odor masking (76). Deo-Fragrances have been developed which blend with the axillary malodorants, to give an overall acceptable odor. In any deodorant, the fragrance level is limited in one daily application while the potential for odor development is continual. Two deodorants introduced in the US have utilized starch-encapsulated fragrances which are released by moisture. Thus sweat produced by stress or exercise causes the coating to be solubilized and additional fragrance released. In another case the fragrance is reencapsulated for later release as well (77). Sulfhydryl agents, such as N-ethylmaleimide, have been suggested as effective in neutralizing axillary odor which was generated *in vitro* from axillary secretions and microorganisms and also for preventing build-up of odor on fabrics (78).

A direct reduction in the perception of the odorants that cause axillary odor can be achieved through techniques of cross-adaptation, the decrease in perceptual sensitivity to one odor after exposure to another. Recent studies demonstrate that exposure to the ethyl esters of E-and Z-3M2H and its higher and lower homologs can reduce the perception of the axillary odorants by 66% (68,70). While all the esters tried demonstrated efficacy, maximum reduction in perception was achieved with the ester that was the most structurally similar to the E3M2H, its ethyl ester. Molecular modeling studies suggested that the greater lipid solubility of the ethyl esters allowed them to have greater access to the olfactory receptors than the acids. Consequently, pleasant-smelling ethyl esters appear to have great potential for reducing the perception of all malodors featuring organic acid malodorants.

C. BACTERIAL METABOLISM

Another approach has been to control the metabolism of odor formation particularly the chemical/enzymatic reactions which take place. These reactions can be modified by materials which specifically inhibit the hydrolysis and/or oxidation reaction of the precursor steroid glucuronides or sulfates or protein/acid complex.

In axillary studies, it was shown that in general "high odor formers" had both arylsulfatase and glucuronidase activity compared with the "low odor formers". In *in vitro* experiments, inhibitors could be tested against these specific enzymes. Zn and Cu ions and hexametaphosphate were all effective against both enzymes, while X-glucarolactone inhibited V- glucuronidase (79). Apocrine secretion incubated with either the above enzymes or the diphtheroid bacteria generated the expected odor which could be controlled by glucarolactone or Zn glycinate. These inhibitors have also been shown to be effective as deodorants *in vivo*. Zn⁺² is not an effective antibacterial and thus is acting primarily as an inhibitor. To take advantage of the useful properties of Zn⁺², an effective delivery system has been developed (80). This involves coating Zinc oxide on nylon particles producing a "hybrid powder" which overcomes drawbacks of Zinc oxide powder. This material provides Zinc for complexing acids and enzyme inhibition and is effective against both foot and axillary odors. An aromatic alcohol ester of a phenol, such as phenoxy-2-benzoyl-benzoate, has been suggested as an esterase inhibitor which on release of phenol would also act as an antibacterial (81).

The findings which demonstrated that an important axillary malodorant appears on the skin surface bound to a protein suggest the possibility that axillary bacteria, adapted for hydrolyzing

proteins can be "fooled" by presenting them with an excess of a compound with amide and ester bonds (see below). This experiment was tried using the amide ester of alanine-11-undecenoic acid which on incubation with axillary bacteria released undecenoic acid, an antibacterial (82).

D. FRAGRANCE PRECURSORS

This metabolic approach can also be used to generate fragrance materials by providing alternate substrates for bacterial enzymes. This profragrance approach involves the hydrolysis of esters (83), orthoesters, ketals/-acetals (84,86), amino acid/ether derivatives (87) or vinyl ethers to form a perfume alcohol and either an acid or aldehyde/ketone to mask axillary malodors. The esters provide substrate for bacterial lipases while the acid sensitive derivatives are hydrolyzed through an expected acidic pH change on the skin following application from a basic deodorant. Acetals, which were combinations of fragrance alcohols and aldehydes/ketones, were prepared and their hydrolysis studied at slightly acidic pH values. Those that had the appropriate hydrolysis rate were suggested as profragrance materials though this was not demonstrated *in vivo* (88). Esters, including sulfates, sulfonates and phosphates, can serve as precursors for use in deodorants to mask axillary malodor. It was demonstrated with several of the esters that hydrolysis occurred with axillary bacteria through detection of the corresponding alcohols both *in vitro* and *in vivo* on t-shirts (89?). Hydrolysis of an amino acid ether derivative such as phenylethyl-o-serine was reported to occur with an amino acid lyase from the bacteria (87). An amide complex of a simple amino acid and undecenoic acid was reported to also be hydrolyzed by axillary bacteria and effective in reducing malodor through the antibacterial effects of the acid (82).

In analogy to the metabolism of androstenol sulfate or glycoside to the odorous androstenone by axillary bacteria, it was demonstrated that fragrance glycosides (or glucosides) such as phenethyl galactoside, an acetal combining phenyl ethanol and galactose, can be hydrolyzed with or without a galactosidase to the perfume alcohol (85,86). This same reaction was demonstrated with skin bacteria with a preference for beta-glycosides.

Other patented chemicals used for control of axillary odor include the antibacterials; chlorhexidine gluconate, hexylcaine, farnesol, Hyamine (a quaternary nitrogen compound) and polyhexamethylene biguanide-HCl. Antibodies have been made to axillary bacteria and claimed to be effective. An adhesive deodorant tape with cyclodextrin for odor absorption has been proposed. Biochemical approaches have included interference with bacterial adhesion using polysaccharides (88).

X. CONCLUSION

The bacterial distribution in the axilla has been well characterized and related to the formation of specific axillary odors. The latter have been classified as acid or steroid materials which can be found in incubations of the bacteria and apocrine secretion as well as detected in *in vivo* extracts. Malodor reduction with sulfhydryl agents suggests that other unidentified odorants may be present. Knowledge of the mechanism of odor formation provides a rationale for both direct and indirect approaches to control or mask malodor. The use of fragrance precursors to generate fragrance materials over time could both mimic and mask the malodorants on the same time scale. These odorants also provide interesting odor perception phenomena for study of odor cross-adaptation, anosmia, induction, age and sex differences and pheromonal communication.

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