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Facts, Fallacies, Fears, and Frustrations With Human Pheromones

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ABSTRACT

Among primates in general, pheromones are of variable importance to social communication. Data on humans have generated the greatest controversy regarding the existence of pheromonal communication. In this review, the likelihood of pheromonal communication in humans is assessed with a discussion of chemical compounds produced by the axilla that may function as pheromones; the likelihood that the vomeronasal organ (VNO), a putative pheromone receptor organ in many other mammals, is functional in humans; and the possible ways pheromones operate in humans. In the human axilla, the interactions between the cutaneous microflora and axillary secretions render this region analogous to scent glands found in other primates. Both the chemistry of axillary secretions and their effects on conspecifics in humans appear to be analogous to other mammalian pheromone systems. Whichever chemical compounds serve a pheromonal function in humans, another unknown is the receptor. Although the VNO has been implicated in the reception of pheromones in many vertebrates, it is not the only pathway through which such information has access to the central nervous system; there is ample evidence to support the view that the olfactory epithelium can respond to pheromones. Furthermore, if a chemical activates receptors within the VNO, this does not necessarily mean that the compound is a pheromone. An important caveat for humans is that critical components typically found within the functioning VNO of other, nonprimate, mammals are lacking, suggesting that the human VNO does not function in the way that has been described for other mammals. In a broader perspective, pheromones can be classified as primers, signalers, modulators, and releasers. There is good evidence to support the presence of the former three in humans. Examples include affects on the menstrual cycle (primer effects); olfactory recognition of newborn by its mother (signaler); individuals may exude different odors based on mood (suggestive of modulator effects). However, there is no good evidence for releaser effects in adult humans. It is emphasized that no bioassay-guided study has led to the isolation of true human pheromones, a step that will elucidate specific functions to human chemical signals.

Key words: chemical communication; olfaction; TRP2; V1R/V2R; vomeronasal organ

Chemical signals are of variable importance to primate social communication (see further discussion in Alport, 2004). Among primates in general, data on humans have generated the greatest controversy in this regard. This review discusses the likelihood of communication among humans via pheromones.

The pheromone concept was introduced in 1959 by Karlson and Lüscher (1959), who studied invertebrate responses to invisible forms of communication. To them, pheromones were "substances which are secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behavior or a developmental process." The first chemically defined pheromone was bombykol, which is released by the female silk moth (*Bombyx mori*) to attract the male to mate (Karlson and Lüscher, 1959). Forty-five years later, scores of invertebrate pheromones have been identified, their responses have been characterized, and some have been incorporated into commercially available products, e.g., pheromone traps for pest insects. For humans, the focus of the current review, a different picture emerges.

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Pheromones were first categorized in two varieties, releasers and primers. The response of the male silk moth to bombykol is an excellent example of the former: an emitted chemical substance elicits an often immediate, specific, behavioral response, e.g., flying upwind to seek a mate. Releaser pheromones have been identified among vertebrates. A good example can be found in pigs. Boars exude 5α-androst-16-en-3-one (androstenone; often called boar taint), which will elicit lordosis in sows that are in heat (Dorries et al., 1997). The response is quick and reliable. Indeed, androstenone is sold as BOARMATE to pig farmers to assist in artificial insemination (information can be found at http://www.antecint.co.uk/main/rm/boarmate.ram). A primer pheromone, typically requiring much more time than a releaser pheromone to reveal its presence, often affects endocrine or neuroendocrine systems related to development or reproductive physiology. Many examples of primer effects have been published and were reviewed in Halpern and Martínez-Marcos (2003). These include effects on puberty, cyclicity in females, the success or failure of pregnancy, and shifts in hormone levels. Some of the pheromones that elicit these responses have been chemically identified, while others have not (Halpern and Martínez-Marcos, 2003).

In the years since the introduction of pheromones, the extensiveness of the concept has expanded. Four categories of pheromones are now identified: the original releaser and primer pheromones, signaler pheromones, and modulator pheromones. To some, releaser and signaler pheromones have been equated (Bronson, 1971), although it may make more sense to speak of them as independent. As noted, releaser pheromones can elicit a specific response, whereas signaler pheromones may only provide information, e.g., the type of genes that one possesses within the major histocompatibility complex (MHC) (Beauchamp et al., 1985; Beauchamp and Yamazaki, 2003), one's dominance status within a social hierarchy (Schilling et al., 1984; Novotny et al., 1990), the type of food that was most recently consumed (Skeen and Thiessen, 1977), or when and where to find food (Luo, 2004).

Other changes have been introduced. For example, Meredith (2001) urged that the definition of pheromone also includes mutual benefit to sender and receiver. He suggested that this limitation would overcome possible ambiguities and overgeneralizations in usage. To date, most have yet to heed this advice. If Meredith's more restrictive definition were accepted, then cross-species communication would not be included [although other concepts have been introduced to limit this possibility while maintaining the broader definition of pheromone; see discussions of allelochemicals, kariomones, and allomones in Wyatt (2003)]. Furthermore, other restrictions would be imposed if the mutual benefit clause were accepted. As Meredith (2001) points out, the well-documented shifts in the human menstrual cycle upon exposure to chemical cues from other males or females would be excluded [for a review, see Weller and Weller (1993); for an opposing view, see Schank (2000)]. Hence, in this review of human pheromonal communication, a broad definition is adopted. In doing so, however, we open the pheromone concept to certain scenarios that might otherwise appear preposterous as pheromone-mediated responses.

HUMAN PHEROMONES

Sufficient evidence, much still accumulating, suggests the presence of four types of pheromones in human chemical communication. These include primers, signalers, modulators, and releasers. Initially, we discuss potential sources of these cues in humans. We then explore the notion that detection of pheromones among humans is via the vomeronasal organ (VNO; an unlikely possibility) and close with a discussion of human responses to pheromones.

Source and Signal: Axillary Chemistry and Pheromone Creation

The axilla is a unique source of human odor. In addition to a high density of eccrine glands, the axilla contains large numbers of sebaceous and apocrine glands (Labows et al., 1982). The interactions between the cutaneous microflora and skin secretions lead to a complex mix of odorants (Leyden et al., 1981; Labows et al., 1982).

As seen in Figure 1, human axillary extracts contain a complex mixture of volatile chemicals. One or more of these volatile molecules may have pheromonal function. Axillary secretions and odorants appear to be ideal sources of pheromones: they are secreted to an area that often contains hair that can greatly increase the surface area for dispersal, are warmed to aid in volatilization, and are positioned nearly at the level of the nose of the recipient when near another person. The axilla is also the focal point for a multibillion-dollar consumer product industry. These factors, both fundamental and applied, have motivated research aimed at identifying the nature, abundance, and biogenesis of the odorous and nonvolatile components found in the underarm.

More than a decade of research has presented both organoleptic and analytical evidence that a mixture of C6–C11 normal, branched, and unsaturated acids present in axillary sweat constitutes the characteristic axillary odor. The details of the chemical identification, exact structures, and synthesis (of noncommercially available compounds) have been described (Zeng et al., 1991, 1992). In terms of relative abundance, these acids, in particular (E)-3-methyl-2-hexenoic (E-3M2H), are present in far greater quantity than volatile steroids, e.g., androstenone, which were previously thought to be important axillary odors (Gower and Ruparelia, 1993). In samples of secretions from the axillae of males that were combined before analysis, the concentration of E-3M2H was approximately 357 ng/μl extract, whereas that of androstenone was 0.5 ng/μl extract (Zeng et al., 1996b). In combined samples from females, the straight-chain acids were present in greater relative abundance than E-3M2H. Further, no androstenone was detected in these extracts. A related steroid, androstenol, was present (3.5 ng/μl extract), albeit in far lower concentration than E-3M2H (150 ng/μl extract) or the other acids (Zeng et al., 1996b). The Z-isomer of 3M2H was also present in the extracts from each gender, but in different relative abundance: 10:1 (E:Z) in males and 16:1 (E:Z) in females. E-3M2H and androstenone have comparable low olfactory thresholds (Baydar et al., 1992; Gower and Ruparelia, 1993; Wysocki et al., 1993; Zeng et al., 1996b).

Recently, researchers at Givaudan (Natsch et al., 2003) identified 3-methyl-3-hydroxylhexanoic acid (HMHA) as an additional important axillary odor constituent; how-

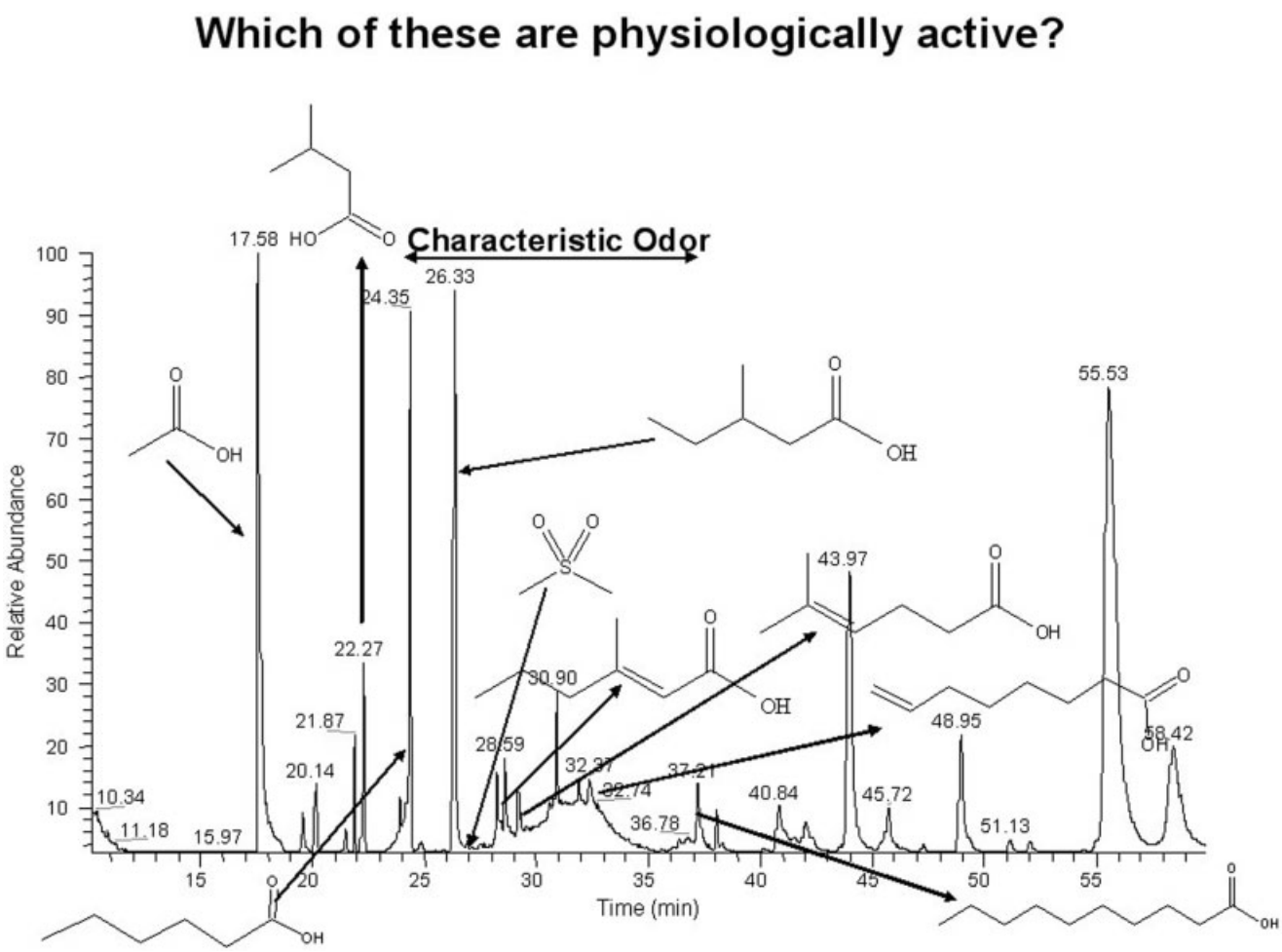

Fig. 1. A gas chromatographic trace of an extract of male axillary secretions. Much is known about axillary chemistry. For example, many of the peaks in the chromatogram have been chemically identified. Furthermore, for many of the compounds, the origins and hence the formation of odor are also understood. Specifying pheromonal components within the GC trace, if they are even visible therein, awaits identification via bioassay-driven methodology. To this end, chemistry alone may not be sufficient. For example, results from bioassays may suggest active components where no peaks appear on the chromatogram, which has been known to occur when trying to identify the active components in foods or fragrances from flowers. In the end, use of the human nose coupled with a biological response and chemical analyses should prove to be successful.

ever, the olfactory threshold for this compound has not yet been reported. Qualitatively, this compound has a cumin-like, "sweaty" note reminiscent of E-3M2H, but more pungent (data not shown).

The precursors to axillary odor reside in the apocrine glands (Labows et al., 1982; Zeng et al., 1992, 1996a, 1996b). The characteristic axillary odor is formed from the interaction of odorless (water-soluble) precursor molecules found in apocrine secretion with the cutaneous axillary microorganisms (Labows et al., 1982; Zeng et al., 1992). In addition, it has been demonstrated that the 3M2H is carried to the skin surface bound to two proteins that have been designated apocrine secretion odor-binding proteins: ASOB1, apparent molecular weight 45 kDa, and ASOB2, apparent molecular weight 26 kDa (Spielman et al., 1995, 1998). The polypeptide chain of ASOB2 is identical to apolipoprotein D (ApoD), a known member of the lipocalin proteins. The ligand carried by the apocrine ApoD is 3M2H. The structure of ASOB1 remains to be fully elucidated but it too appears to carry acidic molecules. The Givaudan group (Natsch et al., 2003) has suggested that a nonodorous precursor they isolated, an amide of 3-methyl-3-hydroxylhexanoic acid and glutamine (Nα-3-hydroxy-3-methyl-hexenoyl-glutamine; HMHA-Gln), is the actual precursor. However, due to their collection procedure, it is difficult to say that the 3M2H and/or HMHA is not initially intercathelated within ApoD.

The studies cited above, which detail the nature and origin of axillary odor, demonstrate the complexity of the components present in either axillary extracts or collected on T-shirts. They further demonstrate the similarity between human axillary secretions and nonhuman mammalian odor sources where lipocalins carry chemical signals used in pheromonal communication. In rodents (Novotny, 2003), pigs (Spinelli et al., 2002), and hamsters (Singer et al., 1989), volatile molecules appear to be bound to lipocalin proteins that transport them and are in part responsible for some of the activity. Hence, the chemistry of

TABLE 1. Some pheromone responses implicating VNO in nonhumans

Pheromone response[a]	VNO involved	Reference[a]
Primer effects		
Acceleration of puberty		
Mouse	Yes	Lomas and Keverne (1982)
Vole	Yes	Wysocki et al. (1991)
Estrus synchrony	Yes	Sánchez-Criado (1982)
Pregnancy failure	Yes	Brennan et al. (1990)
Testosterone surge	Yes	Wysocki et al. (1983)
Releaser		
Mating in sows	No	Dorries et al. (1997)
Matting by male mice	Yes	Del Punta et al. (2002)
Signaler		
Individual recognition	No	Johnston and Rasmussen (1984)
	Yes	Steele and Keverne (1985)
Recognition of MHC	No	Wysocki et al. (2004)
Strain differences in Mice	Yes	Luo et al. (2003)
Modulator		
Mood or emotion	Not demonstrated	

[a]References not intended to be exhaustive.

human axillary secretions appears to be analogous to other mammalian pheromone systems—an interesting and thought-provoking analogy. However, no bioassay-guided study has led to the isolation of true human pheromones, despite claims appearing in popular media (e.g., Web sites) and even suggested in some peer-reviewed articles (Sobel et al., 1999; Grosser et al., 2000; Savic et al., 2001). The axillary extracts discussed above may be thought of as a "medicinal tea" whose active ingredients remain to be isolated, much like the tea made from the extract of the foxglove plant that was given to chest-pain sufferers during the 18th and 19th centuries (Krantz, 1974). From this tea came the isolation and identification of digitalis.

The axillary constituents most often cited as putative human pheromones are volatile steroids: androstenone, androstenol, and 4,16-androstadien-3-one (androstadienone). The concentration and biogenesis of these compounds in human axillae have been examined (Rennie et al., 1991; Gower and Ruparelia, 1993). Additionally, androstenone and androstenol were found to be present in the characteristic odor fraction, at levels 50–100 times below the concentration of 3M2H and other organic acids (Zeng et al., 1992). Shinhoara et al. (2000) found that androstenol (commercially obtained) could alter LH pulsing when applied to the upper lip/nares region of female recipients at concentrations 1,000× above endogenous concentrations. Similarly, Jacob and McClintock (2000) used concentrations (of commercially available androstadienone) that were also 1,000× above reported axillary concentrations to demonstrate modulator pheromone effects for androstadienone. Subsequent work by Lundstrom et al. (2003b) has demonstrated that the concentration used by Jacob and McClintock (2000) yielded vapor-phase concentrations of androstadienone that are about at the average olfactory threshold for this compound, namely, 211 vs. 250 μM used by Jacob and McClintock (2000). Lundstrom et al. (2003a), however, did report a single significant mood effect ("being focused") when they applied 250 μM to the nasal area of subjects.

Although the specific chemical identities remain to be determined, humans carry with them unique chemical signatures. These odorprints are hypothesized to consist of a bouquet of odorants whose relative amounts differ across individuals. These odorants may also be present in all of our bodily fluids and secretions and are regulated and/or produced in part by the set of genes that code for immune function (human leucocyte antigen; HLA). Several studies have demonstrated that axillary volatiles collected on pads and/or T-shirts allow individuals to identify their own odor as well as those of their spouse and close kin (Schleidt, 1980; Porter and Moore, 1981; Schleidt et al., 1981; Cernoch and Porter, 1985; Hepper, 1988). These studies strongly suggest that axillary secretions contain odorants unique to individuals that may be used for identification (signaler pheromone). Some have suggested that they may play a role in mate choice (Jacob et al., 2002). HLA-related proteins have been detected in both the lactiferous ducts of the breast, a structure analogous to the axillary apocrine glands, and the intradermal portion of the sebaceous glands (Murphy et al., 1983). Studies from one laboratory (Zavazava et al., 1990, 1994) have reported the presence of an HLA class 1 molecule in human axillary sweat collected after exercise (a mixture of apocrine, apoeccrine, sebaceous, and eccrine secretion). These investigators also demonstrated that individuals who were HLA-A23, -A24, or -B62 expressed higher levels of soluble HLA molecules in serum than individuals without those specificities. Two-thirds of individuals who had the strongest body odors, when evaluated organoleptically, were from one of the above antigenic specificities, suggesting a direct link between body odor intensity and levels of soluble HLA-related proteins. The only study that has examined the structures of immune system-related odorants was performed with rodents (Singer et al., 1997). Data in this publication suggest that in these animals the urinary odorprint is formed by acidic constituents. Phenylacetic acid was the sole identified acidic compound that was significantly different between the two groups with different MHCs. We currently hypothesize that human odorprints will also be formed by ratios of organic acids in the axillae, urine, and other fluids.

TABLE 2. Comparison between nonprimate, e.g., mouse, and human vomeronasal system at different levels of analysis

Level	Nonhuman	Human[a]	
		Fetus	Adult
Vomeronasal organ (VNO)	Tubular structure in rostral nasal cavity	Present[b]	Present[c]
Bipolar receptor cells within VNO	Typically bilateral on medial surface	Present[d]	Absent[e]
Intact receptor genes presumed to be expressed in VNO	At least two subfamilies, namely, V1R and V2R ($\approx$ 150 in V1R alone)	Unknown	Absent[f]
Transduction mechanisms	Uses TRP2 Ca^{++} channel	Unknown	Absent[g]
Axonal projections to brain (from bipolar neurons)	Traverse nasal septum and cross cribriform plate rostromedially	Present[h]	Absent[i]
Identifiable accessory olfactory bulb	Typically in rostrocaudal location in olfactory bulb	Unknown	Absent[j]

[a]In some instances, references are only a sampling of what is available.
[b]Boehm and Gasser (1993); Boehm et al. (1994); Smith et al. (1996, 1997).
[c]Jacobson (1811); Takami et al. (1993); Smith et al. (1998); Bhatnagar et al. (2002); Smith et al. (2002).
[d]Kjaer and Fischer Hansen (1996a, 1996b).
[e]Trotier et al. (2000); Witt et al. (2002).
[f]One V1R1L gene is expressed in the olfactory epithelium (Rodriguez et al., 2000); others may be intact, but expression has not been identified in the VNO (Rodriguez and Mombaerts, 2002).
[g]Liman and Innan (2003).
[h]Kjaer and Fischer Hansen (1996a, 1996b).
[i]Inferred from Boehm et al. (1994), who note that the vomeronasal nerve disappears during development of the fetus, after neurons that contain GnRH complete their migration from the VNO to the olfactory bulbs and basal forebrain (Schwanzel-Fukuda, 1999; Wray, 2002).
[j]Meisami and Bhatnagar (1998).

Pheromone Receptor: Likelihood of a Human VNO

Among mammals in general, the VNO is involved in the detection of pheromones (Table 1), and this is likely the case in at least some nonhuman primates (see Alport, 2004 in this issue for further discussion). However, the olfactory system also detects pheromones. In pigs, Dorries et al. (1997) reported that sows responded to the boar pheromone, androstenone, after reception by the VNO was prevented. In the lesser mouse lemur (*Microcebus murinus*), a prosimian that possesses a well-developed VNO, responses to chemical cues were mixed after disruption of inputs via the VNO, namely, female-elicited intermale aggression was eliminated, male investigation of females was reduced, and copulations with females was reduced. However, successful inseminations were not significantly different from control levels (Aujard, 1997). In mice, removal of the VNO (VNX) did not affect ability to learn a Y-maze-based task for a reward where reinforcement was provided upon successful chemosensory-based discrimination of MHC-type signals originating from urine obtained from donor mice; mice with VNX continued to discriminate MHC-based individuality among other mice (Wysocki et al., 2004).

Among sheep, results of tests of VNO involvement in maternal behavior are mixed. Levy et al. (1995) generated a strong case for olfactory involvement. They had earlier reported that cutting the vomeronasal nerves had no effects on maternal behaviors. Notably, primiparous and multiparious ewes continued to discriminate own from alien young, whereas rendering olfaction nonfunctional significantly disrupted maternal behaviors. Booth and Katz (2000) later reevaluated a role for the VNO in similar situations by cauterizing the opening of the VNO, thereby preventing access of chemosensory stimuli to receptor cells therein. As stated by the authors: "Cauterized ewes allowed alien lambs to suckle and they were unable to distinguish alien lambs from their own lambs, whereas the ewes . . . with functional vomeronasal organs . . . violently rejected any alien lamb's attempt to suckle. Thus, female sheep use their vomeronasal organs for neonatal offspring recognition" (Booth and Katz, 2000: p. 953).

Importantly, the VNO also detects nonpheromonal chemicals (Tucker, 1971; Sam et al., 2001). Therefore, linking detection of pheromones with the VNO or labeling substances detected by the VNO as pheromones is a non sequitur (Preti and Wysocki, 1999; Wysocki and Preti, 2000, 2002).

Some have claimed that the human VNO is the detector of human pheromones (Monti Bloch and Grosser, 1991; Monti Bloch et al., 1994; Berliner et al., 1996). Supporting evidence comes from electrophysiological recordings obtained from the epithelium within the adult VNO (Meredith, 2001). These findings are puzzling, given the overwhelming preponderance of genomic, proteomic, and anatomical evidence strongly suggesting that the human VNO is nonfunctional, at least in the way that it is understood to work from studies in other mammals (Table 2).

Most of the genes identified as coding for receptor proteins in the VNO of the mouse are pseudogenes in humans (Rodriguez and Mombaerts, 2002). Furthermore, although a few genes that express receptors in the mouse VNO appear to have an intact coding region in the human genome (Rodriguez et al., 2000), none have been found to express proteins within the human VNO.

Among mammals that express functional receptors within the membranes of bipolar receptor cells of the VNO (Fig. 2), sensory transduction associated with these molecular receptors appears to rely on a calcium channel that is encoded by the *trP2* gene (Liman and Innan, 2003). Among humans and other catarrhines, *trP2* is a pseudogene (Liman and Innan, 2003). Hence, at the genomic and

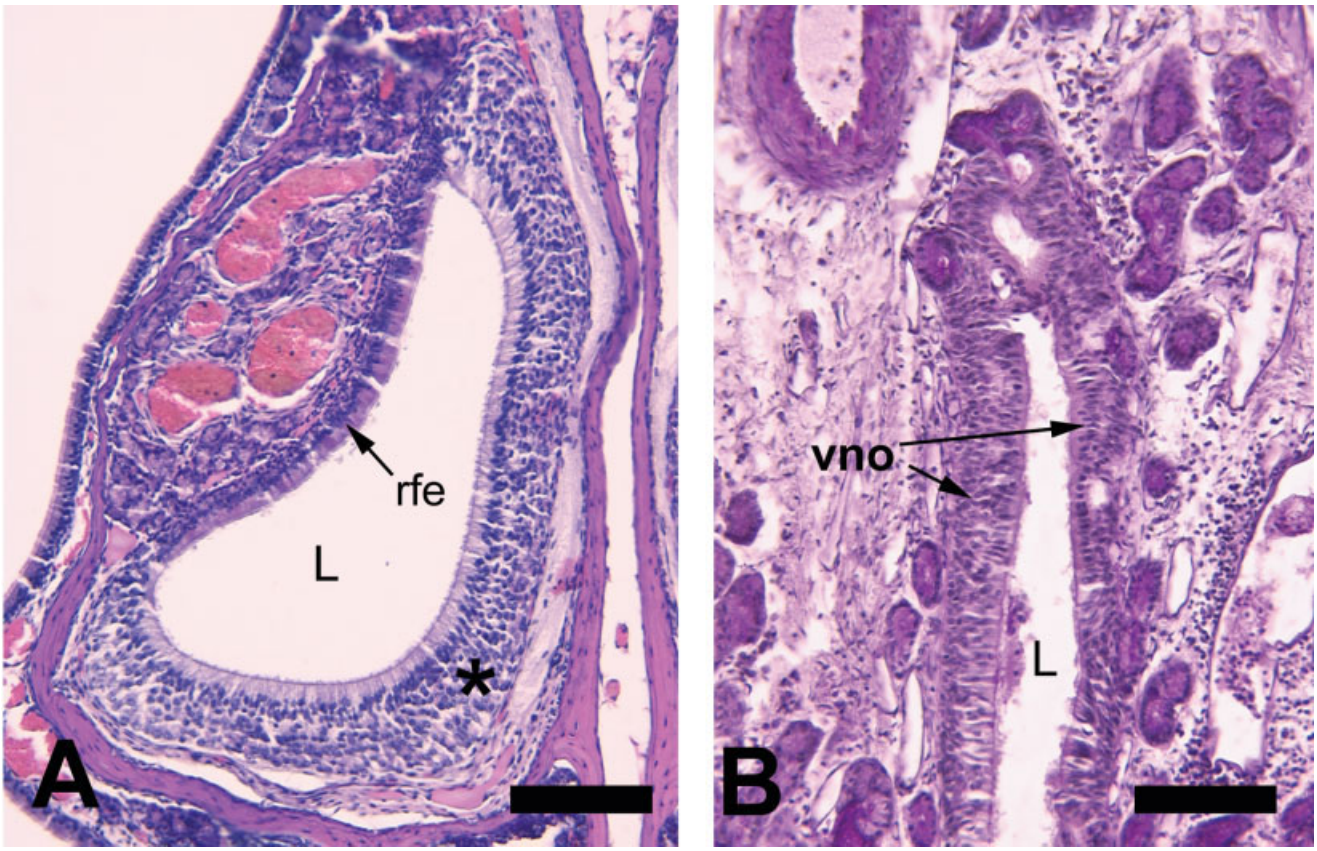

Fig. 2. Coronal sections through the VNO, courtesy of T.D. Smith. **A:** From an adult *Microtus pennsylvanicus*. The midline septum (not shown) is to the right and dorsal is above the VNO. **B:** From an adult human. The midline septum (not shown) is on the right and superior is above the VNO. Scale bar = 100 μm. L, lumen; rfe, receptor (bipolar cell)-free epithelium; asterisk, neuroepithelium.

proteomic levels, the human vomeronasal system cannot function as it is understood to work in nonprimates.

At the anatomical level, bipolar receptor cells can be found within the VNO of the developing human fetus (Boehm and Gasser, 1993; Boehm et al., 1994), but are absent in the adult (Fig. 2). Although these VNO-associated neurons appear to connect with the brain early in development, they degenerate shortly after other neurons that contain gonadotropin-releasing hormone (GnRH), presumably members of the terminal nerve (Wirsig-Wiechmann, 2001), migrate along these vomeronasal nerves from their origins in the olfactory placode/VNO to their destination in the basal forebrain (Wray, 2002). Within the brain, vomeronasal nerves normally terminate within the accessory olfactory bulb (AOB), a structure that is embedded within the main olfactory bulb but has no direct connections with it. In adult humans, the AOB cannot be located (Meisami and Bhatnagar, 1998).

With respect to the human VNO, the anatomical literature reveals an emerging consensus. Jacobson (1811), now known to be incorrect, states that "man is the only terrestrial mammal in which this organ is totally absent"; Boehm and Gasser (1993), in their study of the fetal VNO, report that they "did not observe receptor-like cells" in the oldest fetuses; and in a follow-up study, Boehm et al. (1994) state that "the vomeronasal nerve disappears . . . leaving only a vestigial structure in the nasal septum." Trotier et al. (2000) are quite firm at one point that "the vomeronasal structure does not function as a sensory organ in adult humans." Hence, any pheromone response by humans is likely mediated via the olfactory neuroepithelium rather than by the VNO.

Pheromone Response: Primers, Signalers, Modulators, and Releasers

Among primer effects in humans, those most often discussed are the effects of chemical signals on the menstrual cycle or its underlying hormonal systems (Table 3). In humans, there are many examples of signaling pheromones, including recognition of kin, gender, sexual orientation, and, at least for the MHC, genetic identity by chemical signals. Also included in this category are signals indicative of diet and disease. As an organizing construct, the modulator pheromone is a latecomer, having been recently introduced in Jacob and McClintock (2000) and McClintock (2000). These cues, originally construed as signaler pheromones (which remains possible), are thought to modify extant moods or emotional states. Although the fourth category of pheromones is the most discussed, at least in the lay literature and among the media, little solid evidence for releaser pheromones in adults can be found within the biomedical literature.

TABLE 3. Quick reference to types of pheromones and evidence that humans may use the mode to communicate chemical information

Type of pheromone	Effect	References for human responses
Primer	Endocrine/neuroendocrine	Weller and Weller (1993); Stern and McClintock (1998); Preti et al. (2003)
Releaser	Behavioral	Varendi and Porter (2001)
Signaler	Informational	Cernoch and Porter (1985); Jacob et al. (2002)
Modulator	Influences mood or emotion	Chen and Haviland-Jones (1999, 2000); Jacob et al. (2000); Ackerl et al. (2002); Preti et al. (2003)

Primer pheromones. Excellent examples of primer pheromones have been described for both male and female nonhuman animals (Halpern and Martínez-Marcos, 2003). The effects are numerous. Beginning early in life, exposure to chemical signals from adults of the opposite sex typically will advance the onset of puberty, while exposure to analogous signals from the same sex will retard the onset of puberty (Bronson and Macmillan, 1983). Estrous cyclicity in females can be radically affected by primer pheromones. Female mice living in a densely packed cage alter the composition of their urine such that it inhibits cyclicity among the females (van der Lee and Boot, 1955). Furthermore, exposing an isolated female mouse to bedding laden with chemical cues from the group of female mice will inhibit cyclicity in the isolate (Drickamer, 1974). Alternatively, adding urine from an adult male mouse to the cage of the group-housed females will disrupt the shared cessation of cyclicity (Whitten et al., 1968). In many species, males that are exposed to chemical cues from novel adult females will typically exhibit a spike in luteinizing hormone (Maruniak and Bronson, 1976), followed by a surge in testosterone (Wysocki et al., 1983). In some species, pregnant females exposed to pheromones of adult males that did not impregnate the females will terminate the pregnancy by reabsorbing the fetuses (Bruce, 1959) or, at least in microtine rodents, prematurely deliver unviable offspring (Richmond and Stehn, 1976).

Among humans, the most studied phenomenon that is analogous to those noted concerns the menstrual cycle (McClintock, 1971). Myriad, but not unanimous, reports document menstrual synchrony among females sharing a common environment (Weller and Weller, 1993). Where this occurs, the effects are thought to result from exposure to pheromones from a driver female (Russell et al., 1980) whose cycle is thought to remain unaffected but who provides the temporal cues to synchronize the cycles of other females [(Preti et al., 1986); see Wilson (1992) for a critique]. Depending on the stage of the cycle of driver female, these cues appear either to accelerate or to retard the onset of ovulation in recipient females [(Stern and McClintock, 1998); for an alternative interpretation, see comments by Whitten (1999)].

Recently, another female-female effect on the menstrual cycle has been reported. In this particular instance, however, the effect was not to synchronize but to increase variability among women. Jacob et al. (2004) reported that the odors obtained from the breasts of lactating women disrupted "the normal homeostatic regulation of cycle length" in other nulliparous women who were given the chemical signals. The effect was pronounced—variability in cycles increased threefold—and was suggested to play a role in fertility in the general population of women.

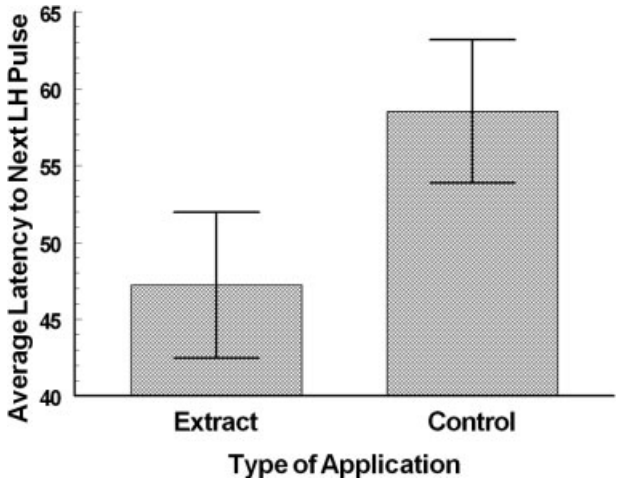

Fig. 3. Average latency to the next LH peak subsequent to the application of male axillary extracts (extract; 47 ± 5 min), applied three times, spaced by 2 hr each, or subsequent to the application of the control solutions (control; 59 ± 5 min), also spaced by 2 hr each (Preti et al., 2003). In an analysis of variance, the main effect of stimulus type on latency to the next pulse was significant ($F(1,16) = 28.34$; $P < 0.001$).

Effects on the menstrual cycle are not limited to pheromones from other females. Apparently, a cue from the underarms of males can affect the menstrual cycle, and at least a subset of the hormones that underlie the cycle. In one study, females were selected for having an aberrant cycle (either much longer or shorter than the prototypical 29.5 ± 3 days). They then received an extract of secretions collected from the underarms of male donors or a control extract. When compared with the results obtained from the control group, females receiving the males' extract had a more regular cycle (Cutler et al., 1986).

The results of a more recent study provide a possible mechanism to support pheromone-mediated shifts in the menstrual cycle (Preti et al., 2003). In this study, female subjects in the first 7 days of their cycle were confined to a hospital setting and had an in-dwelling catheter inserted to collect venous blood every 10 min. In a crossover design, every 2 hr each woman received on the upper lip either an extract of underarm secretions from donor males or a control solution (phase 1). After 6 hr, the conditions were reversed (phase 2). During extract exposure, the onset of the next peak of luteinizing hormone (LH) was advanced by ~ 20% after application of the male pheromones(s) relative to the LH response in the control condition (Fig. 3) (Preti et al., 2003). Across subjects, the effect was robust; the pulse after pheromone application, rela-

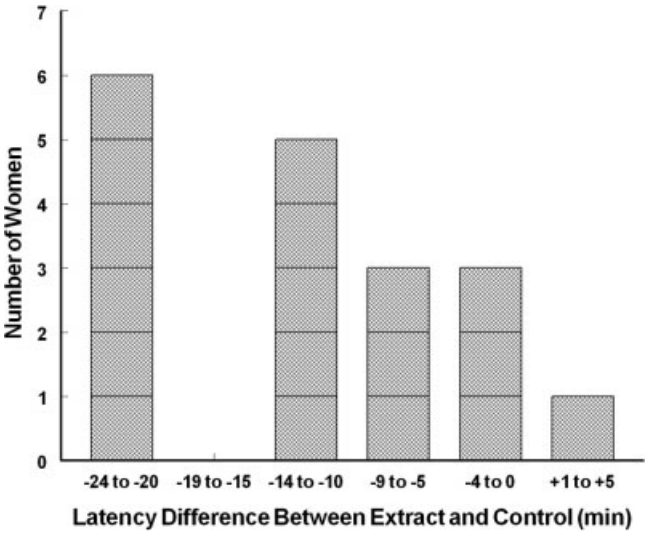

Fig. 4. Average latency difference (in min) generated by subtracting the average latency to the next LH peak subsequent to the application of the control stimulus from the average latency to the next LH peak subsequent to the application of male axillary extracts (Preti et al., 2003). Sixteen of the 18 women had an average latency to the next LH pulse that was shorter in the extract condition than in the control condition; 1 woman had latencies that were equivalent in both conditions (Wilcoxon signed rank test = 3.54; two-tailed $P < 0.0001$).

tive to the control condition, was retarded in only 1 of the 18 subjects (Fig. 4). Although the phase of the study revealed an anticipated diurnal effect, it did not influence the effects of the males' pheromone(s).

Signaler pheromones. Much literature supports the claim that nonhuman animals can recognize kin via odor signatures (Wyatt, 2003). Not to be outdone, human mothers of newborn babies can also recognize their offspring by odor alone (Kaitz et al., 1987); fathers, however, fail at the task. Early exposure to chemical cues circulating in the mother's bloodstream (and thereby stimulating the olfactory epithelium) may be a possible explanation (Beauchamp et al., 1995). The odorprint, while modified by diet, disease, and other environmental factors (Mennella and Beauchamp, 1991), has in part a genetic basis. Genes within the MHC (HLA in humans) confer on an individual a unique odor that is predictive of subtle, perhaps even single gene, differences across individual genotypes (Bard et al., 2000). These odorprint signatures can be discriminated by scent alone (Yamazaki et al., 2000) and have been implicated in or suggested to influence mate choice in some species (Beauchamp et al., 1985), including humans (Jacob et al., 2002).

Much other information can be obtained from signaling pheromones. Herein lies one of the problems with the broad definition of pheromone. Is information per se actually a pheromone? For example, an urbanite has a choice of one of two stairwells into a subway system, but one of them has been scented by an earlier human visitor who was ill and vomited (a chemical cue from a member of the same species). The urbanite detects the odor and chooses the unscented entrance, thereby producing a behavioral response to a conspecific chemical cue. The result may benefit the recipient of the chemical message, e.g., prevent a stimulus-induced, perhaps retching, response. Would an independent naive observer record pheromone-mediated behavior?

Modulator pheromones. This newest addition to the pheromone family was introduced in 2000 by McClintock's laboratory (Jacob and McClintock, 2000; McClintock, 2000). Modulator pheromones were purported to affect moods or emotions. Indeed, the authors state that a purported pheromone "appears to modulate affect" to elicit noted changes "rather than [by] releasing stereotyped behaviors" (Jacob and McClintock, 2000: p. 57).

There are reports that the odor of a body changes with emotional state (Chen and Haviland-Jones, 1999, 2000; Ackerl et al., 2002). People who were placed in situations that provoked anxiety, e.g., watching fear-inducing film clips, changed their body odor. These body odors were different from those collected during unprovoked conditions or when the same individuals were exposed to film clips of comedic situations. Other people were able to discriminate the differences among the various emotion-inducing conditions; however, what was not reported was whether the moods of the volunteers who were sniffing the body odors were affected by the body odors that they were evaluating. Did the mood of the evaluators shift to match that of the donor?

In a much different experimental design, Preti et al. (2003) noted that an extract of sweat, collected from pads that were worn in the armpit of male donors, was able to shift the mood of females who had the extract applied to the upper lip. In a crossover design, the females were "more relaxed" and "less tense" during a 6-hr period when sweat from males was present on the lip than in the 6-hr control condition when only the vehicle was on the lip. These results suggest that modulator responses may indeed occur among humans, but much more research on this topic needs to be performed.

Releaser pheromones. Of the classes of pheromones, releasers are most often associated with sexual attraction. This has in part a historical foundation. The pivotal publication by Karlson and Lüscher (1959) described the upwind-seeking behavior of male moths in the presence of a sexual attractant isolated from female moths. Releaser pheromones, however, exist in many more flavors and elicit various behaviors: aggression from males (Maruniak et al., 1986) and females (Bean and Wysocki, 1989); maternal behavior (Del Cerro, 1998), even from nulliparous females (Saito et al., 1998); suckling in infant rabbits (Schaal et al., 2003). Indeed, among humans, infants are attracted to breast odors of their mother and move in the direction of the odors (Varendi and Porter, 2001). To date, this crawling movement by infants is likely the only human releaser pheromone response documented in the biomedical literature.

CONCLUSIONS

In the human axilla, interactions between the cutaneous microflora and axillary secretions render this region analogous to scent glands found in other primates. Both the chemistry of axillary secretions and their effects on conspecifics in humans appear to be analogous to other mammalian pheromone systems; however, key questions remain, such as the site for pheromonal reception. The

most plausible receptor organ in humans remains the olfactory neuroepithelium, especially given the paucity of convincing evidence for a functional VNO. Despite some uncertainty regarding the actual mechanism of pheromone reception, there is good evidence for at least certain pheromonal effects in humans (e.g., primer, signaler, and modulator pheromones). It is emphasized, however, that no bioassay-guided study has led to the isolation of true human pheromones, a step that will elucidate specific functional responses to human chemical signals.

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