UPDATE

Vomeronasal organ and human pheromones

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Summary For many organisms, pheromonal communication is of particular importance in managing various aspects of reproduction. In tetrapods, the vomeronasal (Jacobson's) organ specializes in detecting pheromones in biological substrates of congeners. This information triggers behavioral changes associated, in the case of certain pheromones, with neuroendocrine correlates. In human embryos, the organ develops and the nerve fibers constitute a substrate for the migration of GnRH-secreting cells from the olfactory placode toward the hypothalamus. After this essential step for subsequent secretion of sex hormones by the anterior hypophysis, the organ regresses and the neural connections disappear. The vomeronasal cavities can still be observed by endoscopy in some adults, but they lack sensory neurons and nerve fibers. The genes which code for vomeronasal receptor proteins and the specific ionic channels involved in the transduction process are mutated and nonfunctional in humans. In addition, no accessory olfactory bulbs, which receive information from the vomeronasal receptor cells, are found. The vomeronasal sensory function is thus nonoperational in humans. Nevertheless, several steroids are considered to be putative human pheromones; some activate the anterior hypothalamus, but the effects observed are not comparable to those in other mammals. The signaling process (by neuronal detection and transmission to the brain or by systemic effect) remains to be clearly elucidated.

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Introduction

A variety of products containing "pheromones" are on offer here and there, especially on the Internet: erotic "pheromone-based" perfumes keep appearing on the market, promising enhanced attractiveness and personal performance. What do the scientists say? Apart from the methodological issues involved in such studies [1], the claim that human pheromones exist implies being able to demon-

strate activation of a sense organ capable of transmitting such information to the brain and to identify relevant behavioral and/or physiological effects. Is the vomeronasal organ, involved in detecting pheromones in other mammals, functional in humans? Can certain steroids be considered as genuine human pheromones, able to induce appropriate effects?

The concept of pheromones

Establishing a hierarchy, encountering members of the opposite sex and estimating their reproductive potential while maintaining genetic diversity, or again signaling a threat are
essential tasks for any animal species. To these ends, individuals deploy a range of sensory signals, in which chemical signals play an important role. When a chemical message triggers specific effects in the receiver, the substance is said to be a pheromone. Two main types are generally distinguished. Releaser pheromones act on the receiver’s behavior: e.g., an alarm releaser pheromone is perceived and quickly interpreted so as to elicit flight or alert behavior. Primer pheromones have a deeper and more enduring action on the receiver’s physiology: e.g., a dominant male’s pheromones alter the endocrine function of subordinate males so as to reduce their sexual aptitude; likewise, a sexually mature male mouse is able to trigger puberty in young females. This concept of “pheromone” thus covers different effects, some eliciting a rapid characteristic response while others produce deep and sustained changes in the target’s hormonal biology and corresponding behavior.

The molecular nature of animal pheromones is not known in most cases. Studies of rodents, however, showed that small airborne molecules are involved along with nonvolatile substances such as steroids, peptides and proteins. Air-transport enables volatile pheromones to reach the olfactory system; nonvolatile substances, however, accompanied by volatile substances in solution, can be detected only by the vomeronasal organ.

The role played by proteins and peptides in pheromonal communication is surprising. One example is aphrodisin, a protein found in the vaginal secretions of the hamster which triggers reproductive behavior in young males by activating the vomeronasal organ. Likewise, major urinary proteins (MUPs) are proteins emitted in abundance in mouse urine (several milligrams per day!). The MUPs set produced by a given individual acts as an authentic signature. Detection of such molecules involves the vomeronasal organ. Aphrodisin and MUPs are lipocalins: i.e., water-soluble proteins but equipped with an internal sac in which small hydrophobic molecules can lodge. Apart from their role as pheromone carriers, these proteins, or peptide derivatives, also seem to play a signaling role themselves.

In invertebrates, the specificity of the pheromonal message often derives from some particular molecule: e.g., bombykol, which enables males to attract females over long distances. In vertebrates, message specificity, particularly as regards primer pheromones, seems rather to derive from a combination of several molecular entities associating small molecules and macromolecules. Information is transmitted via the accessory olfactory bulbs. The organ is vascularized and innervated by sympathetic/parasympathetic fibers. Variation in tissue turgescence actively pumps stimuli into the internal canal. The short-dendrite neurons expressing V1R proteins transmit information to the posterior part of the accessory olfactory bulbs, whereas the long-dendrite neurons expressing V2R proteins transmit information to the anterior part of the accessory olfactory bulbs.

The animal vomeronasal organ

The location of the animal vomeronasal organ [11], in a forward position on the base of the septum near to the nasopalatine duct (Fig. 1A), allows a pumping action providing direct contact with biological substrates emitted by congeners. Information is transmitted via the accessory olfactory bulbs, which lie behind the main olfactory bulbs, toward the amygdala and the anterior hypothalamus, which is directly involved in gonadoliberin (GnRH) secretion and thus in sex hormone activity via the anterior hypophysis [12]. During the evolution of species, the vomeronasal organ appears with the advent of amphibians and adaptation to life on land. Fish do not have it: pheromones are detected by specialized neurons in the olfactory epithelium, and the information is processed in cerebral pathways distinct from those of the general olfactory neurons.

The vomeronasal organ was discovered by Ludvig Jacobson in the 1810s [13]. Jacobson showed that it was to be found in mammals, but also pointed out that in humans it appeared to be vestigial. The organ comprises two tubular structures in a low and forward position on either side of the nasal septum, near the vomer bone (Fig. 1A). Its internal duct is closed at the back and communicates forward via a small aperture which, depending on the species, opens either onto the nasopalatine ducts which connect the oral cavity to the nose, or onto the nasal cavities. The...
The vomeronasal receptor proteins are distinct from those of the olfactory neurodetectors. Two families of protein have been studied (Fig. 1C) [14]: short extracellular chain proteins (V1R), carried by short-dendrite sensory neurons synapsing at the posterior part of the accessory olfactory bulbs; and long extracellular chain proteins (V2R), carried by neurons deep in the epithelium synapsing at the anterior part of the accessory olfactory bulbs. The latter neurons also express a gene family involved in the major histocompatibility complex [15], which is thought to govern individual recognition. In mice, the short-dendrite neurons, carrying V1R, are highly and very selectively sensitive to small pheromonal molecules, at picomolar concentrations. V2R neuron sensitivity is less clearly established, but may select vector proteins or peptide derivatives. Recently, another contingent of vomeronasal neurons has been identified, expressing olfactory receptor proteins and transmitting information to the accessory olfactory bulbs [16]. Receptor protein activation activates the vomeronasal neurons by opening particular ion channels (trpc2) [17] which initiate cell depolarization and action potential emission. All the vomeronasal neurons use these transduction channels: experimental deactivation of the genes involved in their synthesis totally and specifically abolishes vomeronasal function. Mice in which the trpc2 channels have been deactivated are unable to distinguish the sex of partners [18,19]. The vomeronasal organ thus provides information on congener’s sex and social and reproductive status.

Contribution of other sensory systems

Other organs in the nasal cavities are also involved in pheromone detection [20]. The vomeronasal organ was long thought to be the sole pheromone detection organ, the olfactory organ being dedicated to general olfaction; in fact, however, the olfactory organ does indeed seem to contribute to detecting certain pheromones [21], with a cerebral connection between the principal olfactory bulbs and the amygdalar region which receives vomeronasal input.

The nasal cavities of many mammal species also contain the Grüneberg ganglion, which in rodents is located in a guard position in the nasal vestibule and is connected to the olfactory bulbs. Via its ciliary detector neurons, in mice it is involved in detecting alarm pheromones emitted by congeners under stress; experimental destruction abolishes the stereotyped freezing response to alarm pheromones [22]. Finally, there is also the septal organ of Masera, comprising two little islands of detector neurons on either side of and below the rodent nasal septum, but which has not yet been sufficiently well studied for it to be known whether it contributes to detecting certain pheromones. The idea that pheromonal messages result from combined analysis of information deriving from different sensory inputs appears increasingly well founded.

The human vomeronasal organ

The vomeronasal organ develops in utero. Nerve fibers emerge from the developing organ and travel towards the brain. This is a crucial step in the development of the reproductive system: as of puberty, gonad functions depend on hormonal secretion by the anterior hypophysis, and this is governed by peptide GnRH secreting cells in the arcuate nucleus of the hypothalamus. Embryologically, these GnRH secreting cells derive from the olfactory placode, from which the olfactory and vomeronasal organs develop, and migrate along the vomeronasal axons toward the brain [23]. In humans, defective GnRH cell migration induces hypogonadotropic hypogonadism syndrome (LH and FSH pituitary hormone secretion defect), which is associated with absence or aplasia of the olfactory bulbs, orbitofrontal cortex alteration in the olfactory sulcus and reduction in or absence of olfactory sensitivity. After this initial development, however, the vomeronasal organ regresses, leaving only a few vestiges in adults [24,25]. Following Jacobson in the 19th century, Kölliker [26] and then Potiquet detailed the position of the vomeronasal cavities in adults: on base of the nasal partition above the foot, near the vomer bone. The cavity openings are now clearly visible on endoscopy (Fig. 2A) in some but not all individuals [25]. Histologic examination finds an internal canal of variable length, extending back and covered with ciliary epithelium with numerous underlying glands (Fig. 2B). Compared to in other mammals, the general structure shows many signs of regression: notably, absence of any veins or turgent tissue able to produce active pumping. Immunohistochemistry confirms the absence of epithelial receptor neurons and even of underlying nerve fibers that might allow neural information to be transported to the brain [29]. With contrast medium injection, the cavities can be visualized on CT (Fig. 2C and D), at the base of the septum, above the foot of the partition.

The vomeronasal organ is thus nonfunctional in adults [25]. Other decisive arguments back up this conclusion. The genes coding for V1R-type receptor proteins are mostly deactivated by mutation: only five sequences remain in the human genome (whereas mice have more than 180!) [27]; the same is true for those coding for V2R-type receptor proteins [28]. Moreover, the genes coding for the trpc2 channels, essential to vomeronasal neuron activation, are again pseudogenes unable to give rise to functional ion channels [29]. These features are shared by New World monkeys and marine mammals. Finally, on histologic examination of the olfactory bulbs in humans and New World monkeys, the accessory olfactory bulbs are found to be absent [30], whereas they are precisely the target of the vomeronasal axons in those species in which the vomeronasal organ is functional. Taken together, these arguments lead to the conclusion that the vomeronasal function is inoperative in humans. As nothing is known as to the existence of the Grüneberg ganglion or organ of Masera in humans, the only sensory channel that might possibly allow detection of pheromones in the nasal cavities would be the olfactory system itself.
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Human pheromones?

Various studies point to the possible existence of chemical communication in humans, although the molecules involved remain to be identified. Thus, men sniffing T-shirts worn by ovulating women show higher testosterone levels than men sniffing nonovulating women’s T-shirts [31]. Likewise, Stern and McClintock [32] showed that compounds taken from the armpits of women in the terminal follicular phase of the menstrual cycle and applied to the upper lip of recipient women accelerated the luteotropic hormone peak and shortened their menstrual cycle, whereas axillary compounds sampled during the ovulation phase conversely prolonged the cycle. The limitation inherent to such studies lies in the difficulty of distinguishing between sensory and systemic effects.

Other studies have focused on the effects of steroids (Fig. 3) isolated in secretions such as sweat. Possible action is explored by investigating variation in brain activity on functional imaging or evoked potential recording, or cognitive and psychological changes, or again sympathetic/parasympathetic system effects.

One such steroid is androstadienone (delta 4,16-androstadien-3-one), a testosterone derivative found in axillary secretions at levels up to 20 times as high in men as in women. Inhalation of crystal androstadienone by heterosexual women activates the ventroanterior hypothalamus [33], an effect not observed in heterosexual men, in whom the same region is activated by estratetraenol, a substance similar to natural estrogen [33]. According to the authors, the effect as seen on PET scan is too rapid to be due to nasal vessel absorption; eliminating a possible systemic route, the observed activation thus suggests an olfactory contribution. Chronic anosmia due to polyposis abolishes the response to estratetraenol.

In homosexual women, the cerebral activation pattern resembles that of heterosexual men [34] and, in homosexual men, that of heterosexual women [35]; in transsexuals, the activation patterns are specific [36]. Obviously, these findings are of interest only if the idea of individual sexual orientation is considered well founded and stable.

Since the anterior hypothalamus is activated, the question arises as to whether there is a demonstrable neuroendocrine and physiological correlate lending weight to the idea of a pheromonal effect. In the present state of knowledge, the answer has to be “no”. Rather, the effects observed are psychological. Lundström et al. [37], for example, reported that androstadienone presented at a level below the olfactory perception threshold positively modulated mood and psychophysiological alertness in women, but only in the presence of a male experimenter. In this case, the observed activation is outside the nose and the olfactory system.

Figure 3 Some molecules currently under study as candidate pheromones. A: androstadienone (delta 4,16-androstadien-3-one); B: androstenol (5 alpha-16-androsten-3 alpha-ol); C: estratetraenol (estra-1,3,5(10),16-tetraen-3-ol).
regard, it should be borne in mind that improved mood is also observed in both men and women in response to a pleasant odor [38]. Bensafi et al. [39] also reported that high-concentration androstadienone enhanced positive mood in women, with observable sympathetic correlates, whereas in men parasympathetic effects were observed. Lundström et al. [40] describe this effect on women’s mood as “a positive change of women’s feeling of being focused”.

Jacob et al. [41] reported that androstadienone added to an odor of cloves activated brain regions thought to be involved in emotional state and attention processes. Hummer and McClintock [42] reported that androstadienone applied at a non-painful concentration on the upper lip improved attention to certain emotionally charged visual stimuli: there was thus investment of psychological resources; in the experimental setting used in this study (subject alone), no mood change was to be observed.

A study by Saxton et al. [43] suggested that women exposed to androstadienone judged men who were physically present to be more attractive.

One problem with androstadienone is the wide associated intersubject variation in sensitivity [44]. Jacob et al. [45] furthermore showed that repeated sniffing of androstadienone strongly increased sensitivity in certain subjects and was accompanied by a qualitative change in perception of the odor. The mechanisms underlying such potentiation of sensitivity remain unknown.

Evoked potential kinetics during androstadienone stimulation indicated accelerated brain response compared to other odorous compounds [46]. The detection threshold, hedonic valence and induced brain response (evoked potentials) also evolved over repeated stimulation, suggesting differential perceptual learning between men and women [47]. The effects of inhaling androstadienone are more psychological than physiological [48], although neurovegetative system effects have been reported. Androstadienone blended with odor of cloves, applied below the nose, increased skin temperature on men’s hands and decreased it on women’s; it increased skin conductance more strongly in women than in men, but only in the presence of a male experimenter [49].

Another steroid, androstenol (5 alpha-16-androsten-3 alpha-ol), is also a putative human pheromone. Again, mood shifts have been described [50] but without change in sexual alertness [51]. Brain imaging suggested that, in heterosexual women, androstenol induces hypothalamus activation, whereas other odorants activate olfactory areas (piriform, lateral amygdala and anterior cingulate cortex) [52].

Other studies focused on androstenone (5a-Androsten-16-en-3-one), a known pheromone in boars, activating the olfactory system of females, which, when fertile, respond with acceptance behavior toward males. Men stimulated with androstenone showed orbitofrontal cortex activation patterns on PET similar to those found with an odorant stimulus [53], even if they did not perceive the odor. Also, heterosexual women and homosexual men chose androstenone-marked seats in preference to unmarked seats [54]; the choice, however, was directly related to individual androstenone sensitivity, and may thus be a simple matter of olfactory attraction [54].

Conclusion

In rodents, pheromones govern great molecular diversity, from small volatile molecules to peptides and proteins. Three sense organs contribute to detection: the vomeronasal organ, the olfactory organ, and the Grüneberg ganglion.

In humans, the vomeronasal organ develops in utero but subsequently regresses; all studies agree on its nonfunctional status. Nothing is known as to the presence of the Grüneberg ganglion in human nasal cavities.

Steroids, whether odorant or not, have, on the other hand been studied as putative human pheromone prototypes in adults. Some, but not others, activate the anterior hypothalamus. Effects observed after sniffing or upper-lip application strongly depend on experimental context; they are more psychological (mood shift, increased attention) than physiological and are context-dependent. Such effects are very far from the pheromonal effects observed in animals (stereotypic behavioral effects, neuroendocrine changes). They can at most be considered to be possible modulators of certain psychological variables [55].

In menstrual cycle synchronization, the sole index of a neuroendocrine effect, the substances at work and the action mechanism (systemic or sensory) remain unknown.

Human sexuality involves such a diversity of psychological, physiological and cognitive processes that susceptibility to pheromone-analog chemical messengers seems slight indeed. Human sexuality detached from reproduction escapes the pheromonal necessities to which animals are bound in recognizing and encountering the opposite sex to ensure the survival of the species.

Conflict of interest statement

None.

References


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