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Chapter 21

Pheromone effects on the human hypothalamus in relation to sexual orientation and gender

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Abstract

Pheromones are chemicals that serve communicational purposes within a species. In most terrestrial mammals, pheromones are detected by either the olfactory epithelium or the vomeronasal organ and processed by various downstream structures including the medial amygdala and the hypothalamus to regulate motivated behaviors and endocrine responses. The search for human pheromones began in the 1970s. Whereas bioactive ligands are yet to be identified, there has been accumulating evidence that human body odors exert a range of pheromone-like effects on the recipients, including triggering innate behavioral responses, modulating endocrine levels, signaling social information, and affecting mood and cognition. In parallel, results from recent brain imaging studies suggest that body odors evoke distinct neural responses from those observed with common nonsocial odors. Two endogenous steroids androsta-4,16,- dien-3-one and estra-1,3,5(10),16-tetraen-3-ol are considered by some as candidates for human sex pheromones. The two substances produce sexually dimorphic effects on human perception, mood, and physiological arousal. Moreover, they reportedly elicit different hypothalamic response patterns in manners contingent on the recipients' sex and sexual orientation. Neuroendocrine mechanisms underlying the effects of human chemosignals are not yet clear and await future detailed analyses.

INTRODUCTION

Chemical communication is ubiquitous across the animal kingdom and has been shown in humans as well. In 1959, Karlson and Lüscher coined the term "pheromone" to refer to substances that are "secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behavior or a developmental process" (Karlson and Lüscher, 1959). Substances that elicit an immediate behavioral response are classified as releaser pheromones, whereas those that more slowly influence endocrine state or development are primer pheromones. In the same year, Butenandt discovered Bombykol or (*E*,*Z*)-10,12-hexadecadienol, which is released in minute amounts by female silkworms to attract mates. Bombykol was the first pheromone to be characterized chemically. Since then, a number of pheromones serving various communicational purposes have been identified in yeasts, bacteria, insects, fish, and mammals. They come in different chemical forms, from simple molecules like formic acid to more complex ones including steroids, peptides, and proteins (Kikuyama et al., 1995; Sorensen et al., 2005; Fujiwara-Tsujii et al., 2006). More often than not, pheromones are multicomponent, comprising different compounds in a

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specific ratio, and the components work in synergy (Greenwood et al., 2005). There are sex pheromones, aggregation pheromones, alarm pheromones, territorial pheromones, trail and recruitment pheromones, and so on. Some specific mammalian pheromonal effects include regulating sexual receptivity, accelerating puberty, suppressing pregnancy, modulating parental behavior, inducing stress, and conveying identity (Bruce, 1959; Colby and Vandenberg, 1974; Fleming et al., 1979; Dorries et al., 1997; Haga et al., 2010; Brechbuhl et al., 2013). It must be noted that these effects do not all fit into the original rigid definition of pheromone (e.g., the communication of identity). As more forms of intraspecific chemical communication have been identified, the term pheromone is now commonly used for chemical signals that convey information between members of the same species. Apart from releaser and primer pheromones, researchers recognize the category of signaler pheromones, those that convey information such as identity about the sender. In 2000, Jacob and McClintock, based on their work in humans, proposed a further category of modulator pheromones, which modulate the psychological state of the recipient (Jacob and McClintock, 2000). The roles of releaser, primer, signaler, and modulator are likely not mutually exclusive, for instance, two volatiles in male mouse urine dehydro-*exo*-brevicomin and 2-sec-butyl-4,-5-dihydrothiazole have been found to exert both releaser and primer effects (Novotny, 2003).

NEURAL CODING OF MAMMALIAN PHEROMONES

Main and accessory olfactory systems

Most terrestrial mammals, except for humans, have two largely separate olfactory systems, a main olfactory system and an accessory olfactory system. In the main olfactory system, smells are detected by olfactory sensory neurons in the olfactory epithelium, whose axons make contact with the dendrites of mitral and tufted cells in the ipsilateral main olfactory bulb. Via the olfactory tract that contains the axons of the mitral and tufted cells in each bulb, olfactory information is conveyed to the ipsilateral anterior olfactory nucleus, olfactory tubercle, piriform cortex, amygdala (periamygdaloid region, cortical nucleus, medial nucleus, and nucleus of the lateral olfactory tract), and rostral entorhinal cortex, regions collectively termed the "primary olfactory cortex." From the primary olfactory cortex, olfactory information is relayed to downstream regions in and beyond the limbic system, including the orbitofrontal cortex, more amygdala subnuclei, mediodorsal thalamus, hypothalamus, hippocampus, and agranular insula (Gottfried and Zald, 2005). The accessory olfactory system starts from a different structure in the nasal cavity called the vomeronasal organ. Axons of vomeronasal sensory neurons merge together to form vomeronasal nerves that enter the accessory olfactory bulb, which in turn projects, directly and indirectly, to the medial nucleus and cortical nucleus of the amygdala, the medial preoptic nucleus, ventromedial nucleus, and arcuate nucleus of the hypothalamus, and the bed nucleus of the stria terminalis. Sexual dimorphisms have been described in the morphology of the vomeronasal organ and its projection circuit (Keverne, 1999). There is also evidence that inputs from the accessory and the main olfactory bulbs converge in basal telencephalon (Pro-Sistiaga et al., 2007).

Mammalian pheromones are processed by both main and accessory olfactory systems. Some pheromones are solely detected by vomeronasal sensory neurons, like major urine protein 20 (MUP20) in male mouse urine, exocrine gland-secreted peptide 1 (ESP1) in male mouse tear, and exocrine gland-secreted peptide 22 (ESP22) in juvenile mouse tear, whereas others are recognized by the main olfactory epithelium (Stowers and Kuo, 2015). Lesion studies in domestic pigs and rabbits show that the vomeronasal organ is not involved in sows' responses to the boar sex pheromone androstenone or the release of nipple search and suckling by 2-methylbut-2-enal, found in rabbit milk, in rabbit pups (Hudson and Distel, 1986; Dorries et al., 1997). In mice, the main olfactory epithelium also plays an essential role in regulating sexual, maternal, and aggressive behaviors (Mandiyan et al., 2005; Wang and Storm, 2011). As a specific example, the detection of the urinary attractant trimethylamine depends on trace amine-associated receptor 5 (TAAR5) that is expressed in the main olfactory epithelium (Li et al., 2013). Another social attractant, i.e. (methylthio)methanethiol, present in male urine, evokes robust responses in a subset of mitral cells in the main olfactory bulb (Lin et al., 2005). Overall, the main and the accessory olfactory systems seem to function in an integrative and complementary manner (Baum and Kelliher, 2009; Keller et al., 2009).

Medial amygdala

The medial amygdala is well positioned for the processing of pheromones (Fig. 21.1). It receives direct and indirect inputs from the accessory and the main olfactory bulbs and sends projections to central and basolateral amygdala and major hypothalamic nuclei that control motivated behaviors and endocrine responses (Brennan and Zufall, 2006). Of note, the posterior portion of the medial amygdala is subdivided into dorsal and ventral subnuclei, which send anatomically segregated projections to the medial hypothalamus and are heavily involved in reproductive and defensive behaviors, respectively (Choi et al., 2005). In rats, the synaptic organization of the posterodorsal nucleus of the medial amygdala is sexually dimorphic before puberty, and

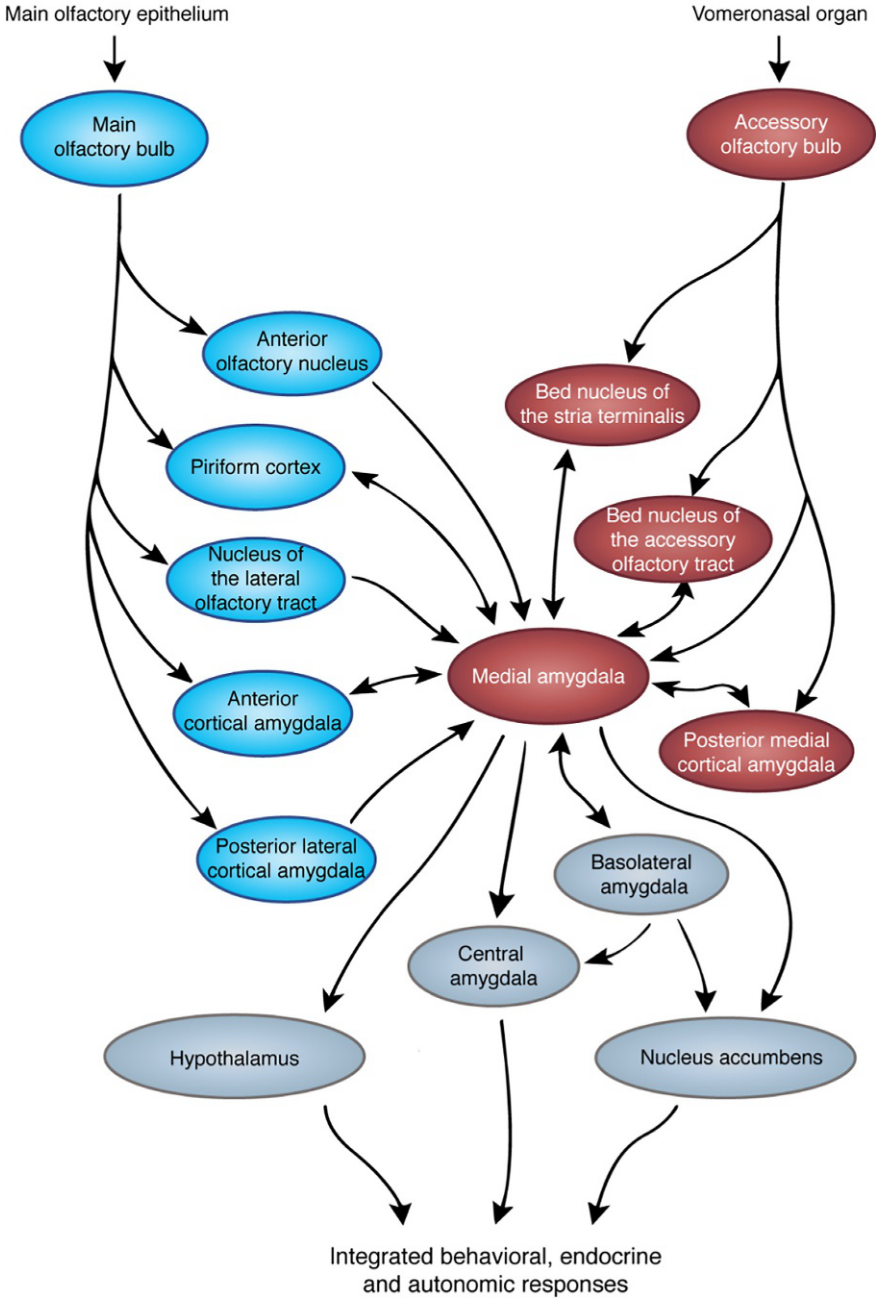

Fig. 21.1. Connections to and from the medial amygdala implicated in the processing of pheromones. The medial amygdala receives projections from both the vomeronasal structures (*red*) and main olfactory structures (*blue*) and sends projections to central and basolateral amygdala and major hypothalamic nuclei that control motivated behaviors and endocrine responses. For clarity, interconnections of the individual structures not involving the medial amygdala are not shown. The figure is based on data from rats and adapted from Brennan PA, Zufall F (2006). Pheromonal communication in vertebrates. Nature 444: 308–315.

under the influence of adult circulating androgen, the size of the nucleus in male adults becomes 50%–80% larger than in females (Cooke et al., 1999; Cooke and Woolley, 2005). In general, responses in the medial amygdala plausibly represent categorical information parsed out from the complex activities induced by natural stimuli and are drastically more frequent to opposite sex stimuli in mice (Bergan et al., 2014). Bilateral lesion of medial amygdala in male hamsters significantly diminishes the sniffing and licking (chemoinvestigative behaviors) of females' anogenital region and eliminates their mating behavior (Lehman et al., 1980).

Hypothalamus

Downstream of the medial amygdala, the hypothalamus critically links the nervous system to the endocrine system via the pituitary gland. Along with the bed nucleus of the stria terminalis and medial amygdala, the hypothalamus exhibits complex patterns of sexually dimorphic gene expression that underlie a range of sex-specific behaviors, many of which mediated by pheromones (Morris et al., 2004; Dulac and Kimchi, 2007; Xu et al., 2012). It is also susceptible to the influence of gonadal hormones both early in life and in adulthood. In terms of gross morphology, the medial nucleus of the preoptic area is larger in males than in females in rats and ferrets, whereas the anteroventral periventricular nucleus is larger in females than in males in both mice and rats. More subtle sex differences have been reported in neuronal number, connectivity, as well as synaptogenesis in this region (Simerly, 2002). For example, in mice, there are more neurons that express progesterone receptors in the female preoptic area including the anteroventral periventricular nucleus, arcuate nucleus, and the ventrolateral division of the ventromedial hypothalamus; those in the female ventrolateral division of the ventromedial hypothalamus also appear to project more to the anteroventral periventricular nucleus. Ablation of the progesterone receptor expressing neurons in the ventrolateral division of the ventromedial hypothalamus significantly diminishes sexual receptivity in females and reduces sniffing, sex discrimination, territory marking, mating, and aggression in males (Yang et al., 2013).

The effects of pheromones on endocrine states are critically mediated by a peculiar type of neuroendocrine neurons called gonadotropin-releasing hormone expressing neurons or luteinizing hormone-releasing hormone expressing neurons (GnRH neurons or LHRH neurons), which integrate information about both the internal state and the external environment of an animal and regulate the secretion of the luteinizing hormone and the follicular-stimulating hormone (Meredith, 1998). These neurons, scattered in the anterior hypothalamus and adjacent areas in adults, originate from the olfactory placode and subsequently migrate from the nose to the brain during embryogenesis (Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989). In mice, cell-specific retrograde tracing identifies the main olfactory system as a major afferent to GnRH neurons. Neurons that are synaptically connected to GnRH neurons are found in the olfactory epithelium, main olfactory bulb, anterior olfactory nucleus, olfactory tubercle, tenia tecta, piriform cortex, entorhinal cortex, basolateral and posterolateral cortical amygdaloid nucleus, as well as the anterior nucleus of the bed nucleus of the stria terminalis, with some sexual dimorphisms in terms of neuronal number (Boehm et al., 2005; Yoon et al., 2005). Moreover, the elicitation of male mating behavior with females and the chemosensory modulation (by female urine) of GnRH neuronal activity strongly depend on the functional integrity of the olfactory epithelium (Yoon et al., 2005).

Oxytocin and vasopressin

Among various hormones produced by the hypothalamus, oxytocin and vasopressin are two structurally similar nonapeptides that function both as neuropeptides and hormones and have a role in reproductive and social behaviors. Receptors for oxytocin and/or vasopressin are expressed, under the modulatory influence of gonadal hormones, in separate sets of neurons in multiple regions of the main and the accessory olfactory systems, including the olfactory epithelium, both the main and accessory olfactory bulbs, anterior olfactory nucleus, olfactory tubercle, piriform cortex, amygdala, bed nucleus of the stria terminalis, and the hypothalamus (Wacker and Ludwig, 2012). Particularly, the central amygdala and the lateral part of the bed nucleus of the stria terminalis show a clear complementary expression of oxytocin and vasopressin receptors, which could underlie the opposite effects of oxytocin and vasopressin on anxiety and fear (Veinante and Freund-Mercier, 1997). It is well established that oxytocin and vasopressin modulate social odor recognition and social signaling, and their actions seem to be localized to distinct regions in the brain (Bielsky and Young, 2004; Wacker and Ludwig, 2012). In mice, oxytocin receptor activation in the medial amygdala during the initial encounter of a conspecific facilitates later social recognition and is believed to be essential for the processing or initial retention of social information (Ferguson et al., 2000, 2001). On the other hand, male mice with a null mutation in the vasopressin receptor V1aR also exhibit a profound deficit in social recognition, and reexpressing V1aR in the lateral septum completely rescues social recognition (Bielsky et al., 2004, 2005). The interplays between oxytocin and vasopressin in the extraction, retention, and retrieval of social identities from conspecific odors and in pheromonal processing in general remain to be elucidated.

HUMAN CHEMOSENSORY COMMUNICATION

Humans, like other terrestrial mammals, are odoriferous. In fact, humans are the most highly scented ape of all in terms of numbers and sizes of sebaceous and apocrine glands (Stoddart, 1990), which endow each individual with a complex, variable, yet individually distinctive odor. Stories have it that in ancient Rome, gladiators' sweat was collected in vials and sold as an aphrodisiac. Helen Keller, when describing the odor of young men,

wrote that "… there is something elemental, as of fire, storm, and salt sea. It pulsates with buoyancy and desire. It suggests all the things strong and beautiful and joyous and gives me a sense of physical happiness." Whereas these and other anecdotes have long hinted that humans also communicate chemically, the scientific quest for human pheromones has met with several challenges. First and foremost, human behaviors are highly complex and multifaceted, and are dominated by vision and cognition rather than olfaction. To demonstrate an odor- mediated behavioral or physiological response in humans requires meticulous control of confounding factors, and the effect size is usually not large. Second, human secretions contain hundreds of chemical compounds that vary from person to person and time to time and are susceptible to influences from many environmental factors from diet, hygiene, to chemical products used in daily life (Penn and Potts, 1998; Havlicek and Lenochova, 2006). High-quality samples where such environmental effects are minimized are necessary for the identification of bioactive molecules or combinations of molecules that are bioactive but are very difficult to obtain and preserve. Third, as humans do not have an accessory olfactory system, animal models for pheromone processing may not yield findings that are directly applicable to humans. Despite these challenges, there has been accumulating empirical evidence for the existence of pheromones that subtly mediate different aspects of human communication.

Pheromonal effects of external body secretions in humans

The initial nipple localization and sucking of a human infant are guided by the mother's breast odor. Newborns tend to crawl to the odor source and preferentially suck from an untreated breast rather than one whose natural odor is eliminated by washing (Varendi et al., 1994; Varendi and Porter, 2001), which represents the strongest case to date for a releaser effect in humans. Chemosensory studies on adult men and women have largely focused on the axillae. The region contains dense aggregations of apocrine, eccrine, apoeccrine, and sebaceous glands. In particular, apocrine glands are inactive at birth and begin to secrete an oily fluid with proteins, lipids, and steroids at puberty as a result of stimulation by sex hormones (Beier et al., 2005). They are also sensitive to adrenaline and readily respond to emotions (Shelley and Hurley, 1953). Given our erect posture, axillary secretion is detectable during interpersonal interactions. Indeed, primer, signaler and modulator effects have all been shown with axillary sweat samples.

Axillary compounds from women in different times of their menstrual cycles differently modulate ovulation of recipient women (Stern and McClintock, 1998): compounds from donors in the late follicular phase accelerate the preovulatory surge of luteinizing hormone of the recipients and shorten their menstrual cycles, whereas those from the same donors but collected in the ovulatory phase produce the opposite effect. Such phase-advance and phase-delay of the preovulatory luteinizing hormone surge seem to be mediated by the increase and decrease, respectively, of the frequency of pulsatile luteinizing hormone secretion—an indicator of the release of GnRH from the hypothalamus—by ovarian-dependent pheromones (Shinohara et al., 2001). Ovulation is influenced by axillary compounds from men and lactating women as well. Male axillary secretions have been found to act on luteinizing hormone pulsing and reduce the variability of cycle lengths and the proportion of aberrant length cycles (Cutler et al., 1986; Preti et al., 2003), whereas compounds from lactating women reportedly increase the variances of the overall cycle lengths and the timing of the preovulatory surge of luteinizing hormone (Jacob et al., 2004). Intriguingly, unexplained repeated pregnancy loss could be linked to altered olfactory responses to men's body odor (Rozenkrantz et al., 2020).

Aside from exerting primer effects on women's menstrual cycle, axillary secretions, and body odors in general, convey rich information about the sender's gender, age, and genetic identity (Russell, 1976; Roberts et al., 2005; Mitro et al., 2012) and possibly play a role in kin recognition and mate choice. In particular, the high levels of polymorphism of the major histocompatibility complex (MHC), while allowing the acquired immune system to recognize "self" and "non-self," provide an almost unique molecular fingerprint of individual identity that is manifested in the chemical makeup of body odors and is recognized by the olfactory system (Bard et al., 2000). Women can identify their newborns by olfactory cues alone after being with them for only an hour (Kaitz et al., 1987). Both men and women, when presented with odors of shirts worn by individuals of the opposite sex in the context of mate choice, show a preference for odors from MHC-dissimilar individuals, which presumably encourages heterozygosity at MHC loci and improves immune response to pathogens in the offspring (Wedekind et al., 1995; Wedekind and Furi, 1997; Havlicek and Roberts, 2009).

Information about more transient states are communicated by body odors as well. Body odors of "sick" individuals, those actively undergoing immune responses, are perceived as more aversive (Regenbogen et al., 2017). Moreover, human recipients can discriminate axillary sweat samples collected from the same donors under different emotional states by smell (Chen and Haviland-Jones, 2000; Zhou and Chen, 2011). A range of modulatory effects have also been demonstrated with

these emotional chemosignals, despite that recipients are typically unaware of the exact emotional contents. Specifically, sweat samples from individuals undergoing anxiety have been found to increase state anxiety, augment the startle reflex, and diminish the positive priming effect of happy faces in facial affect perception (Pause et al., 2004; Prehn et al., 2006; Albrecht et al., 2011). The effects appear to be more pronounced in socially anxious individuals (Pause et al., 2009). Similarly, "fearful" sweat, collected from donors in a state of fear, has been shown to bias recipients toward perceiving emotionally ambiguous faces as more fearful, induce greater cautiousness, and enhance cognitive performance (Chen et al., 2006; Zhou and Chen, 2009a), whereas "happy" sweat elicits a facial expression and perceptual-processing style indicative of happiness in the recipients (de Groot et al., 2015). There is some evidence that such emotional chemosignaling is universal and transcends ethno-cultural boundaries (de Groot et al., 2018).

Interestingly, sociochemosensory and socioemotional functions likely have shared mechanisms (Zhou and Chen, 2009b). Individuals with autism spectrum disorder, a condition characterized by significant impairment in social cognition and social interaction and involves abnormality in oxytocin and/or vasopressin neurotransmission, also show altered behavioral and autonomic responses to various social chemosignals (Meyer-Lindenberg et al., 2011; Endevelt-Shapira et al., 2018).

Sex, sexual orientation, and body odor preference

Not all humans are heterosexual. If mate choice is guided in part by body odor, how does sexual orientation come into play? In an attempt to address this question, Martins et al. (2005) obtained axillary sweat samples from heterosexual males, homosexual males, heterosexual females, and homosexual females, and presented these samples to recipients of different sex and sexual orientation, who were asked to make forced-choice preference judgments for odors from each of the following pairings: (a) heterosexual male versus homosexual male, (b) heterosexual male versus heterosexual female, (c) heterosexual female versus homosexual female, and (d) homosexual male versus homosexual female. The results showed that recipients responded to sex and sexual orientation differences in body odor on the basis of their own sex and sexual orientation. When both the donors and recipients were heterosexual, preferences were given to odors from the opposite sex. When both the donors and recipients were homosexual, preferences were given to odors from the same sex. Particularly, homosexual men differed drastically from heterosexuals and homosexual women in terms of their body odor preferences as well as how their own odors were perceived by the other groups. Homosexual men preferred odors from homosexual men and heterosexual women, whereas their own body odors were the least preferred by heterosexual men and women as well as homosexual women. Taken together, these findings suggest that sexual orientation, in addition to sex, is effectively conveyed by body odor.

Candidates for human pheromones

Chemical components of human body odor

With the advances of gas chromatographic (GC) methods, especially GC–mass spectrometry, qualitative and quantitative analyses have been conducted to characterize the components of human body secretions. Axillary odors from both men and women contain a number of C6–C11 straight-chain, branched, and unsaturated acids, with (E)-3-methyl-2-hexenoic acid as a major odor-causing compound (Zeng et al., 1991, 1996). Typically, 16-androstenes also contribute to the odor (Gower et al., 1994). Although no single compound seems to be universally present in one sex and not in the other, there are some characteristic compounds that as a whole distinguish men from women (in a multivariate manner) (Penn et al., 2007). There also appear to be stable genetically determined individual fingerprints in the composition of body odor—repeat samples from the same individual are significantly more similar than those from different individuals, and samples from monozygotic twins are significantly more similar than those from two unrelated individuals (Penn et al., 2007; Kuhn and Natsch, 2009). An unsaturated aldehyde 2-nonenal appears to be present only in adults over 40 years of age and may be involved in the age-related change of body odor (Haze et al., 2001). Furthermore, the patterns of chemical volatiles, including linear aldehydes, ketones, esters, and cyclic molecules, have recently been shown to differ across emotional states as well (Smeets et al., 2020).

Androstadienone and estratetraenol

Out of the many components of human secretions, efforts to search for human pheromones have largely centered on steroids, particularly the 16-androstenes, as they are likely derivatives of sex hormones and pheromones might have evolved from hormone-like substances (Pause, 2004). Two endogenous compounds, androsta-4,16,-dien-3-one and estra-1,3,5(10),16-tetraen-3-ol, have received particular attention in the literature. Critics argue these are "unevidenced" molecules to study because they were initially touted and patented as "putative human pheromones" by a company with commercial interests in human pheromones, and no details were provided about how the molecules were arrived at (Wyatt, 2015). On the other hand, the accumulating empirical data showing that

androstadienone and estratetraenol exert sex- and sexual orientation-specific effects on recipients, while not without controversy (Hornung et al., 2018b), are hard to ignore.

Androstadienone, a nonandrogenic derivative of gonadal progesterone, is the most prominent androstene present in male semen, axillary hair, and on axillary skin surface (Gower and Ruparelia, 1993). Its concentration in freshly produced apocrine sweat is about 440 μM on average, with large interindividual differences (Gower et al., 1994). Several studies from different labs have reported that androstadienone heightens physiological arousal, maintains elevated levels of cortisol, and promotes positive mood states in female as opposed to male recipients, possibly in a context-dependent manner (Jacob and McClintock, 2000; Jacob et al., 2001; Bensafi et al., 2003, 2004; Wyart et al., 2007). In addition, it is found to modulate women's perception of men's attractiveness in a speed-dating event and to increase the perceived dominance of men's faces and increase gaze avoidance in male observers with high social anxiety (Saxton et al., 2008; Banner and Shamay-Tsoory, 2018; Banner et al., 2019). There is some indication that androstadienone also modulates recipients' attention to and memory for emotional stimuli (Bensafi et al., 2004; Hummer and McClintock, 2009). Estratetraenol, related to the estrogen sex hormones, is first identified in female urine (Thysen et al., 1968). Although studied to a lesser extent than androstadienone, estratetraenol has likewise been shown to influence male recipients' mood and autonomic responses under certain context and to increase their tendency to act in a cooperative manner toward others (Jacob et al., 2001; Bensafi et al., 2004; Oren and Shamay-Tsoory, 2019).

Attempts to directly examine whether androstadienone and estratetraenol communicate sex and facilitate interactions with potential mates have also yielded positive findings. Using stringent psychophysical methods and a basic form of social stimuli called point-light walkers that capture the essential properties of human biological motion, Zhou et al. (2014) demonstrated that androstadienone signals masculinity and estratetraenol signals femininity to their targeted recipients (Fig. 21.2, top panel). Specifically, smelling androstadienone was found to systematically bias heterosexual women, but not men, toward perceiving the walkers as more masculine. By contrast, smelling estratetraenol systematically biased heterosexual men, but not women, toward perceiving the walkers as more feminine. Homosexual men showed a response pattern resembling that of heterosexual women, whereas bisexual or homosexual women fell in between heterosexual men and women. A subsequent study by Ye and colleagues (Ye et al., 2019) adopted a similar psychophysical design and assessed recipients' emotional perception of male and female walkers. They found that smelling androstadienone biased heterosexual women, but not men, toward perceiving the male, but not female, walkers as happier and more relaxed. In contrast, smelling estratetraenol biased heterosexual men, but not women, toward perceiving the female, but not male, walkers as happier and more relaxed. Put differently, androstadienone and estratetraenol seem to prime the identification of emotionally receptive states for the potential mates with whom they are associated, in a manner contingent upon not only the recipient's own sex but also their gender perception of other individuals, which potentially ensures sex-appropriate behavior.

The aforementioned studies used androstadienone concentrations between 200 and 700 μM, which are arguably ecologically relevant. Most studies also employed a mask odor (e.g., clove oil) such that recipients were not subjectively aware of the odor of androstadienone or estratetraenol. Hence, the described effects cannot be explained by the olfactory quality of androstadienone or estratetraenol. To establish whether these or other compounds act as human pheromones requires an understanding of the neuroendocrine substrates subserving their effects, which is currently lacking. A recent study has made an initial effort to tackle this issue and found that the chemosensory communications of masculinity and femininity via androstadienone and estratetraenol, respectively, are critically modulated by oxytocin, but not the structurally similar vasopressin, in homosexual and heterosexual men (Chen et al., 2021).

NEURAL RESPONSES TO HUMAN CHEMOSIGNALS

Whereas all embryonic humans develop a vomeronasal organ that can persist into adulthood, there is no sign of an accessory olfactory bulb in adults (Meisami et al., 1998; Bhatnagar and Smith, 2001). *Trp2* (tyrosinase-related protein-2), a gene that plays an important role in vomeronasal sensory transduction in mice, is a pseudogene in humans (Liman et al., 1999). Most members of the vomeronasal receptor gene family are also pseudogenes. One gene (*V1RL1*: V1r-like gene-1) that shares strong homology with rodent V1r family members is found to be expressed in the human olfactory mucosa (Rodriguez et al., 2000). Humans therefore likely rely solely on the main olfactory system for chemosensory communication. The central structures that receive inputs from the accessory olfactory bulb in other mammals are present in humans. Whether and how they respond to human chemosignals are not entirely clear, but they play similar important roles in motivated behaviors and endocrine functions.

In particular, the hypothalamus, responsible for sex-specific effects of pheromones on reproductive behaviors in other mammals (Wersinger and Baum, 1997), is sexually dimorphic in humans as well (Swaab et al., 2001).

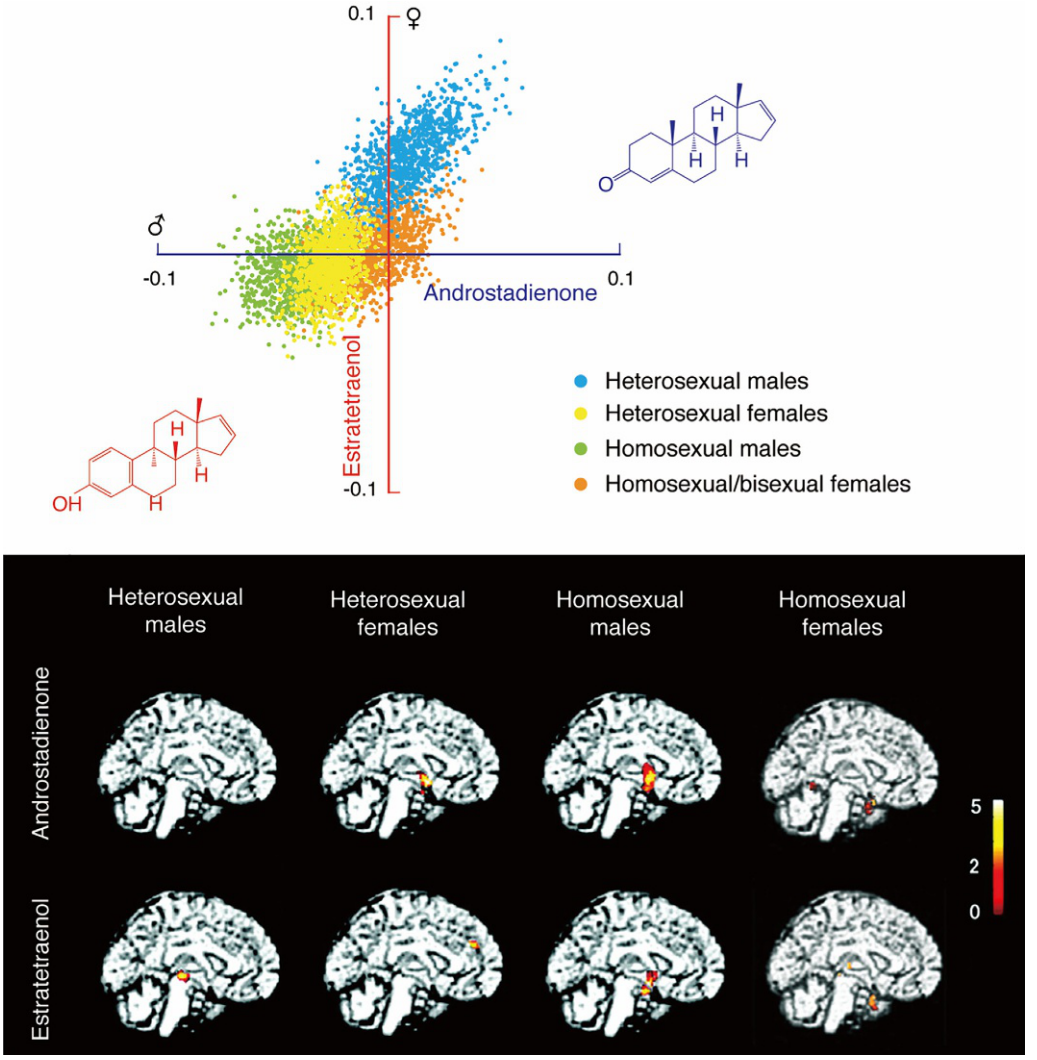

Fig. 21.2. Androstadienone and estratetraenol bias gender perception and activate the hypothalamus in manners contingent upon the recipients' sex and sexual orientation. Top panel: Central tendencies of androstadienone- and estratetraenol-induced gender perception biases (*x*- and *y*- axes, respectively) in a visual gender judgment task of point-light walkers. A positive value on either axis indicates a bias toward perceiving the walkers as more feminine, whereas a negative value indicates a bias toward perceiving the walkers as more masculine. Bottom panel: Hypothalamic responses to androstadienone and estratetraenol in heterosexual and homosexual men and women. As the same brain section is chosen, the figures do not always show maximal activation for each condition. Adapted from Zhou W, Yang X, Chen K et al. (2014). Chemosensory communication of gender through two human steroids in a sexually dimorphic manner. Curr Biol 24: 1091–1095 and Savic I, Garcia-Falgueras A, Swaab DF (2010). Sexual differentiation of the human brain in relation to gender identity and sexual orientation. Prog Brain Res 186: 41–62.

The preoptic area of the human hypothalamus contains a cell group homologous to the sexually dimorphic nucleus of the preoptic area in rats and its volume in young-adult men is more than twice of that in women. The mamillary body complex, paraventricular nucleus, suprachiasmatic nucleus, ventromedial nucleus, arcuate nucleus, as well as the sexually dimorphic nucleus of the preoptic area, all show a stronger androgen receptor staining in men than in women. Also, vasopressin neurons in the supraoptic nucleus are higher in activity and larger in size in young men relative to women. Furthermore, structural differences in the hypothalamus have been associated with sexual orientation. For instance, the vasopressin-containing subnucleus of the suprachiasmatic nucleus in homosexual men is about twice as large as that of the heterosexual men (Swaab and Hofman, 1995).

Neural responses to body odors

Research has only begun to reveal neural activities that are involved in the processing of human body odors. Using positron emission tomography (PET), Lundström and colleagues (Lundström et al., 2008) showed that body odors engage a neural network distinct from that

recruited by perceptually similar nonbody odors, which consists of the posterior cingulate cortex, occipital gyrus, angular gyrus, and the anterior cingulate cortex, and differentiates between body odors from friends and strangers. A correlation was found between the response to a friend's odor and the duration of friendship in an area close to the extrastriate body area. A follow-up PET study (Lundström et al., 2009) comparing women's brain responses to body odors from their sisters and same sex friends suggsted that olfactory-based kin recognition recruites the frontal-temporal junction, insula, and dorsomedial prefrontal cortex. In the same vein, humans can detect and evaluate MHC peptides related to body odors, and a functional magnetic resonance imaging (fMRI) study indicated that allele-specific MHC peptide ligands pertaining to "self" rather than "non-self" activate a region in the right middle frontal cortex (Milinski et al., 2013). Studies using electroencephalography, which has superior temporal resolution but relatively poor spatial resolution, showed that chemosensory event-related potentials are larger and appear with a shorter latency when recipients are exposed to body odors from MHC similar as opposed to dissimilar individuals (Pause et al., 2006). With regard to the choice of potential mates (Lübke et al., 2012), the latency of the P2 component is found to be shorter in response to body odors from heterosexual women (desired mates for heterosexual men) and longer in response to body odors from homosexual men (desired mates for homosexual men) in heterosexual relative to homosexual men. Meanwhile, homosexual men and women exhibit an enlarged P3 component under the exposure to body odors from heterosexual men (undesired mates for homosexuals). Thus the odors of desirable and undesirable mates seem to be processed differently in the brain in accordance to the sex and sexual orientation of the recipients.

Other than identity, transient states like sickness and emotions are also reflected in body odor and recognized by the brain. Regenbogen and colleagues found that smelling body odors from "sick" (induced by lipopolysaccharide injection) as opposed to healthy individuals activates the mediodorsal thalamus, entorhinal/piriform cortex, orbitofrontal cortex, and the inferior frontopolar and middle frontal gyrus (Regenbogen et al., 2017). Other studies on the chemosensory communication of emotions reported that body odors collected under stress or anxiety activate the amygdala in addition to other areas associated with the processing of social emotional stimuli (fusiform gyrus), empathic feelings (insula, precuneus, cingulate cortex), and attentional (thalamus, dorsomedial prefrontal cortex) and emotional (cerebellum, vermis) control systems (Mujica-Parodi et al., 2009; Prehn-Kristensen et al., 2009). "Anxious" odors also modulate brain responses to other social stimuli (e.g., faces) and social situations (e.g., the experience of social exclusion) (Rubin et al., 2012; Wudarczyk et al., 2015). Moreover, "aggressive" odors, collected when donors experience angry feelings, enhance activities in the hypothalamus, insula, and thalamus (Mutic et al., 2017), whereas "sexual" odors, collected when male donors experience sexual arousal, elicit activations in the hypothalamus, orbitofrontal cortex, as well as the right fusiform in female recipients (Zhou and Chen, 2008).

Collectively, existing findings indicate that the processing of human body odors, which are complex and social in nature, takes place both within and beyond the olfactory system in the human brain. Human body odors are likely encoded in a holistic manner rather than specifically for the chemosensory information they carry. Neural circuits underlying the subconscious extractions of chemosensory information such as identity, immune state, and emotion remain unknown and await future detailed analyses.

Hypothalamic responses to androstadienone and estratetraenol

Savic et al. (2001) were the first to examine brain responses to the human steroids androstadienone and estratetraenol. Using PET, they found that androstadienone and estratetraenol, both presented in crystalline form, elicited clearly sexually dimorphic response patterns in the hypothalamus. Androstadienone activated the preoptic area and ventromedial nucleus of the hypothalamus in heterosexual women, whereas estratetraenol activated the dorsomedial and paraventricular nuclei of the hypothalamus in heterosexual men. No hypothalamic activation was seen in response to androstadienone and estratetraenol in heterosexual men and women, respectively. Such a double dissociation with respect to compound and sex is distinctively different from what is known for the processing of common nonsocial odors but is remarkably consistent with the neural responses to sex pheromones in other mammals (Oomura et al., 1988; Wersinger and Baum, 1997). Two follow-up PET studies by the same group of authors (Savic et al., 2005; Berglund et al., 2006) further compared the hypothalamic activations to these two steroids in heterosexual and homosexual men and women (Fig. 21.2, bottom panel). They showed that homosexual men displayed a pattern congruent to that of heterosexual women, with maximal activity observed in the medial preoptic area/anterior hypothalamus in response to androstadienone, whereas homosexual women partly shared activation in the anterior hypothalamus with heterosexual men when smelling estratetraenol. Taken together, these findings neatly corroborate the sex- and sexual orientation-dependent effects of androstadienone and estratetraenol on human perception, mood, and physiological arousal (discussed in Section "Androstadienone and estratetraenol").

The routes by which androstadienone and estratetraenol exert their effects on the hypothalamus are not yet clear but likely involves olfactory transduction rather than absorption by the nasal vasculature, as heterosexual men with chronic anosmia reportedly do not show any hypothalamic response to estratetraenol (Savic et al., 2009). Moreover, sexual dimorphisms in these routes seem to arise early in development independent of puberty. According to an fMRI study by Burke et al. (2014), sex difference in hypothalamic responsiveness to androstadienone is already present in prepubertal children. On the other hand, individuals with gender dysphoria, a condition associated with sex-atypical cerebral programing during perinatal development, have been found to display sex-atypical response patterns to androstadienone and estratetraenol (Berglund et al., 2008; Burke et al., 2014).

Whereas these findings jointly make a strong case for androstadienone and estratetraenol being human sex pheromones, they have not been consistently replicated. An fMRI study reported that androstadienone activated the hypothalamus in both heterosexual men and women, and that women showed stronger hypothalamic activation than man only when the concentration was high (1000 μM) (Burke et al., 2012). Three other fMRI studies using a relatively low concentration of androstadienone (250 μM) and a mask odor (1% musk oil) failed to detect hypothalamic response to androstadienone in women (Chung et al., 2016a,b; Hornung et al., 2018a). The discrepancies could arise from differences in study design and methodology. Due to magnetic susceptibility variations, echo planar imaging (used in most fMRI studies) is prone to spatial and intensity distortions at the interfaces between different tissue types, which could affect image quality in the hypothalamus, located at the base of the brain. In addition, androstadienone at a concentration of 250 μM could be insufficient to evoke a definite hypothalamic response, particularly when delivered through an olfactometer that inevitably introduces additional airflow. Other confounding factors such as olfactory intensity and valence may also be at play. There are large interindividual differences and potentially sex differences in the sensitivity to and hedonic perception of the odor of androstadienone (Lundström et al., 2003; Boulkroune et al., 2007), and the hypothalamus is part of an olfactory network that encodes hedonic value (Royet et al., 2003). It is thus possible, though unlikely, that the sex- and sexual orientation-specific hypothalamic responses to pure androstadienone and estratetraenol, as reported by Savic and colleagues, partly reflected differences in the perception of their odors in homosexual and heterosexual men and women that were not necessarily captured by the overall olfactory intensity and pleasantness ratings.

CONCLUDING REMARKS

Our social lives are subtly swayed by chemosignals from our conspecifics, which exert primer (influencing endocrine state), signaler (conveying information about the sender), and modulator (modulating psychological state) effects, often without us being aware of their presence. The chemosignals are likely detected by the olfactory epithelium and processed in and beyond the olfactory system in manners different from nonsocial odors (e.g., rose and peanut butter). While controversial, the two steroids of androstadienone and estratetraenol have emerged as possible candidates for human sex pheromones. Some studies show that they have sexually dimorphic effects on recipients' perception, mood, and physiological state and also elicit response patterns in the hypothalamus that are contingent on the recipients' sex and sexual orientation. Elucidating the mechanisms underlying the release and the decoding of human chemosignals and molecularly characterizing them represent important directions for future research.

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