

Cairo University

# Journal of Advanced Research



# **REVIEW ARTICLE**

# Pheromones in sex and reproduction: Do they have a role in humans?

Taymour Mostafa<sup>a,\*</sup>, Ghada El Khouly<sup>b</sup>, Ashraf Hassan<sup>c</sup>

<sup>a</sup> Andrology & Sexology Department, Faculty of Medicine, Cairo University, Cairo 11562, Egypt

<sup>b</sup> Psychiatry Department, Faculty of Medicine, Ain Shams University, Cairo 11371, Egypt

<sup>c</sup> Dermatology & Andrology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Received 3 August 2010; revised 28 February 2011; accepted 4 March 2011 Available online 13 April 2011

# **KEYWORDS**

Olfaction; Sex; Pheromones; Libido; Behaviour; Reproduction

ELSEVIER

**Abstract** Pheromones are found throughout the living world and are a primal form of communication. These chemical messengers are transported outside the body and have a direct developmental effect on hormone levels and/or behaviour. This review article aims to highlight the role of human pheromones in sex and reproduction. A review of published articles was carried out, using PubMed, medical subject heading (MSH) databases and the Scopus engine. Key words used to assess exposure, outcome, and estimates for the concerned associations, were; olfaction; sex; pheromones; libido; behaviour; reproduction; humans; and smell. Although there are studies to support this phenomenon, they are weak because they were not controlled; others have proposed that human olfactory communication is able to perceive certain pheromones that may play a role in behavioural as well as reproductive biology. Unfolding the mysteries of smells and the way they are perceived requires more time and effort as humans are not systems that instinctively fall into a behaviour in response to an odour, they are thinking individuals that exercise judgment and subjected to different motivations.

© 2011 Cairo University. Production and hosting by Elsevier B.V. All rights reserved.

\* Corresponding author. Tel.: +20 105150297. E-mail address: taymour1155@link.net (T. Mostafa).

2090-1232  $\odot$  2011 Cairo University. Production and hosting by Elsevier B.V. All rights reserved.

Peer review under responsibility of Cairo University. doi:10.1016/j.jare.2011.03.003

Production and hosting by Elsevier

# Introduction

The term "pheromone" is based on the Greek words *Pheran* – to transfer – and *Horman* – to excite [1]. They are chemical molecules released in humans, insects, and animals to trigger a response to or to elicit specific behavioural expressions or hormonal changes from the opposite sex, the same sex or both sexes of the same species. These signaling molecules are contained in body fluids such as urine, sweat, specialized exocrine glands, and genital mucous secretions [2,3].

Pheromones are broadly divided into two classes: (1) releaser pheromones that produce short-term behavioural changes and act as attractants or repellents; and (2) primer pheromones that produce long-lasting changes in behaviour or development via activating the hypothalamic–pituitary–adrenal axis [4]. Therefore, pheromones are differentiated into aggregation pheromones, alarm pheromones, epideictic pheromones, territorial pheromones, trail pheromones, information pheromones and sex pheromones [5–11].

## Smell and pheromones

The sense of smell is important as an arousal system that calls attention to significant environmental events and changes. Humans have the ability to store odour memories, generating consequential odour preferences or aversions [12]. Olfactory signals were demonstrated to induce emotional responses even if an olfactory stimulus is not consciously perceived, presumably because olfactory receptors not only send projections to the neocortex for conscious processing but also to the limbic system for emotional processing [13,14].

The standard view of pheromone-sensing was based on the assumption that most mammals have two separated olfactory systems with different functional roles: the main olfactory system for recognizing conventional odorant molecules and the vomeronasal system specifically dedicated to detect pheromones [2]. In humans, the vomeronasal organ (VNO) was regarded as vestigial, but different researchers assumed its function to have a distinct sensory passage to detect pheromones. It is reported that nasal receptors near the entrance of the nose had the strongest reaction to air containing pheromones, transferring it to stimulate the hypothalamus with a signal of attraction, sexual desire, arousal etc. [15–18].

Jahnke and Merker [19] described the ultrastructure of the adult human VNO having a duct-like invagination of the epithelium surrounded by numerous exocrine glands with short ducts. Deeper there are pseudostratified columnar epithelial cells with plump processes, kinocilia, and microvilli at the apical cell membrane. Underneath the basement membrane, numerous myelinated and unmyelinated axons are present in the vascular lamina propria.

Monti-Bloch and Grosser [20] evidenced that steroids may act as gender-specific chemical signals in humans, exciting an electrical response from the residual VNO to affect hormone levels. Wood [21] showed that the effectiveness of a chemosensory input to particular brain nuclei depends critically on the simultaneous presence of a steroid hormone in the same nucleus.

Foltán and Sedý [22] hypothesized that a damaged VNO during Le Fort I osteotomy of the maxilla could affect the patient's social life in terms of selecting mates and relations. Keller et al. [23] showed that both the main and accessory olfactory systems are able to process partially overlapping sets of sexual chemo-signals complimentarily supporting aspects of controlling sexual behaviour. Savic et al. [24] added that anosmics are unable to activate the hypothalamus with oestra-1,3,5 (10), 16-tetraen-3-ol (EST), suggesting that in healthy men, EST signals were primarily transmitted via the olfactory system.

However, the adult human VNO, in different studies, has been reviewed as non-functional as it contains few neurons and has no sensory function where no cells were shown to express olfactory marker protein, have synaptic contacts or have evidence for a nerve connecting to/from the VNO. In addition, Trpc2, essential for vomeronasal signal transduction in some animals, is a pseudogene in human. But non-functional VNO does not mean that there are no pheromones in humans, because some pheromone signals may be mediated by olfactory epithelium [25–30].

#### **Odour-producing organ(s)**

In humans the main odour-producing organ is the skin through its apocrine sebaceous glands, which develop during puberty and are associated with sweat glands and tufts of hairs. These glands are located everywhere on the body surface, but concentrate in six areas: the axillae; the nipples; the pubic, genital, circumanal regions; the circumoral region, lips; the eyelids; and the outer ear. The first four regions are generally associated with varying amounts of hair growth, which makes perfect sense where the extremely large surface area of a tuft of hair is effective for spreading an odour by evaporation [31].

The underarms are the ideal location for the dispersion of odours because they are among the warmest parts of the body, the first parts to perspire, are amply endowed with apocrine and sweat glands, have usually strong growth of hair, are well-situated to disperse odours in the region of other peoples' noses and are protected from excessive evaporation. Substances produced by these glands are relatively imperceptible to the human nose because what are smelled are not the original glandular secretions but rather their bacterial breakdown products. Urine and faeces are also other potentially important odour sources [32–34].

#### Sex pheromones

In humans, the claimed secreted male pheromone that attracts a woman is androstenone h exerting a positive effect on her mood, cognition and heightens sympathetic nervous system arousal. Also, the claimed unknowingly secreted female pheromone that attracts a man is androstenol [35–42]. The apocrine axillary glands, regarded as pheromone-producing scent glands, do not begin to function until puberty when sex hormones have an impact on their activity. Beier et al. [43] suggested a possible link between steroid hormone action and induction of pheromone production by investigating the localization of androgen receptor and estrogen receptors ( $\alpha$  and  $\beta$ ) in these glands.

The free steroids present in hair as products of sebaceous glands, and the sulphate ester steroids as products of sweat glands, were isolated also from the axillary sweat of males and females. In 1 g axillary hair, the free 4-androstene-3 beta, 17 beta-diol, testosterone, 5 alpha-dihydrotestosterone, dehydroepiandrosterone, androsterone, 4-androstene-3,17-dione and 5 alpha-androstane-3,17-dione occurred in nanomole amounts, whereas DHAS, androsterone sulphate and 5-androstene-3 beta,17 beta-diol-3-sulphate were 1000 times these amounts [44,45].

# Vaginal secretions

Whether or not human vaginal secretions contain a kind of sex pheromone (copulin) influencing male perception of females and inducing hormonal changes in males, is still debated. Human vaginal secretions contain various short chain (C2–C6) fatty acids, with predominated acetic acid suggesting a possible correlation with the rise and fall of hormone levels during the menstrual cycle [46,47]. To verify this, Waltman et al. [48] collected vaginal samples by tampon from 50 healthy young women, demonstrating that volatile aliphatic acids were increased during the late follicular phase of the cycle and declined progressively during the luteal phase, where women on oral contraceptives had lower amounts of volatile acids and did not show rhythmic changes in acid content during their menses.

In addition, Keith et al. [49] determined the odour composition of vaginal secretions before and after coitus using a condom to prevent male secretions or seminal fluid from entering vaginal secretions. They estimated 13 odourous compounds occurred regularly where components with acidic odour appeared at lower retention rates in post-coital samples concluding that differences exist in the odours of preand post-coital vaginal secretions.

# Scientific studies suggesting human pheromones

Different scientific studies have suggested the possibility of pheromones in humans.

- McClintock [50], and Stern and McClintock [51] tested the synchronization of the menstrual cycles among women based on unconscious odour cues (McClintock effect) where a group of women were exposed to a whiff of perspiration from armpits of other women. This caused their menstrual cycles to speed up or slow down depending on the timing of when the sweat was collected; before, during, or after ovulation.
- Russell [52] proposed that men secrete musk-like substances that women are maximally sensitive to during ovulation coupled with a noticeable increase in coitus during this period. If valid, this phenomenon might be responsible for women's reputed tendency for unusual foods during pregnancy and menses.
- Russell [52] tested the ability of sleeping babies to differentiate between pads worn by their own or by strange mothers indicating either that the baby imprints on its mother's odour, or that the mother unconsciously marks her baby with a distinctive scent. This is supported by the common observation that a child rejects his favourite blanket or stuffed toy after it has been washed, presumably because it has lost a specific odour acquired in previous contacts.

- Comfort [53] reported that the age of onset of menstruation for girls had a direct correlation with the time that young girls spend with boys, due to their exposure to odours of the opposite sex. This phenomenon was documented in mice (Vandenbergh effect) where female mice raised alone have a higher age of maturation than those raised in cages filled with a male mouse's bedding material. When the bedding belonged to a castrated male mouse, this effect was not observed.
- Preti et al. [54] indicated that constituents from the axillary region of donor females shifted the time of menstrual onset of another group even in the absence of social contact.
- Preti et al. [55] extracted underarm secretions from pads worn by men and placed that extract under the noses of women volunteers while monitoring serum LH and emotion/mood. The putative male pheromone(s) was demonstrated to advance the onset of the next peak of LH after its application, with reduced tension and increased relaxation, suggesting that male axillary secretions had constituent(s) that act as modulator pheromones.
- Cutler et al. [56] showed that the application of male axillary secretions to the upper lips of female volunteers had a regulatory effect on their menses.
- Ellis and Garber [57] reported that girls in stepfather-present homes experienced faster puberty than girls in single-mother homes. The younger the daughter when the new male arrived on the scene, the earlier her pubertal maturation.
- Wyart et al. [39] showed that the smell of androstadienone of male sweat maintains higher levels of cortisol in females and therefore has the ability to influence the endocrine balance of the opposite sex.
- Van Toller et al. [58] showed that skin conductance in volunteers exposed to androstenone was higher than that of non-exposed volunteers, providing evidence of the physiological effects of pheromone exposure.
- Filsinger et al. [59] asked males and females to rate vignettes of a fictional target male and female using semantic differentials, and to provide a self-assessment of mood. The test materials, sealed into plastic bags, were either impregnated with androstenol, androstenone, a synthetic musk control, or a no-odour control. Females exposed to androstenone produced a lower sexual attractiveness rating of the target male, while males exposed to androstenol perceived the male targets to be more sexually attractive.
- Benton [60] reported that androstenol application influenced rating of subjective mood at ovulation.
- Grammer [61] found that females rated androstenone differently at various phases of their menstrual cycle. Contraceptive pill use appeared to influence female perception of androstenone suggesting that it may affect smell sensitivity or gonadal hormone levels, disrupting pheromone detection.
- Thorne et al. [62] employed a repeated measures, double blind, balanced cross-over design to assess the possible influence of menstrual cycle phase and contraceptive pill use in both pheromone-present and -absent conditions. During four sessions, the volunteers (n = 32) rated male vignette characters, and photographs of male faces, on various aspects of attractiveness. Pheromone exposure resulted in significantly higher attractiveness ratings of vignette characters and faces. Use of contraceptives or menstrual

cycle phase had equivocal effects on some vignette items but had no influence on female ratings of male facial attractiveness.

- Morofushi et al. [63] examined the relation between menstrual synchrony and the ability to smell putative pheromones, 3alpha-androstenol and 5alpha-androstenone, among 64 women living together in a college dormitory. Twenty four (38%) of them became synchronized with roommates within three months indicating that women who showed menstrual synchrony had a higher sensitivity to 3alpha-androstenol but not necessarily to 5alphaandrostenone.
- Shinohara et al. [64] examined the effect of axillary compounds collected from women in the follicular phase (FP), ovulatory phase (OP) treated with isopropyl alcohol (IPA) on pulsatile secretion of serum LH. The recipients were not exposed to either axillary compounds or to IPA for the first 4 h and were exposed to FP or OP compounds, or to IPA, during the next 4 h. The frequency of LH pulse was increased by FP compounds and was decreased by OP compounds, but was not changed by IPA.
- Watanabe et al. [65] investigated changes of olfactory perception during the menstrual cycle using cyclopentadecanolide vapour. The results obtained from 18 trials showed that olfactory contrast was significantly enhanced at the ovulatory and/or menstrual phases.
- Spencer et al. [66] demonstrated that natural compounds collected from lactating women and their breast-fed infants increased the sexual motivation of other women, measured as sexual desire and fantasies where those with a partner experienced enhanced sexual desire whereas those without a partner had more sexual fantasies.
- Moshkin et al. [67] assessed the scent attractiveness to female students of sweat samples collected from male students before and during exams. Male students with low basal salivary cortisol were assessed as more scent-attractive than students with high levels. A high level of salivary testosterone was associated with low scent attractiveness of the male students, but only for recipients in the non-receptive phase of the menstrual cycle. Females in the receptive phase were shown to assess the scent attractiveness of male students higher than those in the non-receptive phase. It is concluded that basal variation of stress-related physiological indices, such as salivary cortisol, are mirrored in male chemical signals, which are recognized by females.
- Kwan et al. [68] showed that substances similar to androstenone are secreted in the smegma and the apocrine glands of the underarm and pubic areas of men. Also, the male pheromones  $5\alpha$ -androst-16-en-3-one and 4,16-androstadien-3-one were found to be concentrated in human semen. The fact that men's bodies secrete these substances and that women are maximally sensitive to them when they are most fertile may point to an olfactory-sexual role for these substances in human sexuality.
- Schaal et al. [69] showed that mammalian females release olfactory attraction in their offspring by mammary odour. These signals and cues confer success for the offspring's approach, exploration of the maternal body surface ensuing effective initial feeds and rapid learning of maternal identity.

- Vaglio et al. [70] analyzed the chemical content of volatiles of sweat patch samples from the para-axillary and nippleareola regions of women during pregnancy and after childbirth. There were five volatile compounds (1-dodecanol, 1-1'-oxybis octane, isocurcumenol, alpha-hexyl-cinnamic aldehyde, and isopropyl myristate) that were absent outside pregnancy. It is concluded that differentiation of volatile patterns in pregnant women may help newborns to distinguish their own mothers.
- Marazziti et al. [71] suggested that the application of male axillary extracts to women may modify the affinity of their platelet 5-HT transporter and of some impulsiveness and romantic attachment characteristics.

# Pheromones and sexual preference

Different opinions assume that human body odour may contribute to selection of partners or may influence sexual preference.

- Oliva [72] assumed that a simple biological explanation of homosexuality could be a working VNO able to recognize pheromones of the same sex.
- Martins et al. [73] tested that human body odour may contribute to the selection of partners. Heterosexual and homosexual males and females made alternative forcedchoice preference judgments for body odour, obtained from other heterosexual and homosexual males and females. The subjects chose between odours from (a) heterosexual males and gay males, (b) heterosexual males and heterosexual females, (c) heterosexual females and lesbians, and (d) gay males and lesbians. It was indicated that differences in body odour are detected and responded to based on an individual's gender and sexual orientation.
- Savic et al. [74] compared the pattern of activation induced by 4,16-androstadien-3-one (AND) and estra-1,3,5(11),16tetraen-3-ol (EST) among homosexual men, heterosexual men, and heterosexual women (n = 12 each). In contrast to heterosexual men, and in congruence with heterosexual women, homosexual men displayed hypothalamic activation in response to AND, maximally in the medial preoptic area/anterior hypothalamus. As opposed to putative pheromones, common odours were processed similarly in all groups and engaged only the olfactory brain (amygdala, piriform, orbitofrontal, and insular cortex). These findings showed that the brain reacts differently to the two putative pheromones compared with common odours, suggesting a link between sexual orientation and hypothalamic neuronal processes.
- Berglund et al. [75] performed identical positron emission tomography experiments on 12 lesbians. In contrast to heterosexual women, lesbians processed AND stimuli by the olfactory network but not the anterior hypothalamus. When smelling EST, they partly shared activation of the anterior hypothalamus with heterosexual men. These data support the differentiated processing of pheromone-like stimuli in humans and strengthen the notion of coupling between hypothalamic neuronal circuits and sexual preferences.

- Sergeant et al. [76] examined the influence of men's sexual orientation on women's perceptions of body odour by asking homosexual (n = 10) and heterosexual (n = 9) men to produce samples of body odour using T-shirts. Heterosexual women (n = 35) rated these samples, and a set of unused T-shirts, using a series of hedonic scales. Women rated the body odour of homosexual men as being comparatively more pleasant, sexier, and more preferable than that of heterosexual men but not different from the unused T-shirts. It is concluded that an individual's sexual orientation significantly impacts their olfactory function in terms of body odour production and olfactory perceptions of certain compounds.
- Savic and Lindström [77] showed sex-atypical cerebral asymmetry and functional connections in homosexual subjects that cannot be primarily ascribed to the learned effects but suggest a linkage to neurobiological entities.
- Bodo and Rissman [78] suggested a role for androgen receptors in humans in the sexual differentiation of social preferences and neural responses to pheromones.
- Savic et al. [79] showed that women smelling an androgenlike compound activate the hypothalamus, in the pre-optic and ventro-medial nuclei. In contrast, men activate the hypothalamus in the paraventricular and dorsomedial nuclei when smelling an estrogen-like substance. This sexdissociated hypothalamic activation suggests a potential physiological substrate for a sex-differentiated behavioural response in humans.
- Saxton et al. [80] showed that AND may modulate women's judgments of men's attractiveness. Men were rated more attractive when assessed by women exposed to AND suggesting that AND can influence women's attraction to men.
- Lundström et al. [81] suggested that social olfactory stimuli of high ecological relevance are processed by specialized neuronal networks similar to the auditory or visual stimuli. Smelling a friend's body odour activated regions previously linked to familiar stimuli, whereas smelling a stranger activated amygdala and insular regions akin to what has previously been demonstrated for fearful stimuli.

## Pheromones and facial characteristics

Studies of human attraction have demonstrated that men and women advertise heritable mate qualities such as body and face symmetry, masculine/feminine face shapes, body shape, body odour and vocal characteristics [82–85]. It was demonstrated that women prefer body odours collected from men with a high degree of bilateral symmetry compared with odours from asymmetrical men [86]. In turn, men and women indicated preferences for voices from individuals with higher degrees of bilateral body symmetry than lower bilateral symmetry [87].

Cornwell et al. [88] investigated whether preferences for masculine or feminine characteristics are correlated across two modalities, olfaction and vision. It was demonstrated that for long term relations, women's preferences (n = 56) for masculine face shapes were correlated with rating of AND, and men's preferences (n = 56) for feminine face shapes were correlated with rating of EST. These studies linked sex-specific

preferences for putative human sex pheromones and sexually dimorphic facial characteristics. It was suggested that putative sex pheromones and sexually dimorphic facial characteristics convey common information about the quality of potential mates.

#### Pheromones as a mediator for proper psychosexual behaviour

Multiple opinions were gathered concerning pheromonal influence on psychosexual behaviour.

- Kalogerakis [89] indicated that at some point in early childhood, a boy shows an aversion to the odours of his father and feel attraction to his mother that may act as a biological trigger for the Oedipus response.
- Lombardi and Vandenbergh [90] proposed that the psychosocial environment may influence the fertility of females by altering urinary pheromone activity in the male.
- Cutler et al. [91] tested whether synthesized human male pheromones increased the psychosexual behaviour of 38 heterosexual men that completed a 2-week baseline period and six-week placebo-controlled, double-blind trial administering either a pheromone or a placebo. Each subject kept daily behavioral records for six sociosexual behaviors: petting/affection/kissing, formal dates, informal dates, sleeping next to a romantic partner, sexual intercourse, and self-stimulation to ejaculation (masturbation). Significantly, more pheromone than placebo users demonstrated an increase above baseline in terms of sexual intercourse, in petting/affection/kissing, and informal dates, but not in self-stimulation to ejaculation or in formal dates.
- Chen [92] showed an immediate effect of airborne chemicals on human mood. He collected six groups of underarm odours, from pre-pubertal girls and boys, college women and men, older women and men, and odours from homes of these donors as a control. Odour observers (n = 308) assessed their depressive, hostile, and positive moods twice, before and a few minutes after sniffing one of these odours. They showed that exposure to underarm odours for < 2 min led to rapid changes in the non-clinical depressive mood of the odour observers independent of the observers' perceptions of odour qualities.
- McCoy and Pitino [93] conducted a double-blind, placebocontrolled study with regularly menstruating women (n = 36) with a vial of either synthesized pheromone or placebo-selected blindly and added to a subject's perfume. A significantly greater proportion of pheromone users compared with the placebo users increased over baseline in the frequency of sexual intercourse, sleeping next to a partner, formal dates and petting/affection/kissing but not in the frequency of male approaches, informal dates or masturbation.
- Cutler and Genovese [94] showed in three separate, doubleblind, placebo-controlled investigations that a synthesized topical pheromone increased sexual attractiveness.
- Bensafi et al. [95] showed in a within-subjects (n = 24), double-blind experiment, the physiological and psychological effects of the two human sex-steroid derived compounds, AND and EST, in 24 subjects. A dissociation was evident in the physiological effects of AND, in that it increased physiological arousal in women but decreased it in men.

EST did not significantly affect physiological arousal in women or men. Neither compound significantly affected mood.

- Bensafi et al. [38] showed that the effects of sniffing different concentrations of the human sex-steroid derived compound AND on the autonomic nervous system function and mood were sex-specific and concentration-dependent. In 60 subjects, only high AND concentrations increased positive mood and decreased negative mood in women compared with men, and had sympathetic-like effects in women, and parasympathetic-like effects in men.
- Friebely and Rako [96] tried to determine whether a putative human sex-attractant pheromone increases specific psychosexual behaviour in post-menopausal women (n = 44) by testing a chemically synthesized formula from the underarm secretions of heterosexually active, fertile women over six weeks. A significantly greater proportion of the participants using the pheromone formula recorded an increase over their own weekly average baseline frequency of petting, kissing, and affection, compared with those on a placebo (40.9% vs. 13.6%).
- Lundström et al. [97] showed that exposure to the endogenous steroid androstadienone has the ability to modulate women's mood to make them feel more focused.
- In 37 women, Lundström and Olsson [98] showed that exposure to a non-detectable amount of AND modulated their psychophysiological arousal and mood in a positive direction but did not change their attention performance. Mood effects were only evident when an experimenter of the opposite sex conducted the test suggesting that the social context is important.

## Pheromones and sexual functions

The applied influence of pheromones on the sexual functions of both sexes has been investigated by different researchers. In fact, most studies have been carried out on animals, few on humans.

Udry [99] delineated the relation between coitus, orgasm and position in the menstrual cycle demonstrating that women engage in sexual intercourse about six times more frequently and are much more likely to have an orgasm at the time of ovulation. During and in the 2–3 days after menses, they were several times less likely to have sexual intercourse or have an orgasm. Coupled with women's odour sensitivity, these results could indicate a possible pheromonal trigger for sexual behaviour. In addition, Campieri et al. [100] demonstrated improvement of impotence, taste and olfactory deficits in periodically hemodialyzed patients treated with zinc chloride.

## Is body odour attraction based on our immune system?

Studies on subjective body odour rating have suggested that humans exhibit preferences for the human leucocyte antigen (HLA) of dissimilar persons. A female mouse would choose a mate whose major histocompatibility complex (MHC) genes were the least similar to her own [101]; and human females too prefer men whose MHC genes are the least similar to their own.

In an experiment, men were given an unscented T-shirt and were asked to wear it for two nights where they were not to use deodorants or scented soaps. Women were then presented with six shirts, three from men with similar MHC genes, and three from men with different MHC genes. The women preferred the scents of men whose MHC genes were different. Women on birth control pills would often choose the T-shirts of men with similar MHC genes. A possible explanation is that birth control pills trick the body into thinking it is pregnant, and women on the pill often report that they prefer smells that remind them of home and relatives [102].

Pause et al. [103] showed that pre-attentive processing of body odours of HLA-similar donors is faster and that late evaluative processing of these chemo-signals activates more neuronal resources than the processing of body odours of HLA-dissimilar donors. In the same-sex smelling conditions, HLA-associated brain responses showed a different local distribution in male (frontal) and female (parietal) subjects. They concluded that odours of HLA-similar persons function as important social warning signals in inter- and intra-sexual human relations. Such HLA-related chemo-signals may contribute to female and male mate choice and to male competitive behaviour.

However, due to the extreme polymorphism of the HLA gene loci, the behavioural impact of the proposed HLA-related attracting signals seems to be minimal as the role of HLA-related chemo-signals in the same- and opposite-sex relations in humans has not been specified so far.

Finally, the importance of these substances in generating a definite physiological response and in affecting our attitudes and our life as a whole remains an open question. In conclusion, unfolding the mysteries of smells and the way we perceive them requires more time and effort. Human are not systems that instinctively fall into a behavioural response to an odour: they are thinking beings moved towards a type of behaviour by pheromones in concert with the highest intellect in the animal kingdom. In mammals, olfaction plays a major role in sexual attraction, excitement and even in triggering ovulation. However, in humans, because of their large and complex brains, it plays a minor role and is significantly supplanted by vision and/or fantasy in men and by hearing and/or touch in women. Also, although olfaction alters the neuroendocrine balance in mammals, olfaction is altered by hormones in humans.

#### References

- Karlson P, Luscher M. Pheromones': a new term for a class of biologically active substances. Nature 1959;183:55–6.
- [2] Tirindelli R, Dibattista M, Pifferi S, Menini A. From pheromones to behaviour. Physiol Rev 2009;89:921–56.
- [3] Kohl J, Atzmueller M, Fink B, Grammar K. Human pheromones: integrative neuroendocrinology & ethology. Neuro Endocrinol Lett 2001;22:309–21.
- [4] McClintock MK. Human pheromones: primers, releasers, signallers or modulators? In: Wallen K, Schneider E, editors. Reproduction in context. Cambridge, MA: MIT Press; 2000. p. 335–420.
- [5] Graham JM, Desjardins C. Classical conditioning: induction of luteinizing hormone and testosterone secretion in anticipation of sexual activity. Science 1980;210:1039–41.
- [6] Halpern M. The organization and function of the vomeronasal system. Annu Rev Neurosci 1987;10:325–62.
- [7] Lamprecht I, Schmolz E, Schricker B. Pheromones in the life of insects. Eur Biophys J 2008;37:1253–60.

- [8] Wardle AR, Borden JH, Pierce Jr HD, Gries R. Volatile compounds released by disturbed and calm adults of the tarnished plant bug, Lygus lineolaris. J Chem Ecol 2003;29:931–44.
- [9] Le Conte Y, Bécard JM, Costagliola G, de Vaublanc G, El Maâtaoui M, Crauser D, et al. Larval salivary glands are a source of primer and releaser pheromone in honey bee (*Apis mellifera* L). Naturwissenschaften 2006;93:237–41.
- [10] Burger BV, Viviers MZ, Bekker JP, le Roux M, Fish N, Fourie WB, et al. Chemical characterization of territorial marking fluid of male Bengal tiger, Panthera tigris. J Chem Ecol 2008;34:659–71.
- [11] Sobel N, Brown WM. The scented brain: pheromonal responses in humans. Neuron 2001;31:512–4.
- [12] Engen T. The human uses of olfaction. Am J Otolaryngol 1983;4:250–1.
- [13] McClintock MK. On the nature of mammalian and human pheromones. Ann NY Acad Sci 1998;855:390–2.
- [14] Grammer K, Fink B, Neave N. Human pheromones and sexual attraction. Eur J Obstet Gynecol Reprod Biol 2005;118:135–42.
- [15] Bhutta MF. Sex and the nose: human pheromonal responses. J R Soc Med 2007;100:268–74.
- [16] Moran DT, Jafek BW, Rowley JC. The vomeronasal (Jacobson's) organ in man: ultrastructure and frequency of occurrence. J Steroid Biochem. Mol Biol 1991;39:545–52.
- [17] Garcia-Velasco J, Mondragon M. The incidence of the vomeronasal organ in 1000 human subjects and its possible clinical significance. J Steroid Biochem Mol Biol 1991;39:561–3.
- [18] Monti-Bloch L, Jennings-White C, Dolberg DS, Berliner DL. The human vomeronasal system. Psychoneuroendocrinology 1994;19:673–86.
- [19] Jahnke V, Merker HJ. Electron microscopic and functional aspects of the human vomeronasal organ. Am J Rhinol 2000;14:63–7.
- [20] Monti-Bloch L, Grosser BI. Effect of putative pheromones on the electrical activity of the human vomeronasal organ and olfactory epithelium. J Steroid Biochem Mol Biol 1991;39:573–83.
- [21] Wood RI. Thinking about networks in the control of male hamster sexual behaviour. Horm Behav 1997;32:40-5.
- [22] Foltán R, Sedý J. Behavioural changes of patients after orthognathic surgery develop on the basis of the loss of vomeronasal organ: a hypothesis. Head Face Med 2009;22;5:5.
- [23] Keller M, Baum MJ, Brock O, Brennan PA, Bakker J. The main and the accessory olfactory systems interact in the control of mate recognition and sexual behaviour. Behav Brain Res 2009;200:268–76.
- [24] Savic I, Hedén-Blomqvist E, Berglund H. Pheromone signal transduction in humans: what can be learned from olfactory loss. Hum Brain Mapp 2009;30:3057–65.
- [25] Trotier D, Eloit C, Wassef M, Talmain G, Bensimon JL, Doving KB, et al. The vomeronasal cavity in adult humans. Chem Senses 2000;25:369–80.
- [26] Witt M, Georgiewa B, Knecht M, Hummel T. On the chemosensory nature of the vomeronasal epithelium in adult humans. Histochem Cell Biol 2002;117:493–509.
- [27] Wysocki CJ, Preti G. Facts, fallacies, fears, and frustrations with human pheromones. Anat Rec A Discov Mol Cell Evol Biol 2004;281A:1201–11.
- [28] Zufall F. The TRPC2 ion channel and pheromone sensing in the accessory olfactory system. Naunyn Schmiedebergs Arch Pharmacol 2005;371:245–50.
- [29] Mast TG, Samuelsen CL. Human pheromone detection by the vomeronasal organ: unnecessary for mate selection? Chem Senses 2009;34:529–31.
- [30] Stevenson RJ. An initial evaluation of the functions of human olfaction. Chem Senses 2010;35:3–20.

- [31] Grosse-Wilde E, Gohl T, Bouché E, Breer H, Krieger J. Candidate pheromone receptors provide the basis for the response of distinct antennal neurons to pheromonal compounds. Eur J Neurosci 2007;25:2364–73.
- [32] Wang Z, Nudelman A, Storm DR. Are pheromones detected through the main olfactory epithelium? Mol Neurobiol 2007;35:317–23.
- [33] Hays, Warren ST. Human pheromones: have they been demonstrated? Behav Ecol Sociobiol 2003;54:89–97.
- [34] Stoddart D. Mammalian odours and pheromones. London: Edward Arnold Ltd.; 1976.
- [35] Gower DB, Mallet AI, Watkins WJ, Wallace LM. Transformations of steroid sulphates by human axillary bacteria. A mechanism for human odour formation? Biochem Soc Trans 1997;25:16S.
- [36] Jacob S, McClintock MK. Psychological state and mood effects of steroidal chemosignals in women and men. Horm Behav 2000;37:57–78.
- [37] Lundström JN, Goncalves M, Esteves F, Olsson MJ. Psychological effects of subthreshold exposure to the putative human pheromone 4,16-androstadien-3-one. Horm Behav 2003;44:395–401.
- [38] Bensafi M, Tsutsui T, Khan R, Levenson RW, Sobel N. Sniffing a human sex-steroid derived compound affects mood and autonomic arousal in a dose-dependent manner. Psychoneuroendocrinology 2004;29:1290–9.
- [39] Wyart C, Webster WW, Chen JH, Wilson SR, McClary A, Khan RM, et al. Smelling a single component of male sweat alters levels of cortisol in women. J Neurosci 2007;27:1261–5.
- [40] Jacob S, Hayreh DJS, McClintock MK. Context-dependent effects of steroid chemosignals on human physiology and mood. Physiol Behav 2001;74:15–27.
- [41] Tóth I, Faredin I. Steroids excreted by human skin. II. C19steroid sulphates in human axillary sweat. Acta Med Hung 1985;42:21–8.
- [42] Benton D. The influence of androstenol-a putative human pheromone- on mood throughout the menstrual cycle. Biol Psychol 1982;22:141–7.
- [43] Beier K, Ginez I, Schaller H. Localization of steroid hormone receptors in the apocrine sweat glands of the human axilla. Histochem Cell Biol 2005;123:61–5.
- [44] Gower DB, Mallet AI, Watkins WJ, Wallace LM, Calame JP. Capillary gas chromatography with chemical ionization negative ion mass spectrometry in the identification of odourous steroids formed in metabolic studies of the sulphates of androsterone, DHA and 5alpha-androst-16-en-3beta-ol with human axillary bacterial isolates. J Steroid Biochem Mol Biol 1997;63:81–9.
- [45] Gower DB, Ruparelia BA. Olfaction in humans with special reference to odourous 16-androstenes: their occurrence, perception and possible social, psychological and sexual impact. J Endocrinol 1993;137:167–87.
- [46] Sokolov JJ, Harris RT, Hecker MR. Isolation of substances from human vaginal secretions previously shown to be sex attractant pheromones in higher primates. Arch Sex Behav 1976;5:269–74.
- [47] Michael RP, Bonsall RW, Kutner M. Volatile fatty acids, "copulins", in human vaginal secretions. Psychoneuroendocrinology 1975;1:153–63.
- [48] Waltman R, Tricomi V, Wilson Jr GE, Lewin AH, Goldberg NL, Chang MM. Volatile fatty acids in vaginal secretions: human pheromones? Lancet 1973;2:496.
- [49] Keith L, Draunieks A, Krotoszynski BK. Olfactory study: human pheromones. Arch Gynakol 1975;218:203–4.
- [50] McClintock MK. Menstrual synchrony and suppression. Nature 1971;229:244–5.
- [51] Stern K, McClintock MK. Regulation of ovulation by human pheromones. Nature 1998;392:177–9.

- [52] Russell MJ. Human olfactory communication. Nature 1976;260:520–2.
- [53] Comfort A. Likelihood of human pheromones. Nature 1971;230:432–3.
- [54] Preti G, Cutler WB, Garcia CR, Huggins GR, Lawley HJ. Human axillary secretions influence women's menstrual cycles: the role of donor extract of females. Horm Behav 1986;20:474–82.
- [55] Preti G, Wysocki CJ, Barnhart KT, Sondheimer SJ, Leyden JJ. Male axillary extracts contain pheromones that affect pulsatile secretion of luteinizing hormone and mood in women recipients. Biol Reprod 2003;68:2107–13.
- [56] Cutler WB, Preti G, Krieger A, Huggins GR, Garcia CR, Lawley HJ. Human axillary secretions influence women's menstrual cycles: the role of donor extract from men. Horm Behav 1986;20:463–73.
- [57] Ellis BJ, Garber J. Psychosocial antecedents in variation in girls' pubertal timing: maternal depression, stepfather presence, and marital and family stress. Child Dev 2000;71:485–501.
- [58] Van Toller C, Kirk-Smith M, Lombard J, Dodd GH. Skin conductance and subjective assessments associated with the odour of 5a-androstan-3-one. Biol Psychol 1983;16:85–107.
- [59] Filsinger EE, Braun JJ, Monte WC. An examination of the effects of putative pheromones on human judgements. Ethol Sociobiol 1985;6:227–36.
- [60] Benton D. The influence of androstenol, a putative human pheromone on mood throughout the menstrual cycle. Biol Psychol 1982;15:249–56.
- [61] Grammer K. 5-a-Androst-16en-3a-on: a male pheromone? A brief report. Ethol Sociobiol 1993;14:201–8.
- [62] Thorne F, Neave N, Scholey A, Moss M, Fink B. Effects of putative male pheromones on female ratings of male attractiveness: influence of oral contraception and the menstrual cycle. Neuro Endocrinol Lett 2002;23:291–7.
- [63] Morofushi M, Shinohara K, Funabashi T, Kimura F. Positive relationship between menstrual synchrony and ability to smell 5alpha-androst-16-en-3alpha-ol. Chem Senses 2000;25:407–11.
- [64] Shinohara K, Morofushi M, Funabashi T, Kimura F. Axillary pheromones modulate pulsatile LH secretion in humans. Neuroreport 2001;12:893–5.
- [65] Watanabe K, Umezu K, Kurahashi T. Human olfactory contrast changes during the menstrual cycle. Jpn J Physiol 2002;52:353–9.
- [66] Spencer NA, McClintock MK, Sellergren SA, Bullivant S, Jacob S, Mennella JA. Social chemosignals from breastfeeding women increase sexual motivation. Horm Behav 2004;46:362–70.
- [67] Moshkin MP, Gerlinskaia LA, Kolosova IE, Litvinova NA, Saval' LA, Berezina MG. Scent attractiveness and endocrine status in male students before and during a stress situation. Ross Fiziol Zh Im I M Sechenova 2006;92:1250–9.
- [68] Kwan TK, Trafford DJ, Makin HLJ, Mallet AI, Gower DB. GC-MS studies of 16-androstenes and other C19 steroids in human semen. J Steroid Biochem Mol Biol 1992;43:549–56.
- [69] Schaal B, Coureaud G, Doucet S, Delaunay-El Allam M, Moncomble AS, et al. Mammary olfactory signalisation in females and odour processing in neonates: ways evolved by rabbits and humans. Behav Brain Res 2009;200:346–58.
- [70] Vaglio S, Minicozzi P, Bonometti E, Mello G, Chiarelli B. Volatile signals during pregnancy: a possible chemical basis for mother-infant recognition. J Chem Ecol 2009;35:131–9.
- [71] Marazziti D, Masala I, Baroni S, Polini M, Massimetti G, Giannaccini G, et al. Male axillary extracts modify the affinity of the platelet serotonin transporter and impulsiveness in women. Physiol Behav 2010;100:364–8.

- [72] Oliva D. Mating types in yeast, vomeronasal organ in rodents, homosexuality in humans: does a guiding thread exist? Neuro Endocrinol Lett 2002;23:287–8.
- [73] Martins Y, Preti G, Crabtree CR, Runyan T, Vainius AA, Wysocki CJ. Preference for human body odours is influenced by gender and sexual orientation. Psychol Sci 2005;16:694–701.
- [74] Savic I, Berglund H, Lindström P. Brain response to putative pheromones in homosexual men. Proc Natl Acad Sci USA 2005;102:7356–61.
- [75] Berglund H, Lindström P, Savic I. Brain response to putative pheromones in lesbian women. Proc Natl Acad Sci USA 2006;103:8269–74.
- [76] Sergeant MJ, Dickins TE, Davies MN, Griffiths MD. Women's hedonic ratings of body odour of heterosexual and homosexual men. Arch Sex Behav 2007;36:395–401.
- [77] Savic I, Lindström P. PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects. Proc Natl Acad Sci USA 2008;105:9403–8.
- [78] Bodo C, Rissman EF. Androgen receptor is essential for sexual differentiation of responses to olfactory cues in mice. Eur J Neurosci 2007;25:2182–90.
- [79] Savic I, Berglund H, Gulyas B, Roland P. Smelling of odourous sex hormone-like compounds causes sexdifferentiated hypothalamic activations in humans. Neuron 2001;31:661–8.
- [80] Saxton TK, Lyndon A, Little AC, Roberts SC. Evidence that androstadienone, a putative human chemosignal, modulates women's attributions of men's attractiveness. Horm Behav 2008;54:597–601.
- [81] Lundström JN, Boyle JA, Zatorre RJ, Jones-Gotman M. Functional neuronal processing of body odours differs from that of similar common odours. Cereb Cortex 2008;18:1466–74.
- [82] Perrett DI, Burt DM, Penton-Voak IS, Lee KJ, Rowland DA, Edwards R. Symmetry and human facial attractiveness. Evol Hum Behav 1999;20:295–307.
- [83] Tovee MJ, Maisey DS, Emery JL, Cornelissen PL. Visual cues to female physical attractiveness. Proc R Soc Lond B 1999;266:211–8.
- [84] Penton-Voak IS, Perrett DI. Male facial attractiveness: perceived personality and shifting female preferences for male traits across the menstrual cycle. Adv. Study Behav 2001;30:219–59.
- [85] Singh D, Bronstad PM. Female body odour is a potential cue to ovulation. Proc R Soc Lond B 2001;268:797–801.
- [86] Hughes SM, Harrison MA, Gallup GG. The sound of symmetry. Voice as a marker of developmental instability. Evol Hum Behav 2002;23:173–80.
- [87] Thornhill R, Gangestad SW. The scent of symmetry: a human sex pheromone that signals fitness? Evol Hum Behav 1999;20:175–201.
- [88] Cornwell RE, Boothroyd L, Burt DM, Feinberg DR, Jones BC, Little AC, et al. Concordant preferences for opposite-sex signals? Human pheromones and facial characteristics. Proc R Soc Lond B 2004;271:635–40.
- [89] Kalogerakis MG. The role of olfaction in sexual development. Psychosom Med 1963;25:420–32.
- [90] Lombardi JR, Vandenbergh JG. Pheromonally induced sexual maturation in females: regulation by the social environment of the male. Science 1977;196:545–56.
- [91] Cutler WB, Friedmann E, McCoy NL. Pheromonal influences on sociosexual behaviour in men. Arch Sex Behav 1998;27:1–13.
- [92] Chen D, Haviland-Jones J. Rapid mood change and human odours. Physiol Behav 1999;68:241–50.
- [93] McCoy NL, Pitino L. Pheromonal influences on sociosexual behaviour in young women. Physiol Behav 2002;75:367–75.

- [94] Cutler WB, Genovese E. Pheromones, sexual attractiveness and quality of life in menopausal women. Climacteric 2002;5:112–21.
- [95] Bensafi M, Brown WM, Tsutsui T, Mainland JD, Johnson BN, Bremner EA, et al. Sex-steroid derived compounds induce sexspecific effects on autonomic nervous system function in humans. Behav Neurosci 2003;117:1125–34.
- [96] Friebely J, Rako S. Pheromonal influences on sociosexual behaviour in postmenopausal women. J Sex Res 2004;41:372–80.
- [97] Lundström JN, Goncalves M, Esteves F, Olsson MJ. Psychological effects of subthreshold exposure to the putative human pheromone 4,16-androstadien-3-one. Horm Behav 2003;44:395–401.
- [98] Lundström JN, Olsson MJ. Subthreshold amounts of social odourant affect mood, but not behaviour, in heterosexual women when tested by a male, but not a female, experimenter. Biol Psychol 2005;70:197–204.
- [99] Udry JR, Morris NM. Distribution of coitus in the menstrual cycle. Nature 1968;220:593–6.

- [100] Campieri C, Ben Dardeff A, Prandini R, Borgnino LC, Scolari MP, Stefoni S. Improvement of impotence, taste and olfactory deficits in periodically hemodialyzed patients treated with zinc chloride. Minerva Nefrol 1980;27:377–82.
- [101] Furlow FB. The smell of love: how women rate the sexiness and pleasantness of a man's body odour hinges on how much of their genetic profile is shared. Psychology Today 1996;29:38.
- [102] Richardson S. Scent of a man: the sexiest part of a man, a Swiss zoologist has found, may be his armpits: they're an odouriferous window on his genes. Discover 1996;17:26.
- [103] Pause BM, Krauel K, Schrader C, Sojka B, Westphal E, Müller-Ruchholtz W, Ferstl R. The human brain is a detector of chemosensorily transmitted HLA-class Isimilarity in same- and opposite-sex relations. Proc Biol Sci 2006;273:471–8.