



Review

Cite this article: Wyatt TD. 2015 The search for human pheromones: the lost decades and the necessity of returning to first principles. *Proc. R. Soc. B* **282**: 20142994. <http://dx.doi.org/10.1098/rspb.2014.2994>

Received: 9 December 2014

Accepted: 2 February 2015

Subject Areas:

neuroscience, behaviour, physiology

Keywords:

humans, 5α -androst-16-en-3-one, 5α -androst-16-en-3 α -ol, $\Delta 4,16$ -androstadien-3-one, sex, estra-1,3,5(10),16-tetraen-3-ol

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The search for human pheromones: the lost decades and the necessity of returning to first principles

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As humans are mammals, it is possible, perhaps even probable, that we have pheromones. However, there is no robust bioassay-led evidence for the widely published claims that four steroid molecules are human pheromones: androstenone, androstenol, androstadienone and estratetraenol. In the absence of sound reasons to test the molecules, positive results in studies need to be treated with scepticism as these are highly likely to be false positives. Common problems include small sample sizes, an overestimate of effect size (as no effect can be expected), positive publication bias and lack of replication. Instead, if we are to find human pheromones, we need to treat ourselves as if we were a newly discovered mammal, and use the rigorous methods already proven successful in pheromone research on other species. Establishing a pheromone relies on demonstration of an odour-mediated behavioural or physiological response, identification and synthesis of the bioactive molecule(s), followed by bioassay confirmation of activity. Likely sources include our sebaceous glands. Comparison of secretions from adult and pre-pubertal humans may highlight potential molecules involved in sexual behaviour. One of the most promising human pheromone leads is a nipple secretion from the areola glands produced by all lactating mothers, which stimulates suckling by any baby not just their own.

1. Introduction

Pheromones are chemical signals that have evolved for communication with other members of the same species. Over the last 45 years, some scientists have claimed that a number of molecules are human pheromones but, as I explain in this review, these claims have little scientific validity. The molecules include four androstene steroids: androstenone, androstenol, androstadienone and estratetraenol. While the field has attracted much eager scientific activity, experiments (however well designed and executed) using these molecules do not lead us nearer to discovering human pheromones, because these molecules have never been shown to be biologically relevant.

Apart from the waste of scientific effort, the potential damage goes further as even flawed studies on 'human pheromones' may have far reaching clinical and even social and legislative influence. For example, a questionable brain imaging study [1] of the responses of gay men to non-physiological concentrations (about a million times natural quantities) of androstadienone and estratetraenol has received more than 200 citations (Google Scholar, 23 October 2014) including academic papers on sexual orientation (e.g. [2]), textbooks on sexual medicine in clinical practice (e.g. [3]) and medical commentary on legislation (e.g. [4]).

I start with a summary of what pheromones are and how we establish that molecules fit these criteria, before exploring why we might anticipate humans could have pheromones. I then discuss the problematic history of androstene 'putative pheromones'. The second half of this review offers positive proposals and methods for restarting the search for human pheromones from first principles, notwithstanding the many challenges this task will present.

2. Pheromones are chemical signals that meet well-established criteria

Pheromones are chemical signals that have evolved for communication between members of the same species (conspecifics). Pheromones are signal molecules that are characteristic of, for example, all males of a species, not a particular individual male, though some males may have more of the pheromone and females may prefer these males [5]. Pheromones are not the individual smells that allow animals to be distinguished as individuals (§3c).

A pheromone signal elicits a specific reaction such as a stereotyped behaviour (releaser effect) and/or a developmental process (primer effect) from a conspecific [5,6]. Some pheromones can have both effects. For example, in the house mouse, *Mus musculus domesticus*, the male pheromones dehydro-*exo*-brevicommin and 2-*sec*-butyl-4,5-dihydrothiazole have the releaser effects of eliciting aggression from other males and attracting females, as well as the developmental (primer) effects of apparently inducing oestrus in mature females and accelerating puberty in young females [7]. Most responses to pheromones are 'innate', meaning that they do not seem to require learning. However, responses may be modified by experience, can be subtle, and may be context dependent [5, p. 206 ff]. For example, male moths that have recently mated do not respond to female sex pheromone [8].

Pheromones have been identified in every part of the animal kingdom, including mammals, and can be involved in a wide range of functions including attraction of the sexes, mate choice, trail following, and interactions between parents and offspring, depending on the species [5,9]. Most pheromones, including the female sex pheromones of most moths and some mammalian pheromones, are *not* single compounds. Instead they tend to be a species-specific multi-component combination of molecules [5,10]. For example, in the house mouse, sulfated oestrogens and a particular fraction of female urine form a multi-component mouse pheromone, produced by oestrous females, which promotes male mounting [10,11]. Most pheromones are detected by the sense of smell. Pheromone molecules can be volatile or involatile, soluble or insoluble, large or small, depending on whether they are carried to the receiver in air or water or, for example, deposited on the nose of the receiver [5]. Pheromones can be short or long range, or act on contact. In house mice, volatile pheromone molecules detected at a distance of centimetres include dehydro-*exo*-brevicommin and 2-*sec*-butyl-4,5-dihydrothiazole, whereas the non-volatile male peptide pheromone ESP1 (exocrine gland-secreting peptide 1) gets transferred from the male's tear glands to the nose (and thus vomeronasal organ, VNO) of the female during courtship contact [12].

(a) The essential steps for identifying a pheromone

The steps were demonstrated in the first chemical identification of a pheromone, the silk moth's female sex pheromone (bombykol), achieved by the German chemist Adolf Butenandt and his team [13]. The steps essential to identifying a pheromone are: demonstrate a behavioural or physiological response (quantified in a repeatable experiment called a bioassay) which is mediated by a potential chemical stimulus, such as a secretion, from a conspecific; isolate, identify and synthesize the bioactive molecule(s); then confirm that the proposed molecule(s) at natural concentrations are necessary

and sufficient to recreate the original activity with the original bioassay [5, p. 49 ff]. I have suggested that these steps are the guiding criteria required for identifying pheromones, analogous to 'Koch's postulates' for establishing causal relationships for infectious agents [9].

We will need to follow the same steps in a renewed search for human pheromones. There are no short cuts. The identifications of 'human pheromones' claimed to date (§4) are severely flawed, because they do not result from this methodical bioassay-led approach.

3. We can reasonably anticipate that humans have pheromones

We can anticipate finding human pheromones on evolutionary grounds, because we are mammals but it is possible that we have lost responses to them over evolutionary time due to a lack of selection pressure.

(a) Other mammals use pheromones, so humans may do so

Many mammals have pheromones that fit the classical definition [5,10,14]. These include the rabbit mammary pheromone 2-methylbut-2-enal (2MB2) [15] and 4-ethyloctanal in male goats (figure 1) [16], as well as protein pheromones such as ESP1 and darcin in the house mouse [12,17].

Darwin [18] noted that adult males of mammals such as goats and elephants have characteristic strong odours during the breeding season. He reasoned that the evolution of specialized odour glands in male mammals is 'intelligible through sexual selection, if the most odouriferous males are the most successful in winning the females, and in leaving offspring to inherit their gradually perfected glands and odours' [18, vol. 2, p. 281].

If we were any other kind of mammal, the changes in our smell-producing secretions as we develop through puberty to sexual maturity would suggest that these could have a pheromonal role [5]. The changes are due in large part to the development of sebaceous and apocrine skin glands at puberty (see §6). Other primates show similar gland development with sexual maturity and many species from lemurs to monkeys use chemical communication extensively [19,20]. Although we and our nearest relatives, the great apes (the bonobos, chimpanzees, gorillas and orangutans) do not appear to use odour communication as much as other primates, odours are still important to us and we have secretory glands that could be used to produce pheromones [5,20,21].

(b) Humans have a good sense of smell

The possibility of human pheromones has been downplayed in part because in the past it has been assumed erroneously that we have a poor sense of smell [5]. On the contrary, we are, if anything, excellent smellers able to make subtle smell distinctions, though this in itself is not evidence that we have pheromones [19,21–23]. We have a 'main olfactory system' but we do not have a functional VNO or 'second nose' [24]: however, this is no barrier to our potential use of pheromones as many mammals, including rabbits and sheep, detect pheromones with the main olfactory system [14,25].

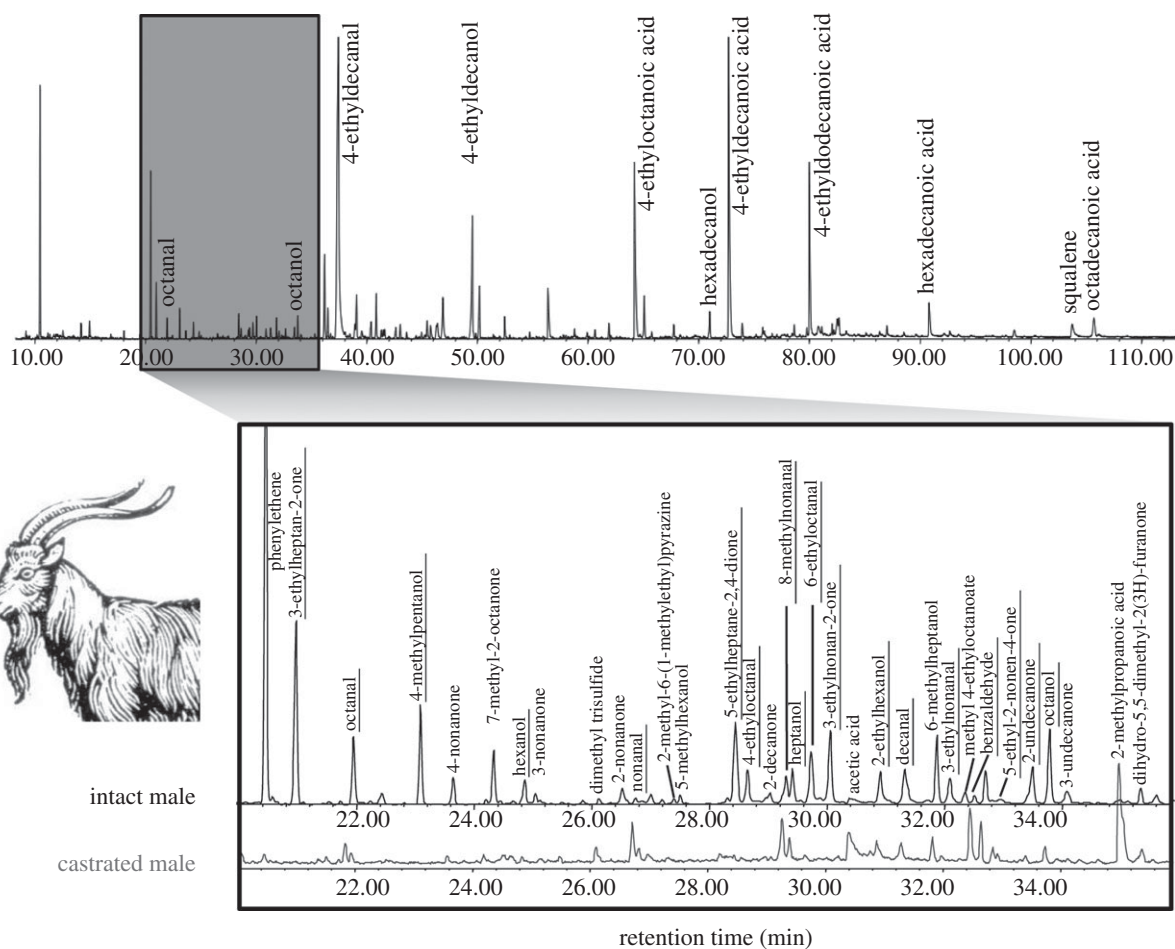


Figure 1. How pheromone molecules can be identified against a background of many hundreds of molecules in a scent sample from a mammal. Scents from the heads of male goats *Capra hircus* switch seasonally anoestrous females into the oestrous state. The gas chromatograph trace (top) shows the large number of peaks (each corresponding to a molecule) from a sample of volatiles from the heads of male goats [16]. The highlighted section, enlarged (below), was the region that contained the activity, detected in bioassays of female response. As the pheromone secretion was androgen-dependent, Murata *et al.* [16] looked for molecules missing from the secretions of castrated males (lower, grey chromatogram) and created a synthetic cocktail of 18 molecules (underlined) in the concentrations found in the original headspace analysis of intact males. Most, but not all, of the bioassay activity could be reproduced by one molecule, 4-ethyloctanal, so the pheromone may include other molecules from the 18. Note that the candidate molecules were *not* the highest peaks. Reproduced from Murata *et al.* [16] in *Current Biology* with permission from Elsevier. Goat image, non-copyright.

(c) Not all human smells are pheromones: humans also respond to non-pheromone individual odours

Pheromones, molecules characteristic of all males of the species for example, appear among the other molecules of a male's chemical profile (figure 1). It is the large variation in these non-pheromone molecules between individuals, owing to genetic variation and diet for example, which allow animals to be distinguished by smell as individuals. These differences are used by tracker dogs as cues to distinguish different people.

These non-pheromone individual body odours are important as cues in many human interactions. For example, we are good at recognizing close family by smell [26] and smell may influence our choice of partner. Both phenomena are responses to individual body odours that we have learned [5, p. 278 ff, 27]. These body odours reflect the individuality of our genetic make-up, including the enormously variable major histocompatibility complex (MHC) of the immune system [28,29]. It is possible that we can use smell to choose partners who differ genetically from us in the MHC. This was first shown in humans by Wedekind's 'smelly T-shirt' experiments [30,31] though replications have been inconsistent and confirming MHC-based choice of partners in natural human populations

is a challenge [5, p. 281 ff, 28,32]. The idea of choosing partners by smell has prompted the so-called 'Pheromone Parties', at which participants sniff T-shirts worn by other party-goers (e.g. [33]). However, the 'parties' are misnamed: they are about *individual* odours and possible genetic compatibility, not pheromone molecules identical in all males or in all females.

4. There is no scientific basis for calling androstene molecules 'human pheromones'

There have been two waves of experiments on androgen-related androstene steroid molecules claimed to be 'human pheromones' (helpfully tabulated in [34]). From the late 1970s through the 1990s, the molecules used were androstenone (5α -androst-16-en-3-one) and androstenol (5α -androst-16-en-3 α -ol, abbreviated variously as 5α -androstenol or 3α -androstenol). Then from 1991 and particularly after 2000, two different molecules, androstadienone ($\Delta^4,16$ -androstadien-3-one) and estratetraenol (estra-1,3,5(10),16-tetraen-3-ol), came to be adopted instead as the molecules termed 'putative human pheromones', based on unpublished identifications by a US corporation.

Remarkably, there is simply no peer-reviewed, bioassay evidence (of the systematic kind described in §2) that any of these four molecules *is* a human pheromone [5,35–38]. Calling the molecules ‘putative human pheromones’, as many authors do, does not avoid the problem: they have never been shown to be human pheromones, ‘putative’ or otherwise.

(a) Androstenone and androstenol

The finding that molecules with pheromonal effects in pigs were also detectable in human armpits was enough to lead some researchers (e.g. [39,40]) to consider androstenone and/or androstenol as human pheromones [35,37,38,41]. While pheromones do not have to be unique to a species, it does not follow that because one species uses a molecule, other unrelated species are necessarily likely to use it as a pheromone [5]. What likely made androstenone popular with experimenters was the commercial availability of the molecule in aerosol cans as Boarmate™, for use in pig husbandry. Experiments included, for example, spraying the underside of some chairs in a waiting room and seeing which chairs were chosen by women and men. Doty [35, p. 141 ff] critiques many of the experiments in detail, pointing out poor experimental design, statistical errors and small sample sizes. The more fundamental criticism is simply that there was no evidence to justify using these molecules with humans in the first place, rather than any of the hundreds of other molecules found in human armpits (e.g. [42]).

(b) Androstadienone and estratetraenol

These molecules were presented as ‘putative human pheromones’ by Monti-Bloch & Grosser [43] at a 1991 conference sponsored by the EROX Corporation, which had commercial interests in human pheromones. The two molecules were among five, described only by code numbers, which had been tested by Monti-Bloch & Grosser [43]. The authors gave no details at all of how these molecules were extracted, identified, bioassayed and demonstrated to be the ‘putative pheromones’ of the paper’s title, just a footnote: ‘These putative pheromones were supplied by EROX Corporation’ [43]. A later patent, assigned to the EROX Corporation, on ‘Fragrance compositions containing human pheromones’ [44], gave no details about how the molecules were arrived at but revealed that the two code numbered molecules claimed to have the greatest and most sex-specific effects on the opposite sex in Monti-Bloch & Grosser [43] were androstadienone and estratetraenol, apparently from men and women, respectively.

These two molecules, androstadienone and estratetraenol, might have rested in obscurity had it not been for a paper by Jacob & McClintock [45] on the effect of these molecules on the mood of men and women. Though the researchers were not associated with the EROX Corporation, the molecules were explicitly chosen because they had been proposed by Monti-Bloch & Grosser [43], Berliner [44] and Monti-Bloch *et al.* [46].

Jacob & McClintock [45] has been cited more than 150 times (Google Scholar, 23 October 2014) and the molecules and the concentrations used by them have become traditional across much of the field to this day. However, while Jacob & McClintock [45] were fairly cautious, commenting that ‘... it is premature to call these steroids human pheromones’ [45, p. 76], this advice has been forgotten by most later authors.

(c) Positive results from un-evidenced molecules are likely due to false positives, positive publication bias and other problems

The fundamental problem with the experiments using androstene molecules such as androstenone, androstenol, androstadienone or estratetraenol is that, however well designed and carried out the experiments are, there is no scientific basis for treating these molecules as human pheromones. This has been pointed out often from the 1980s to the present (e.g. [35,37,38,41,47]) but the attraction of studies on androstadienone and/or estratetraenol seems unstoppable.

More than 40 papers claiming psychological and/or physiological effects of androstadienone and/or estratetraenol have been published since 2000 (many studies are tabulated in [34]). These range from studies of physiological effects such as Bensafi *et al.* [48] to the assessment of the gender of computer-generated walking figures [49].

Detailed critiques of some individual studies are presented in Doty [36], Wysocki & Preti [37], and at book length in Doty [35]. More generally, however, because there is no evidence that these molecules have any pheromone activity we should be sceptical about positive results as we have no justified expectation of an effect. Experiments in this and related fields tend to be statistically underpowered, not least because of small sample sizes and overestimates of effect size in the absence of *a priori* evidence of effects [50–52]. Both the direction and magnitude of the effects in ‘significant’ findings in underpowered studies are likely to be wrong [50,52–55]. Such problems can be compounded by experimenter phenomena such as stopping experiments when significance is reached and flexible statistical analysis [56], combined with positive publication bias (the ‘desk-drawer effect’), when positive results are more likely to be published [51,57]. As in other areas of biology, full replication is rare. In summary, apparently positive results do not, in isolation, demonstrate that these molecules are pheromones.

Even if some of these reported effects should turn out not to be false positives, they do not establish that the androstenes are pheromones: all sorts of non-pheromone odours such as plant odours are reported to have measurable effects on physiology and mood [35, p. 164 ff]. For example, inhaling volatile plant essential oils such as pepper oil, fennel oil or rose oil affects sympathetic activity in adults, shown by changes in blood pressure and plasma catecholamine levels including adrenaline concentrations [58]. In a study of the effects on mood, lemon oil odours reliably enhanced positive mood compared with lavender oil and a water control [59]. However, even these kinds of results can depend on what human subjects are primed to expect (e.g. [60]).

(d) Why have androstadienone and estratetraenol been so popular with researchers despite the lack of evidence?

Two main factors may have led to the widespread adoption of these two molecules despite the lack of evidence that they were pheromones: first, the initial endorsement in 2000 [45] by an influential scientist, McClintock, from a prestigious institution, the University of Chicago; second, the attractive illusion that, by using these now endorsed and commercially available molecules, researchers could contribute to an

interesting area of science without access to the kind of laboratory, chemical expertise or collaboration needed to study pheromones. Researchers would have been reassured by a growing and self-referential literature which took as a given that these were 'putative human pheromones', which would have been reinforced by peer-review by others using the molecules. The source Monti-Bloch & Grosser (1991) paper [43] is frequently cited (about 150 times to-date, Google Scholar, 23 October 2014) but seems to be rarely read so the lack of any evidence is missed.

5. Some studies have used human armpit or other secretions

Some studies have investigated natural secretions of molecules (reviews in [35,61]). These studies have the advantage that, even though the molecules are unknown, the concentrations used are natural. For example, studies have explored the effect of sniffing axillary (armpit) sweat from individuals watching sexually arousing films (e.g. [62]) and other studies have used sweat from people exposed to exam stress (e.g. [63]). Both situations, sexual or fearful, would lead to emotional release from armpit apocrine glands [64] and we currently do not know if the secretions differ between the situations [5].

Female tears are reported in one study to affect men's blood testosterone levels but the biological significance or relevance is not clear [65]. As the researchers note, they were not able to test male tears. Female axillary and vulvar scents sampled at periovulatory and late luteal phases of young women are reported to modify men's salivary testosterone and cortisol levels [66].

Pheromone-mediated menstrual synchrony (the convergence in the cycles of women living in close proximity) was reported in 1998 by Stern & McClintock [67]: extracts of armpit secretions from women at different stages in their cycles were put on the upper lip of other women. There has been lively debate about the phenomenon of synchrony itself, quite apart from pheromones. While some studies since the original 1971 paper by McClintock [68] have found synchrony, other studies have failed to do so. There is also a lack of evidence that it occurs in situations where we might expect it, for example among Dogon women in Mali, who share accommodation at menstruation [69]. Methodological questions and statistical doubts suggest that the phenomenon of synchrony might be an artefact (see [35, p. 168 ff, 36]).

6. We should restart the search for human pheromones from scratch using the techniques well established for other organisms

At the turn of the twentieth century, Havelock Ellis [70] was inspired by Darwin [18] to speculate at length about the possible role of musk-like smells in sexual selection in humans. In 1971, Comfort [71] was upbeat about a search for human pheromones, prompted by McClintock's [68] paper on menstrual synchrony and the apparent pheromonal effects of vaginal fatty acids ('copulins') in rhesus monkeys [72] (later questioned, see [73] and references therein). Sadly, reading the current literature, I conclude reluctantly that our understanding of human

pheromones has hardly advanced in the more than 40 years since Comfort [71].

If we are to find pheromones we need to treat ourselves just as if we were a newly discovered mammal. We need a scientific and systematic search for potential molecules, common to one or both sexes, which have reliable effects. These will be real candidate molecules (in contrast to the current 'putative' pheromones). This kind of approach has worked well in other animals, including mammals, so I find no reason that it should not work in principle in humans, notwithstanding the greater controls for the complexity and sophistication of our behaviour and influences of culture that we will need to include [5].

In any event, the isolation of human pheromones needs to be guided by the essential steps outlined in §2: demonstration of a behavioural or physiological response mediated by an odour, development of robust bioassays, identification and synthesis of the bioactive molecule(s), followed by bioassay confirmation of activity [5, p. 49 ff].

(a) Identifying appropriate bioassays will be a major challenge

A fundamental problem for studying humans is that, with few exceptions (e.g. §7), we have not identified biological phenomena, involving olfaction and potentially mediated by pheromones, that are sufficiently well defined to allow for an unambiguous bioassay [5]. Among the other challenges is cultural conditioning of responses to odours which may render them unimportant or repellent. We know from other mammals, such as the hamster, that responses depend on a complex interaction of previous experience and the context of the message; we should expect human responses to be no less complex [5]. There are many unknowns. For example, if we do have sex pheromones they might be involved in intimate foreplay, not distance attraction. It may be that the first human pheromones to be identified will concern babies not sex (§7).

When we do have appropriate bioassays and have identified well-based potential molecules to test, the expertise and techniques for stimulus delivery and experiments already developed by the many teams currently investigating olfaction in humans and other primates will be invaluable (e.g. [19,74–81]). They have developed careful double-blind designs, controls, sophisticated delivery of molecules, and many refined approaches to measure responses.

(b) The search for molecules needs to cover the whole body

While there are exceptions (e.g. [65,66]), traditionally, human pheromone researchers have tended to look at armpits. There are some good reasons, as axillary (armpit) scent glands are unique to humans and the great apes [20]. Armpits may also simply be among the least embarrassing places to sample.

However, there are many reasons for looking beyond our armpits. First, is that the odours thought by (mostly) Western scientists to be characteristic of armpits are largely absent in most people in northeast Asia, who comprise about 20% of the World's population. About 95% of people in China are homozygous for a variant of gene *ABCC11* which means they secrete very little of the odour precursors secreted by most people of European and African descent [82]. The single nucleotide polymorphism (SNP) was first noted as it also leads to white earwax. Whatever the reason for the spread of

the SNP, it seems that having less smelly armpits is not a disadvantage in finding a partner; perhaps these molecules are not important for sex [5]?

Second, while the apocrine glands, which provide most of the odorous secretions in the human armpit, may turn out to be involved, in most other mammals it is the sebaceous glands that are most important in chemical communication (and which differ most between species) [5,35, p. 126]. Perhaps sebaceous glands are the ones we should be researching. Sebaceous glands are found over most of the body, notably on the upper chest, back, scalp, face and forehead. The eyelids, the ear canals, the nostrils, the lips, the buccal mucosae, the breasts, the prepuce and the anogenital region all contain specialized sebaceous glands [36].

(c) The sampling and analytical techniques are ready

Recent advances in analytical techniques make the search for human pheromones more achievable than ever before. The search should use the well-established protocols established for sampling and identifying the pheromones and other molecules produced by other animals (e.g. [5,80,83]). We are simply another animal. Guidelines for good practice in reporting identifications of molecules in pheromone studies already exist, for example, in the *Journal of Chemical Ecology* [84].

(d) Methods for narrowing down the candidate molecules for bioassay

A major challenge when researching mammals is that secretions often include hundreds if not thousands of different molecules (figure 1) (e.g. human armpits analysed by Penn *et al.* [42]). One strategy to cope with this is illustrated by a study of male goat pheromones: since activity of the male scents was androgen-dependant, Murata *et al.* [16] looked for the molecules missing in the secretions of castrated male goats to find candidate molecules to test on females (figure 1). Only a systematic bioassay-led approach allowed Murata *et al.* [16] to identify the main pheromone component, 4-ethyltolanal. This molecule barely showed above the baseline at approximately 28:30 min in the top trace (figure 1) (compare upper and lower traces). Tens of other molecules on the upper trace had higher peaks.

For humans, we could compare, for example, differences in the molecules given off by adult males, adult females and children before puberty. The changes in the smells we give off as we become adults are due in large part to the development of sebaceous and apocrine skin glands at puberty, as in other mammals [5], including other primates [19,20].

Another potential approach to find candidate pheromone molecules in the distant future could be based on identifying the ligands for human olfactory receptors (ORs) [85] that are highly conserved (in contrast to most human ORs which are highly variable between individuals [86,87]). Highly conserved ORs might result from strong stabilizing selection against mutations reducing sensitivity in pheromone-detecting ORs [5]. (Incidentally, receptors involved in detecting androstenone and androstadienone are among the ORs that are highly variable between individuals [88].) However, to-date few human ORs have been characterized and only approximately 10% have been linked to their ligands [85,86] so such an approach is currently hypothetical. In addition, some ORs might be

highly conserved because they are also expressed in other tissues (e.g. OR17-4 in sperm, [89]). In any event, we will still need bioassays of candidate molecules discovered in this or other ways.

(e) To avoid publication and other biases, we need to encourage best practice including preregistration and replication

As we restart the search for real phenomena, I hope researchers on human pheromones will become pioneers of approaches to remove the biases such as positive publication bias and use sufficiently high-powered experiments (for examples of potential bias and suggested solutions, see [50–52,57,90]). These approaches could include preregistration of studies (e.g. [91]) to avoid cherry-picking of analysis afterwards in search of a desired result and to encourage publication of null results. Similarly, we should separate hypothesis-generating (exploratory) and hypothesis-testing confirmatory research [92]. Adoption of large-scale collaborative research with a strong replication culture would be a big challenge but it could transform the field [90].

7. The suckling response of human babies to areola gland secretions points to our best candidate pheromone

Historically, human pheromone research has focused on sex pheromones, but given our other highly developed senses in adulthood, sex may not be the right place to look first. Instead, suckling is one behaviour in mammals where smell is known to be ubiquitously important [93]. The secretion produced by lactating human mothers from areola (Montgomery's) skin glands around their nipple may contain a good candidate human pheromone [93–95]. The glands combine sebaceous and milk glands. If the secretion, taken from any mother, is put under any sleeping baby's nose, the baby responds with sucking and nipple-search behaviour [94,95]. This bioassay opens up the possibility of finding the stimulus molecule(s) common to all human mothers' areola secretions. Identifying and synthesizing this pheromone could be medically important as the healthy survival of newborns depends crucially on successful suckling in the hours just after birth [93,94]. As a study focus, newborns have the advantage that their behaviour is the least complicated by learning and cultural differences.

8. There are wider future challenges beyond experimental ones

Quite apart from the experimental issues described above, there are other challenges.

(a) Funding for research into human olfaction and pheromones is a low priority

As well as its intrinsic scientific and human interest, if human pheromones were to be found this could open up new medical interventions and drug leads. A human mammary pheromone, if found, could be a lead for an externally

applied drug facilitating prompt initiation of suckling by newborn babies (crucial for their healthy survival, [93]). If reproductive effects of human pheromones were to be found, such as the controversial phenomenon of menstrual synchrony (above), then this could provide leads for new concepts in contraceptive drugs, for example.

However, human olfaction is not seen as a health funding priority, even though losing your sense of smell significantly reduces the quality of life [96–98]. An indication of society's relative concerns is perhaps given by the founding dates of United Kingdom's organizations for blind people (1868), deaf people (1911), but not until 2012 for people affected by smell and taste disorders (Fifth Sense). Perhaps indicative of funding agencies worldwide, the UK Medical Research Council's priorities may be reflected by specific mentions of vision and hearing (but not smell) under its 'sensory neuroscience research' remit [99].

Research funding may have to specifically encourage serious study on human pheromones. The research is interdisciplinary by its nature and though good chemistry is essential, the molecules are unlikely to be exciting in themselves to chemists. Breakthroughs are unlikely to come within 3 year timescales common to grants. Instead we will need to provide long-term funding to get the subject moving.

(b) Human sex research is also a low priority

If we want to research the possible role of pheromones in human sexual activity, we will need to research intimate sexual behaviour itself; for example, oral sex (cunnilingus and fellatio) may allow partners to sample odours. Without an understanding of sexual behaviours we will not be able to design bioassays. However, despite the importance of

sex in human life and health, research on the physiology and behaviours involved is surprisingly little funded.

9. Conclusion

We do not yet know if humans have pheromones. However, to find out, we will need a new approach, applying the rigorous techniques that have been effective in the discovery of pheromones in other mammals. The steroid molecules, such as androstadienone and estratetraenol, which have been claimed to be pheromones so widely and inappropriately, should be put aside. The new search will benefit from the techniques developed by olfactory researchers including those who have worked on the steroids previously. Human pheromone researchers could lead the field in embracing more rigorous protocols to reduce study biases. Some behaviours of babies do appear to be mediated by pheromones. These should perhaps be our focus initially before we take on other human behaviours for which we do not yet have robust bioassays. If a human mammary pheromone were to be found it would give greater confidence to researchers contemplating the search for other human pheromones.

It may be that we will find that there are no pheromones in humans. But we can be sure that we shall never find anything if we follow the current path. We need to start again.

Acknowledgements. I thank Dorothy Bishop, Victoria Braithwaite, Pau Carazo, Heather Eisthen, David Karlin, Sujai Kumar, Darren Logan, Robert Taylor, Joan Wyatt and Vivian Wyatt for valuable comments on drafts. I thank Yukari Takeuchi for kindly supplying figure 1. Two anonymous referees are gratefully thanked for their constructive comments on the manuscript.

Competing interests. I have no competing interests.

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