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Pheromone receptors and their putative ligands: possible role in humans

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Abstract. **Pheromones are ectohormones that play an important role in communication and behavior. Pheromones and pheromone receptor genes are important in mice and other mammals that rely heavily on pheromone cues to survive. Although there is controversy about whether pheromones and pheromone receptor genes have the same importance or are even active in humans, there are some hints that they might have roles in sociosexual behavior and mental disorders. The aim of this qualitative review was to provide an overview of the state of the art regarding pheromones and pheromone receptors in humans and their possible implications in human physiology and pathology.**

An electronic search was conducted in MEDLINE, PubMed and Scopus databases for articles published in English up to December 2018. The search concerned a possible role of pheromones and pheromone receptors in humans with implications for sociosexual behavior, mental disorders, the menstrual cycle and nutrition.

Pheromone communication in humans has not been definitively demonstrated. However, the potential ability of putative pheromones to activate the hypothalamus, which controls the release of many hormones, suggests they could have a role in systemic functions in humans. Future confirmation of the effects of pheromones and pheromone receptors in humans could be useful in the prevention and treatment of various human disorders.

Key Words:

Human pheromone, Vomeronasal receptor, Trace amine associated receptor, Pheromone exogenous steroid receptor.

Introduction

Pheromones are secreted chemical messengers that act like hormones outside the body, triggering signals between individuals of the same species and affecting the behavior of those receiving the signals[1]. To establish whether a molecule is actually a pheromone it is necessary to use repeatable experiments designed to measure a biological response (bioassays). Since these bioassays have only been designed for animal pheromones, the prospect of pheromone communication in humans has so far been controversial[2].

In 2014, Wyatt[1] proposed a series of criteria for the definition of pheromones: a synthetic pheromone should trigger the same response as the natural stimulus in a bioassay; it should be functional at natural concentrations; in the case of a multicomponent pheromone, all components in combination should be necessary and sufficient to generate the complete response; only that molecule/combination of molecules should elicit the effect; and finally, there should be a credible pathway for the pheromone signal to have evolved by natural selection[1].

It is difficult to study human pheromones because many human scents are produced by bacteria and other microorganisms which confound the results. The existence of pheromones is therefore not yet clearly demonstrated in humans, and no reproducible bioassays have been designed to study pheromone communication in humans.

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The best candidates for human pheromones are the secretions produced by lactating mothers. It seems that babies suck in response to secretions from the areola gland around the nipple[3]. Unlike odors, these hormone-like scents may activate a specific area of the human brain: the hypothalamus[4]. The hypothalamus is a gland that secretes a number of hormones, including gonadotropin releasing hormone, important in sex steroid secretion. The aim of this qualitative review was to provide an update on the state of the art regarding pheromones and pheromone receptors in humans and their possible implications in physiological and pathological conditions.

Materials and Methods

This paper is a qualitative review of all original research papers on pheromones published in scientific journals. It focuses on the roles of pheromones in physiological and pathological states. An electronic search was conducted in MEDLINE, PubMed database and Scopus using combinations of the following search terms: "pheromones in humans", "human pheromone receptors", "vomeronasal receptors", "trace amine associated receptors", "pheromone exogenous steroid receptors", "pheromones and nutrition", "pheromones and psychiatric disorders" and "pheromones and menstruation". Inclusion criteria required the term or topic "pheromones" in the title or abstract. Articles were included if they contained detailed data on cohorts of patients and/or animal models. Reference lists were scanned to retrieve additional relevant articles. A comprehensive systematic manual selection of articles identified as relevant for this review aimed to include as many studies as possible. The selection was limited to articles in English. The screening process was conducted independently by all authors. Disagreements on the conclusions of papers were settled through discussion until consensus. The final search was conducted in December 2018.

Results

Mouse and Human Pheromone Receptors

Mice and humans have vomeronasal receptors (VRs) and trace amine associated receptors (TAARs), but the intact and active genes encoding VRs and TAARs differ between them, humans lack the VNO-formyl peptide receptors, TAAR3, TAAR4 and TAAR7. Phenotypes of knockout mice for genes encoding VRs and TAARs are useful for understanding the roles of pheromones (Figure 1)[5-7].

Vomeronasal receptors (VRs) are classified into two major groups, V1Rs and V2Rs. In humans, only V1Rs are encoded by functional genes. V1Rs are class A GPCRs, however they have no significant sequence homology with other receptors of this class. The ligand binding sites are located in transmembrane regions. Vomeronasal sensory neurons have several subunits of heterotrimeric G proteins: $G\gamma_2$ associates with V1Rs. The ligand induces a cascade that leads to the synthesis of diacylglycerol that in turn induces opening of the transient receptor potential calcium channel[8].

The TAARs belong to a group of GPCRs characterized by distinct sequence motifs. They are activated by trace amines, such as β-phenylethylamine, p-tyramine, tryptamine and octopamine. They have a structure typical of the rhodopsin/β-adrenergic receptor superfamily. There are few distinct TAAR subtypes (15 in mice; 6 in humans). TAARs are associated with G proteins $G\alpha_{olf}$ and $G\alpha_{i2}$, which activate adenylate cyclase, triggering two pathways: G-protein-dependent stimulation of protein kinase A/C, and G-protein independent activation of protein kinase B (AKT)/glycogen synthase kinase 3β[8].

Pheromone receptors are expressed in different types of tissue in humans and mice, suggesting different functions of pheromone receptors in the two species. However, mice-to-human studies do help identify the putative role of pheromones in human sociosexual behavior and their implications in various diseases. The main functional VR and TAAR receptors in humans are described below, along with their different locations in tissues of mice and humans (Table I).

Mammalian Vomeronasal Receptors

In mammalian pheromone transduction, sensory neurons are located in the olfactory system (that forms from main olfactory epithelium, MOE), the vomeronasal organ (VNO), the Grueneberg ganglion (GG) and the septal organ (SO), which in turn express chemosensory receptors and project axons to the olfactory bulb to stimulate distinct limbic circuits. Mammalian pheromones are mainly detected by the peripheral sensory organ of the accessory olfactory VNO[22]. After embryogenesis, the VNO regresses in hu-

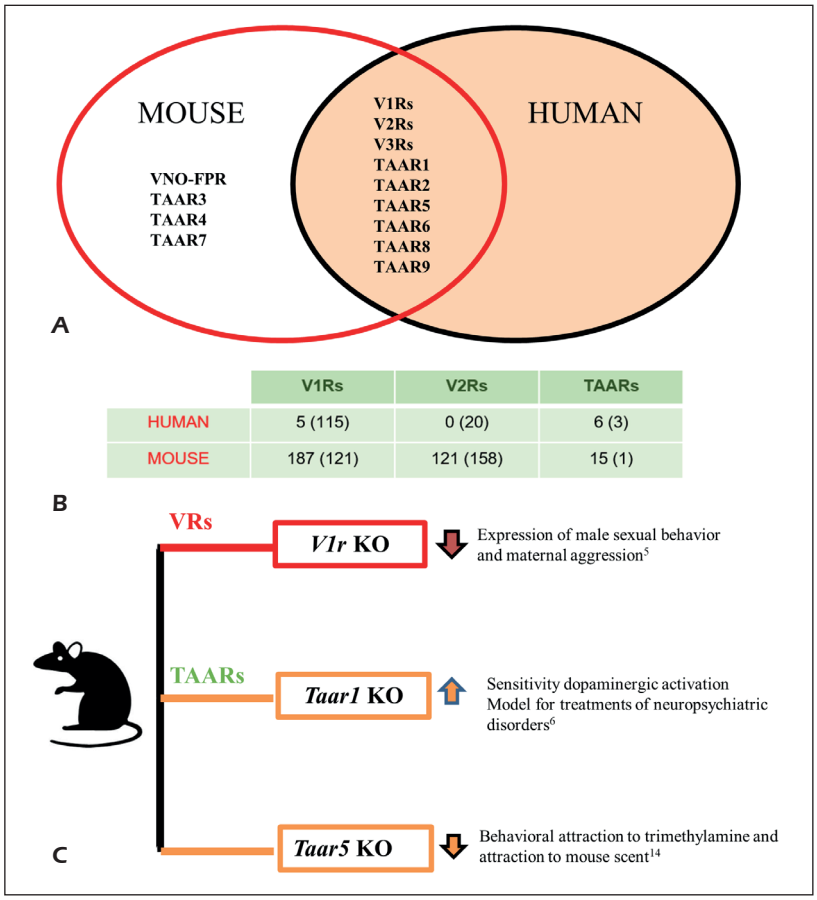

Figure 1. **A**, Venn diagram showing vomeronasal receptors (VRs) and trace amine associated receptors (TAARs) in mice and humans. **B**, Number of intact and non-intact genes, including pseudogenes and potentially intact genes (in parentheses), concerned with VRs and TAARs in humans and mice. **C**, Phenotypes of knockout mice for VR and TAAR receptor genes. VNO-FPR = vomeronasal organ formyl peptide receptor.

mans[23]. However, it has been demonstrated that this small VNO pouch is functional and responds to chemicals, altering autonomic processes. It has been postulated that these effects occur through stimulation of the ethmoidal branch of the trigeminal nerve[24].

Since in humans the genes coding for V1R-type and V2R-type receptor proteins are mostly deactivated by genetic variations (Figure 1b), it is debated whether humans truly have functional pheromone receptors. Only five genes coding for V1R-type receptor proteins remain apparently active in the human genome, whereas mice have more than 187 genes with intact open reading frames. A positive correlation has been observed between V1R repertoire size, vomeronasal system complexity and accessory olfactory bulb size, the latter being where the axons of the vomeronasal neurons project[25].

Furthering the controversy, in humans only 20 pseudogenes originate from the ancient V2R-type receptor-encoding genes. These genes are subject to strong positive selection, fundamental for survival and propagation of the species[26].

Finally, in mice, there is a third category of seven-pass transmembrane domain receptors, encoded by the V3R gene family, predicted to function as pheromone receptors and including about 100 to 120 receptor genes. A human V3R sequence containing a complete open reading frame and predicted to generate a fully functional transcript and receptor has also been detected. In VNOs, V3R-positive neurons are distinct from neurons expressing the V1R and V2R pheromone receptor families[27].

The vomeronasal receptors are G protein-coupled receptors (GPCRs)[28]. In mammals, the receptor proteins activate vomeronasal neurons through the transient receptor potential cation channel, subfamily C, member 2 (Trpc2)[29]. In humans, the genes coding for Trpc2 channels are pseudogenes unable to give rise to functional ion channels[30]. Non-functional Trpc2 and the small number of functional vomeronasal receptor genes in humans suggest that they are vestiges of ongoing pseudogenization during human evolution[31]. Although there are different signal transduction pathways, most pheromone signal transduction cascades include human VN1-type receptors[32].

Table I. Summary of putative human pheromone receptors and single nucleotide polymorphisms associated with human traits.

Human gene/ protein	Mouse orthologous	Site of expression in humans/mice	SNPs associated with a human trait	Trait	Known ligand	References
VN1R1/V1R1		Brain, lung, kidney, plasma	rs28649880	Sociosexual behavior in women	Hedione	9,10
VN1R2/V1R2	*Vmn1r224*	Brain, adipocytes, testis/membrane of VNO sensory neurons				11
VN1R3/V1R3		Testis				11
VN1R4/V1R4	*Vmn1r237*	Testis, cervix/membrane of VNO sensory neurons				11
VN1R5/V1R5		Testis	rs1578862	Monocyte percentage		11
TAAR1/TAAR1	*Taar1*	Central nervous system, amygdala, astrocytes, stomach, kidney, lung, duodenum, small intestine, white blood cells/stomach, kidney, lung, brain	rs184898731	Mosquito bite reaction	β-phenylethylamine, tyramine	12
TAAR2/TAAR2	*Taar2*	Cerebellum, leukocytes/olfactory epithelium	rs9385619 rs184898731	Heart rate response to beta blockers Mosquito bite reaction	β-phenylethylamine, tryptamine	13
TAAR5/TAAR5	*Taar5*	Skeletal muscle, amygdala, hippocampus, caudate nucleus, thalamus, hypothalamus/olfactory epithelium			Trimethylamine, dimethyl ethylamine	14
TAAR6/TAAR6	*Taar6*	Kidney, amygdala, hippocampus, human fetal liver/olfactory epithelium	rs9399032 rs4305746	Migraine disorder Major mood disorders, schizophrenia, depression and risk of suicide	Dopamine, norepinephrine, serotonin, histamine	14-16
TAAR8/TAAR8	*Taar8a* *Taar8b* *Taar8c*	Kidney, amygdala/olfactory epithelium			N-dimethyl alkylamines	13
TAAR9/TAAR9	*Taar9*	Pituitary gland, skeletal muscle, kidney/olfactory epithelium			N-methylpiperidine	17
GABRA5/GABAAR	*Gabra5*	Hippocampus			Androstenol	18
GPRC6A/GPRC6A	*Gprc6a*	Prostate, skeletal muscle, brain, leukocytes, kidney, salivary gland, adrenal gland	rs6901250	C-reactive protein concentration	All androgen steroids	19,20
OR7D4/OR7D4	*Olfr39*	Olfactory system	rs61729907 rs5020278	Acceptability of pork meat, truffles	Androstenone, androstenedione	21

Human VN1Rs may recognize linear aldehydes and alcohols as ligands. In particular, an aldehyde group is necessary on ligands for activity of VN1R1, VN1R3 and VN1R4, and an alcohol moiety for activity of VN1R2[9,32].

Human VN1Rs share about 15% amino acid identity with the olfactory receptors (ORs), highlighting differences in putative pheromones between the species. In mice, V1Rs are typically expressed in the VNO and their axons project to the olfactory bulb, however it is not known whether human VN1R axons project to specialized brain areas distinct from those of ORs. Unlike the corresponding mouse receptor V1rb2, human VN1Rs have the same functional attributes as ORs, as well as OR-typical cAMP signaling via $G\alpha_{olf}$/$G\alpha_s$[32]. Interestingly, in the MOE of mice, cAMP signaling via $G\alpha_{olf}$/$G\alpha_s$, activated by binding of specific odorants to G protein-coupled receptors, is necessary for male sexual behavior and aggressiveness[33].

On the other side of the controversy is the relative similarity between VN1R and OR activity that may explain the effects that body odors which bind to ORs can putatively exert on human social behavior, as pheromones do in other mammals. For instance, newborns and parents are apparently able to identify each other by smell[34].

In other cases, the postulated role of body odor as a pheromone has been refuted. For instance, in HLA-associated body odor selection theory, humans were thought to choose mates through body odor differences associated with specific HLA types. However, a study on a sample of 872 spousal pairs in 2018 showed no significant role of HLA dissimilarity in human mate choice[35].

Alleles 1a and 1b in the human *VN1R1* gene (allele 1a: S241F; allele b: A269D) were studied to determine whether there were differences in allele frequencies between Hellenic males and females. After population screening, the authors concluded that there was no gender-specific allelic frequency[36]. In newer data, the rs28649880 (c.722C>T; p.S241F) variant of the *VN1R1* gene was associated with sociosexual behavior in women (Table I)[10]. Healthy volunteers were analyzed by functional magnetic resonance imaging (fMRI) to evaluate the effects of hedione, a synthetic ester ligand for VN1R1 with a jasmine-like smell, on the human brain. They found that hedione induces enhanced activation of limbic areas (amygdala, hippocampus) and elicits a sex-differentiated response in the hypothalamic region that is associated with hormone release[37]. Finally, exposure to hedione causes differentiated behavioral effects in reciprocal punishments and rewards, two types of behavior necessary for the development and maintenance of cooperation[38].

Human Trace Amine Associated Receptors

The human genome includes six functional genes (*TAAR1, TAAR2, TAAR5, TAAR6, TAAR8* and *TAAR9*) and three pseudogenes for trace amine associated receptors (TAARs), all localized on chromosome 6. TAARs belong to family A of G protein coupled receptors[39] and are ubiquitously expressed in humans, for example in various brain regions, skeletal muscle, stomach, kidney, fetal liver, pancreas, pituitary gland and leukocytes. There is also high expression of TAARs, except TAAR1, in the olfactory system of vertebrates[12].

Trace amine associated receptor genes define a unique population of canonical sensory neurons scattered in a single area of the olfactory epithelium[40]. This class of pheromone receptors is involved in the olfactory detection of social cues in rodents[13]. Carnicelli et al[41] found all human TAARs (mainly TAAR5 and only traces of TAAR1) in olfactory marker protein-positive nasal biopsies. The predominant signaling pathway for TAARs exploits activation of stimulatory G proteins ($G\alpha_{olf}$ and $G\alpha_s$)[42].

The best characterized receptor of the TAAR family is TAAR1. The ligand-binding region of TAAR1 is very similar to other aminergic GPCRs. Trace amines such as phenylethylamine, tyramine, tryptamine and the neurotransmitter octopamine (closely related to norepinephrine) activate human TAAR1 via the $G\alpha_s$ protein/adenylyl cyclase pathway[43].

TAARs are homologous with biogenic amine receptors and have the same amine recognition capacity[44]. They can also be activated by amphetamine derivatives, monoamine metabolites, iodothyronamines and adrenergic and serotonergic drugs[45].

Trace amines exert their effect at low concentrations by activating TAARs in the mammalian brain and peripheral nerve tissue, but their levels are high in neurological and neuropsychiatric diseases. Understanding molecular mechanisms and developing selective agonists and antagonists for TAARs could therefore be a valid approach for treating these diseases. For instance, TAAR1 has an inhibitory influence on dopamine neurotransmission, controlling cognition including

movement, and therefore has potential therapeutic value for neurological and neuropsychiatric diseases such as schizophrenia, depression, attention deficit hyperactivity disorder and Parkinson's disease[46]. Genetic variations in the *TAAR6* gene have been associated with increased susceptibility to schizophrenia, depression and major mood disorders (Table I)[15], but links between variants in the *TAAR6* gene and these psychiatric diseases have not been confirmed in all ethnic groups[47,48]. Variations in the *TAAR6* gene have also been associated with drug response (e.g., to aripiprazole) in psychological disorders[16]. The *TAAR2* gene is a probable pseudogene in 10-15% of Asians as a result of a polymorphism that produces a premature stop codon at amino acid 168[49].

Although all the aforementioned receptors have been linked to psychological or psychiatric disorders, there is no direct link between the disorders and the putative role of human pheromones.

Finally, it was recently observed that human TAAR1 expressed in the pylorus of the stomach responds to tyramine and β-phenylethylamine from fermented food products, stimulating cAMP and consequently gastric secretion. This effect suggests the physiological importance of aromatic amines, beneficial food constituents, which are also involved in hypertension and migraines through their action on TAAR1[50].

Deorphanization of human TAAR5, specifically due to activation by trimethylamine, a bacterial metabolite found in some animal odors and in an odor repulsive to humans associated with bad breath and spoiled food, has been reported[50]. Also in these cases the role of TAAR1 and TAAR5 in pheromone communication is highly debatable, as their function in humans is apparently linked to recognition of whether or not a food is edible.

The *TAAR9* gene appears to be functional in most individuals but has a polymorphic premature stop codon at amino acid 61 (rs2842899) with an allele frequency of 10-30% in different populations[51].

Human Pheromone Exogenous Steroids

The underlying mechanisms of response to steroidal pheromones are not known. Steroidal effects are mediated through nuclear receptors and direct genomic action, but rapid steroid responses can also take place through ligand-receptor complexes at membrane level[52]. Four androstane steroids are recognized as putative pheromone molecules: androstenone, androstenol, androstadienone and estratetraenol[3]. Effects of exogenous administration of these compounds include hypothalamic activation[53].

Putative pheromone effects of steroids in humans appear to be mediated via the MOE, for example the 16-androstenes, androstadienone and androstenone have been shown to function as agonists on the olfactory receptor OR7D4, expressed selectively in the MOE[54]. The principal pheromone exogenous steroid receptors involved in pheromone signaling are summarized in Table I. 17β-estradiol has very powerful effects on reproductive physiology in female mice. In humans, such experiments are too invasive, so it is uncertain whether estradiol has the same role in women[55]. Estratetraenol, an estradiol derivative, is an endogenous steroid found in women. It has been described to have pheromone-like activities in humans. Its estrogen receptors (ERs) are ER-α and ER-β. In women it has been associated with positive mood and increased focus to capture emotional information. However, since these effects depended on the socio-experimental context, a definite association has not yet been established[56].

Androstenol is another important steroid with a pheromone function in humans. Regarded as a sex pheromone (putative female pheromone), it has a musk-like odor and is found in small quantities in human sweat glands. It is a powerful positive allosteric modulator of the $GABA_A$ receptor. The pheromonal activity of androstenol has yet to be demonstrated, although the olfactory system may have $GABA_A$ receptors because androstenol is detected as an odorant by 70% of humans. Functional GABA neurons have been identified in the nose during embryogenesis, however, $GABA_A$ receptors have not been found in olfactory receptor cells in the adult olfactory epithelium[18].

Androstenone was the first mammalian pheromone to be identified. It is a steroid found in male and female sweat and urine. It is also found in saliva and celery cytoplasm. In humans it is detected by the OR7D4 receptor[21]. It is apparently linked to a preference for pork (see next section). Human pheromone exogenous steroid receptors are described in detail in Table I.

Despite all this evidence, various studies have been unable to reproduce the findings described above. For instance, one study did not find any effects on gender perception, attractiveness ratings or unfaithfulness judgements of faces of people of the opposite sex in relation to putative sex-specific human pheromones, such as androstadienone and estratetraenol[57].

Roles of Putative Pheromone Exogenous Steroids in Humans

Roles of pheromone exogenous steroid receptors have been postulated in different physiological and pathological conditions (Figure 2). Putative steroid pheromones may be implicated in the etiology of psychiatric diseases.

At the turn of the millennium, it was postulated that anorexia nervosa syndrome is a pheromone-induced delay in puberty[58] and that androstadienone plays a role in emotions[59]. The former association has not been confirmed, whereas the latter has been studied in greater depth. In particular, it has been observed that passive inhalation of minute amounts of androstadienone increases attention to emotional stimuli[60]. Androstadienone may also act as a chemical signal to increase attention to positive information via modifications to amygdala connectivity[61]. This evidence seems confirmed by fMRI investigations[61].

Pherins (odorless synthetic neuroactive steroids that engage nasal chemosensory receptors and bind to pheromone receptors) could be effective and well-tolerated treatment options for anxiety disorders if more researches were performed to demonstrate their efficacy. In a placebo-controlled study of 30 patients with major depressive disorder it was observed that an intranasally administered pherin (PH10) elicited a rapid antidepressant effect, while in a phase-two placebo-controlled study of 91 women with anxiety disorder, administration of another pherin (PH94B: 3b-androsta-4,16-dien-3-ol) significantly decreased anxiety[62,63]. Both unpleasant and intense or pleasant odors can relieve depressive mood[64]. Further trials and studies are needed to determine whether these results can be replicated.

In humans, pheromone-like molecules, like androstenone, bind to the OR7D4 receptor and play an important role in food choices. Androstenone is a steroid reported by some to have an unpleasant, sweaty, urinous smell and by others to have a pleasant floral smell. Foods that contain androstenone include pork and truffles. Foods containing androstenone are more palatable for people who have two variations of the *OR7D4* gene, rs61729907 (c.262C>T; p.R88W) and rs5020278 (c.398C>T; p.T133M)[21,65], however it is still debated whether androstenone functions as a pheromone in humans (Table I).

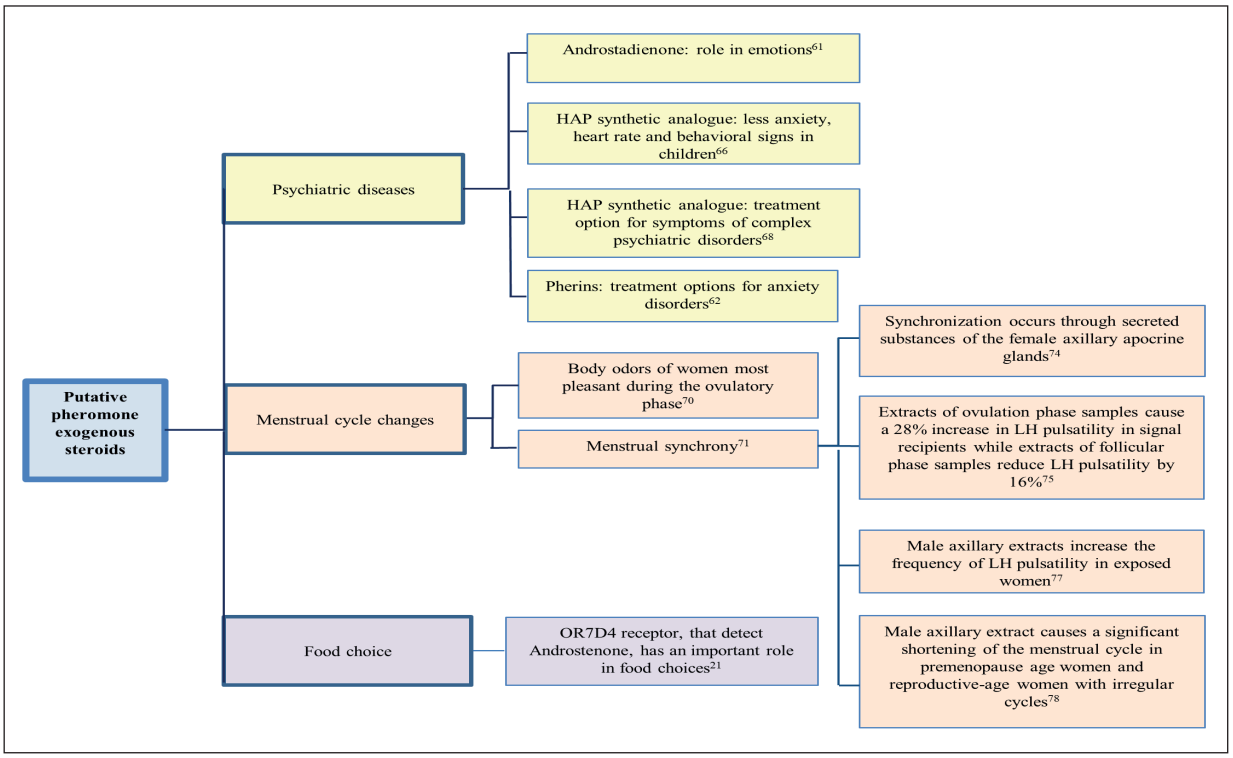

Figure 2. The possible roles of putative pheromone exogenous steroids in human physiology. HAP = human appeasing pheromones.

Future Perspectives

Potential therapeutic applications have been postulated for human appeasing pheromones (HAPs) in psychiatric disorders[66]. HAPs are secreted in the maternal breast region soon after delivery. They are effective in the control and prevention of acute and chronic stress and aggression in animals, but also in the treatment of anxiety disorders in dogs[67]. A HAP synthetic analogue was tested in a placebo-controlled study with 100 children who consequently showed a reduction in anxiety, heart rate and behavioral symptoms of stress[68]. Piccinni et al[62] recently showed the potential of HAPs as an add-on strategy in standard psychopharmacological treatment of behavior and residual symptoms of complex psychiatric disorders in two subjects with bipolar disorder type I and one with autism and self-injurious behavior. Exposure to HAPs determined a significant improvement in social anxiety and separation anxiety, obsessive-compulsive symptoms and behavioral disturbances in these individuals[69]. However, these two human studies were not replicated in other independent research and were not performed in a controlled environment.

Menstrual synchrony is an alleged process whereby women who live together in close proximity synchronize onset of their menstrual cycles in the course of time[70]. The proposed mechanisms of menstrual synchrony have, however, been questioned[71]. Menstrual cycle synchrony is complex to define because the normal menstrual cycle varies from 21 to 35 days and can last 2 to 7 days, while anovulatory cycles, stress and illness may lead to menstrual irregularities outside the normal range[72]. Synchronization of the menstrual cycle might occur through substances secreted by the female axillary apocrine glands under conditions of poor ventilation[73]. However, there are no definitive studies that can confirm menstrual synchronization among women who live in close proximity, and any potential effects of pheromones on the menstrual cycle need further validation[56].

Extract of ovulatory phase secretions has been observed to cause a 28% increase in LH pulsatility in signal recipients, whereas extract of follicular phase secretions caused a 16% decrease in LH pulsatility[74]. Male axillary extracts increase the frequency of LH pulsatility in women exposed to them[75,76]. Voznessenskaya et al[77] demonstrated that male axillary extract can cause a significant shortening of the menstrual cycle in reproductive-age women with irregular and abnormally long (>32 days) cycles and in premenopausal women (46-51 years) with irregular cycles, compared to women with normal or shorter menstrual cycles (Figure 2)[77]. This could be the first proof that pheromone communication can influence the menstrual cycle, although more investigations in a controlled environment are needed.

Conclusions

Pheromone communication is important between conspecific invertebrates and non-human vertebrates. Conspecific communication in humans has also been postulated, however it has not yet been definitively demonstrated. Indeed, the potential ability of putative pheromones to activate areas of the brain, such as the hypothalamus, which controls the release of many hormones, suggests they could have a role in systemic functions in humans. For example, pheromones might affect how and what we eat, whether we develop mental disorders, and how the menstrual cycle is regulated.

A series of controversies about the presence or function of pheromones in humans persist:

1) mammalian pheromones are mainly detected by the vomeronasal organ, whereas in humans this organ regresses after embryogenesis;
2) most pheromone receptor genes in humans are inactive;
3) it is difficult to replicate studies on human pheromones and to perform them in a controlled environment.

Other elements, however, suggest the existence and function of pheromones:

1) the small vomeronasal organ pouch seems functional and responsive to chemicals;
2) although most pheromones receptor genes are inactive in humans, those that are still active seem to have a biological function.

Despite these controversies, the pharmaceutical industry aims to develop synthetic pheromones in the search for compounds that could have effects on human behavior. Effects of interest include decreasing the symptoms of anxiety disorders and premenstrual syndrome[50]. Further research into the real effects of putative human pheromones on such states will be important for these areas of science and will help us understand how humans interact with each other and respond to their environment.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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