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Pheromones: Honey's and Queens

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Abstract

Forty years of research of putative pheromones in humans yielded inconclusive results. While the research in other species as the honey bee is overwhelming for the presence of pheromones as discussed in this article there are still considerable doubts about the existence of its human counterpart.The reasons for this discrepancy are discussed by reviewing the relevant studies Recommendations for future pheromones research are given.

Introduction

Pheromones are chemicals secreted or excreted to trigger a social response to members of the same species.They are capable to act outside the body of the secreting individual to impact the behavior of the receiving individual [1]. There are alarm pheromones,food trail pheromones,sex pheromones and many others that affect behavior or physiology.Their use among insects have been particularly well documented.Plants and humans can also communicate by pheromones [2]. This article will focus on the pheromones in the insect world (bees, ants) and bees in particular,providing basic information about pheromones,necessary to interpret the results of studies of "Pheromones in humans." These will be discussed in the second part of the article. Bees are necessary for a long healthy life of humans as essential pollinators.To play this role they are dependent on pheromones.Discussions about the existence of human pheromones are a recent topic [3,4]. It will become clear it is hardly to imagine a life without sense organs as well for bees as humans.

Pheromones in the bee's world

Bees use pheromones in almost all aspects of their life. This includes reproduction and development of brood, mating, swarming, foraging, defense and more. It is the single most important way in which bees communicate. The honey bee society consists of three castes, the queen, worker and the male and non-self sufficient brood. Pheromones are the key factor in organizing this society. They allow communication between all castes, queen-workers, workers-workers, queen-drones and between adult bees and brood [5,6]. There are two types of pheromones, primer pheromones and releaser pheromones. Primer pheromones act at a physiological level, triggering complex and long-term responses in the receiver and generating developmental and behavioral changes. Releaser pheromones have a weaker effect, generating a simple and transitory response that influences the receiver only at the behavioral level. Most of the pheromones in the insect world are of the releaser type. Releaser pheromones are involved in sexual response, aggregation, disporal, alarm, recruitment, trail, territorial and recognition [7]. Primer pheromones are the major driving force in the evolution of social harmony and in maintaining colony homeostasis [8].

a. Queen pheromones: The queen is the chief of the bee colony. She produces pheromones by different glands resulting in a blend known as "the queen signal". The "queen signal" maintains worker cohesion,suppression of queen rearing,inhibition of worker reproduction and stimulation of workers activities as cleaning, building, guarding, foraging and brood feeding. When the queen is old or sick (low pheromone signal) or dies (no pheromone signal) workers are driven to rear new queens from young brood within 1-24 hours. The removal of the queen in the absence of young brood soon leads to the decline of the colony. The workers stop performing their activities and start to lay unfertilized eggs that develop into male adults (drones). The colony becomes disorganized, unfit, susceptible to diseases, rapidly depopulates and dies.

In addition to the primer effect the queen has also a weaker releaser effect. It calls workers around the queen in a retinue group,which is stimulate to feed her and groom her. In youg premating queens it acts as an attractant for drones during the

mating fights, during swarming it keeps the swarm together. The queen mandibular pheromone (QMP) is by far the most important and was first identified in 1960 [9]. It is secreted by the queens mandibular glands and it is simply known as 9-ODA (9-oxodec-2-enoic-acid). In 1988 four other compounds were found to be secreted in concert with 9-ODA. Together they form the main constituent of the "queen signal" [10]. However the single role of the constituents of the "queen signal" is not fully understood. Mating is a crucial factor for the development of the queens pheromone signal [11]. In the absence of the mandibular glands after artificially removing them the queen can still attract workers in the retinue suggesting other substances can take its role [12]. Swarming is the way the colony reproduces itself.

Workers rear new queens and the first emerging one will kill the others and after mating will become the new colony regnant, while the old queen drives the swarm to a new nest. The QMP is essential for swarming but a synthetic blend of the 5 compounds showed comparable effects, while the queen alone had the srongest attractiveness. This suggests as with induction of retinue behavior that other extramandibular components could be involved in swarm clustering [13]. QMP is used by the virgin queen to attract drones during mating fights. Experiments with queen dummies showed that each of the 5 components attracted drones [14,15]. An increase in the frequency of mating behavior was observed also when tergal glands extracts were added to 9-ODA [16]. Thus the relative contributions of different components of the QMP and other glands on the sex pheromone level is not clear.

Many insect societies are monogynous which means that a single queen is present in a single colony. In small colonies of primitive species dominance is achieved by fight and physical competition among females. In large monogynous colonies this is not possible. This needs a system based on pheromones. The rearing of new queens has two main scopes:reproduction of the colony during swarming and replacement of the queen when she is old or weak (this phenomenon is called "supersedure") or dies. QMP suppresses both supersedure and swarming by its dispersal through the colony [17]. One of the main features of a honey bee society is the presence of two female castes,the queen and the workers.Workers are anatomically equipped with ovaries which contain a lower number of ovarioles than the queen but development of the oocytes is inhibited by the presence of the queen.If the hive or colony is queenless the workers can lay eggs [18]. However they can only produce unfertilized (haploid) eggs that give rise to male offspring.

The specific role of QMP in the suppression of worker reproduction has been debated for a long time.In the workers population young workers do the cleaning,building and feeding during the first 2-3 weeks of life. These tasks are under the workers juvenile hormone (JH) control, made in the workers hemolymph.In the last 3 weeks the workers are busy with ventilating,guarding and foraging. JH increases with age. However QMP can also suppress JH depedent on the colony needs under special circumstances. So the queen can in some way determine the amount of foragers or nest bees [18]. The defense behavior is also under the influence of QMP. Queenless colonies showed increased aggressive behavior and vice versa. Administraton of synthetic QMP reduces aggression of the colony [19].

Mandibular glands are not the only source of chemicals although they are unique for 9-ODA. The other components of the QMP can also produced by the tergal, tarsal, Dufour's and Koschevinikov glands. The tergal glands are located under the abdominal tergites and secrete primer as well as releaser substances. The tarsal glands are present in queens, workers and drones. The pheromones are released when the bee is walkingand are called "footprint pheromones" therefore. Dufour's gland is located in the dorsal vaginal wall of the queen. Its secretion is mainly linked to reproduction. Near them in the sting apparatus are the Koschevinikov glands secreting acid secretions in the sting. The senses of the honey bee:

A. Can honey bees smell like we do?

Yes, but in a different way.

Honey bees have 170 odorant receptors in their antenna's. This is quite much for an insect. Fruit flies have only 69. Their sense of smell is so precise that they can differetiate between hundreds of different flowers. They can tell if a flower contains nectar from meters away. The antenna contain odorant binding proteins (OBPs) and pheromone binding proteins (PBPs). The bee translates this information by biogenic amines or neurotransmitters as octapamine, dopamine and serotonine [20-22]. The last two are also known as human neurotransmitters. Bees don't like the smell of onion, garlic, alcohol, sweat and strong perfumes. That can bring them to the point of stinging and losing their lives.

A. Can bees taste like we do?

Yes, bees can differentiate between sweet, salty, sour and bitter. The difference is that bees are more sensitive to salt than humans but less sensitive to bitter.

B. Can they touch like we do?

Better Bees can feel vibrations in the air. They can feel the direction of the wind flow and can tell if it's gonna rain. With their antenna's they can gauge the width and depth of cells, while constructing combs. They also communicate via touch during their dances.

C. Can they speak like we do?

No, but they communicate between odors and dancing. When a honey bee detects a food source it returns to the colony to tell the others about location and nectar quality. This is done by dancing. They are great dancers. It is called the "Waggle Dance".

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b. Pheromones in Humans

Armed with this far from complete but substantial knowledge about pheromones in honey bees a look at possible pheromones in humans might be easy, one should think. Nothing is less true but it helps certainly. Unfortunately the research on pheromones in humans didn't study the broad area of the role pheromones can play in anxiety, defense, reproduction, aggression and social behavior as discussed above for the honey bee. Actually most research was directed at human pheromones and sexual attractiveness. Smell dominates this subject while taste and touch are neglected or underexposed. Marha McClintock gave the starting shot in pheromone research in humans when she postulated in 1971 that women living together in dormitories synchronize menstrual cycle and that this was caused by human pheromones [23,24].

McClintock postulated an estrogen-dependent pheromone shortening or suppressing the estrous cycle that acts on the vomeronasal organ, similar to the Lee-Boot effect in mice named to the Dutch biologists van der Lee and Boot [25]. She hypothesized this must be a primer pheromone and not a "releaser one". McClintock didn't identify this primer pheromone at that time. The McClintock study was followed by a lot of criticism, not unexpected. However in this research field first of all we must realize that our nose and smell is inferior to the nasovomeral organs in other mammals as eg the honey bee. Humans still have a nasovomeral organ but in fact this is rudimentary. In other words if our smell can't reproduce the odors of pheromones it dosn't mean they don't exist Critiques were mainly methodological. These included failure to control adequately for the convergents of onsets by chance,sampling biases and inflation on the initial differences in onsets resulting in the spurious conclusions over time [26,27].

In 1980 Winnifred Cutler supposed a relationship between the lunar cycle and menstrual synchronicity. 28.3% of mensruations in a study of 826 women occured at new moon. Later others claimed full moon and Supermoon as important determinants. This is controversial until now [28,29]. In 1986 Cutler et al. [30] reported an association between a compound of male sweat,hormones and natural body odors showing that when it was regularly inhaled by women with unusually long or short menstrual cyvles they moved closer to average cycles. In addition she reported that women who have sex with men at least once a week have regular menstrual cycles and fewer fertility and menopause problems,apparantly because of exposure to pheromones [31,32]. So is it "just walk in a men's locker"? Not so easy. Which coumpounds could be possible pheromones then?

i. Axillary Steroids: Axillary steroids become only active at puberty. They are produced by the testes, ovaries, apocrine glands and adrenals. Potential axillary steroids with pheromone properties are androstadienole, and rostenedione, and rostenol and and rosterone. They are all derived from testosterone by different metabolic pathways in steroid genesis. Androstenol is the putative female pheromone used in the Tuckler studies [30-32]. In 1978 Kirk-Smith et al. [33,34] looked at people wearing surgical masks treated with androstenol or untreated who were shown pictures of people, animals and buildings and asked to rate the pictures on attractiveness. Individuals with their masks treated with androstenol rated their photographs as "being warmer" and "more friendly".

Androstenol is believed in marketing to make you "more approachable" [35]. It would have also an effect on product evaluation. In a laboratory experiment 120 participants randomly assigned to either an experimental group or control group rated three magazines. It was found that male consumers evaluated male magazines as more masculine and more positively under the influence of the putative male pheromone androstenol, whereas no such effects were found for magazines rated neutral or feminine with respect to female consumers [36]. Androstenone is believed to increase sexual arousal. Androstenone would affect how women emotionally evaluate men. Women might also react more positively on androstenone when they ovulate [37]. Androstenone is said to improve female mood, dampening nervousness and anxiety [38].

ii. Copulins as pheromones: Copulins are a class of volatile fatty acids and are found in the vaginal fluid. They were first found in the Rhesus monkey. Copulins are thought to signal ovulation. However as human ovulation is concealed they might be pheromones also. Acetic acid is the predominantly one of these 6 volatile copulins. In a 2016 study Williams and Jacobson suggest copulins have a positive effect on rating of female attractiveness, mate guarding and self-perceived sexual desirability [39-41].

iii. Estratetraenole as a pheromone: Estratetraenole is an endogenous steroid that has been described to have pheromone-like activities in primates and humans. It is synthesized from androstenedione in the ovaries by an aromatase pathway. It is related to the estrogens yet i t has no known estrogen effect and it is regarded as a metabolic inactive degradation product of androstenedione. Surprisingly it was first identified from the urine of pregnant women.

Like androstenedione it is believed that estratetraenole has a role in the opposite gender communication as a putative pheromone [42-45]. In a study by Zhou et al. [46] estratetraenole was differential effective in the two study groups based on their sexual orientation.They also showed that human visual gender perception draws on subconscious chemosensory biochemical cues. Lindstrom et al. [47]

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found "supersmellers" for androstenedione but could not find a detection limit for estratetraenole. Remarkably the "supersmellers" were bimodal distributed among men and woman. Some data suggest that the brain processing of androstenedione and estratetraenole is different in heterosexual women and lesbian [48]. Estratetraenole has never been found in sweat.

iv. Stimulators of the vomeronasal organ: The vomeronasal organ (VNO) is an auxillary olfactory sense organ.In mammals it is mainly used to detect pheromones. These pheromones are detected by VNO receptors. They can only detect pheromones in the liquid and not in the volatile phase and require for that reason direct contact. As discussed above the receptors use binding proteins as odorant bonding proteins (OBPs) and pheromone binding proteins (PBPs) in the case of the honey bee. Information is transferred by the the already mentioned neurotransmitters to the bee hypothalamus.

The presence of a VNO in humans has been a matter of debate for a long time. Macroscopic studies looking for a visible opening of the organ during nasal septal surgery yielded conflicting results. Some feel the VNO goes in regression during fetal life [49,50] while others believe it is a rudimentary organ in humans and the key genes present in other mammals have "pseudogenized" in human beings [51-53]. Nerve and axon connections between the VNO and the human brain have not been found [52]. The absence of sufficient evidence for a functional VNO and accessory olfactory bulb in humans is not incompatible with the possibility of human pheromonal signalling. During the last decade investigations of mice and pigs have shown that the pathway via the main olfactory epithelium (MOE) and main olfactory bulb is necessary for pheromone signalling to function [54,55].

While in rodents hundreds of VNO receptors genes are present these are pseudogenes in humans [56,57]. Only 5 (VN1R1-5) have been found in humans [56,57]. They don't express in the VNO as expected but in the MOE and respond in a similar way to other olfactory receptors in cell cultures [57]. The putative pheromones androstenedione and androsterone have been shown to function as agonists on these receptors [58]. Recently Henningsson et al. [59] showed a significant association between VN1R1 polymorphism and sociosexual behavior in women, supporting the hypothesis that human social interaction is modulated by communication via chemo-signalling. While testosterone can pass the blood-brain barrier when administered intranasally surprisingly studies delivering putativeandrogenic pheromones intranasally are not available. Neither there are studies delivering putative androgenic pheromones by transdermal patches while testosterone is used in transdermal patches for years [60].

Use of these two modes of administration (intranasally and transdermally) would benefit the research on pheromones greatly. It offers the way to study the clinical pharmacology, pharmacokinetics and pharmacodynamics of known concentrations of the putative pheromones [61]. Together with the devolopment of reliable bio-assays for pheromones, which at present are totally absent, pheromone science can make big leaps forward. Then it will be interesting to study pheromones in sweat and sebaceous glands and to look for the influence of common daily used deodorants on putative axillary pheromones. Studies concerning the recognition of putativepheromones in combined smell and taste as in oral sex are not available. May be the word putative will disappear one day. A light at the horizon for the existence of pheromones in humans is the strong fact that babies suckle at all alveolar aural mammary secretions of any mother. So Wyatt's suggestion to start the research from scratch overthere is still valid [53]. The market for pheromones will not be interested in these considerations. IPM predicts pheromones market to reach a $2,4 billion by 2020 [62].

Conclusion

Forty years of research of putative pheromones in humans is inconclusive. Studies are often too small or uncontrolled and use unknown concentrations of putative pheromones often far above natural hormone levels. Endpoints are not well defined and biases by visual perception and memories are not uncommon. Bio-assays of pheromones still don't exist. Controlled modes of administration of pheromones as intranasal or transdermally delivery are not used until now. The clinical pharmacology, pharmacokinetics and pharmacodynamics of the putative pheromones are totally unknown. Nevertheless the existence of putative pheromones can't be denied completely but research should make a restart from scratch. In the meantime the pheromone retail market has its own truth and facts and is predicted to reach a value of $ 2,4 billion by 2020.

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62. IPM Pheromones Market Analysis by Product (Sex Pheromones,Aggregation Pheomones, Oviposition-Deterring Pheromones,Alarm Pheromones) and Segment Forecasts to 2020.

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