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Human Pheromones

*Psychological and Neurological Modulation of a
Putative Human Pheromone*

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Abstract

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The notion that humans have specialized chemicals used for communication between conspecifics, so-called pheromones, has attracted much attention and discussion. This thesis demonstrates in four separate studies that a human endogenous steroidal compound that is abundant in male sweat, androstadienone, affects women in several ways that differ to that of common odors. Specifically, androstadienone was found in Study I to have unique psychophysical characteristics in that the sensitivity distribution of the odor is bimodal with a smaller subpopulation consisting of highly sensitive individuals. Trigeminal mediation of this bimodality was experimentally excluded. Moreover, Study II demonstrated that women's cortical activation of androstadienone exposure was found to differ to that of common odorants in that androstadienone was processed faster than two perceptually similar control odors. It was further demonstrated that a non-detectable amount of androstadienone can reliably modulate both mood and physiology in women (Study III & IV); in particular mood referring to attention processes. Study IV showed that androstadienone-induced mood changes in heterosexual women were only evident when the experiment was administered by an experimenter of different sex. The combined results from these studies suggest that androstadienone serves as a human modulator pheromone that guides our behavior by inducing subtle changes in higher cognitive processes in relation to the ecological context at hand. A new definition of human pheromones is proposed and discussed in relation to the obtained results.

Keywords: Pheromones, Odor, Olfaction, Sensitivity, Psychophysiology, Attention, ERP, Mood, Androstadienone, Estratetraenol, Bimodal distribution, Speed of processing

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“Do not bite my finger; look where I am pointing.”

- **Warren McCulloch**
1899-1969

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Abbreviations

μM	Micromolar
2MB2	2-methylbut-2-enal
Androstadienone	4, 16-androstadien-3-one
Androstenol	5 α -androstenol
Androstenone	5 α -androst-16-en-3-one
ANS	Autonomic nervous system
EEG	Electroencephalogram
ERP	Event-related potential
Estratetraenol	1,3,5(10) 16-estratetraen-3-ol
H ₂ S	Hydrogen sulfide
HLA	Human leukocyte antigen
LH	Luteinizing hormone
LHRH	Luteinizing hormone releasing hormone
M	Molar
MHC	Major histocompatibility complex
PEA	Phenyl ethyl alcohol
PET	Positron emission tomography
rCBF	Regional cerebral blood flow
STAI-S	State trait anxiety inventory- State
STAI-T	State trait anxiety inventory- Trait
VAS	Visual analogue scale
VNO	Vomeronasal organ

Introduction

“Man and primates generally are microsmatic, and the sense of smell evidently plays a relatively minor role in their behavior” (Herrick, 1924)

Consumers worldwide annually spend billions of dollars on scented products in an effort to eliminate, to hide, or to enhance our natural body odors. This behavior directly contradicts the general view that the olfactory sense plays a subordinate or unimportant role in our everyday social life. The standpoint highlighted in the quote above that human olfaction is almost non-functional in comparison to our other senses is a view that has propagated in science ever since Broca (1888) divided mammals into either microsmatic or macrosmatic animals; a division entirely based on the relative size of their olfactory system. Microsmatic animals, according to Broca’s description, pay little attention to odors in their daily life and possess an olfactory apparatus with little to none functional capacity. Humans were labeled as a microsmatic animal based on the relatively small size of their olfactory system in comparison with that of other species classified. Indeed, modern genetic techniques have demonstrated that mankind expresses a less functional olfactory genome than other comparative species (Glusman, Yanai, Rubin, & Lancet, 2001; Rouquier, Blancher, & Giorgi, 2000; Young et al., 2002). Genomic studies thus seem to corroborate Broca’s view that the olfactory sense in man is less functional compared to other species. Comparative psychophysical studies on olfactory functions in humans and other species have, however, demonstrated that actual performance is not directly correlated with either size of anatomical structures or functional coding genome (Laska & Freyer, 1997; Laska, Genzel, & Wieser, 2005; Laska & Teubner, 1998; Laska, Trolp, & Teubner, 1999). Rather, olfactory functions appear to be dependent on the relevance of the message being conveyed by the specific odorant to the perceiving individual (Laska et al., 2005). Together with recent advances in the scientific field of olfaction, these findings support the notion that odors exert a significant impact on a range of behaviors and contradict Broca’s influential conclusion that humans are microsmatic. In turn, odors that exert the most significant impact on behavior in both vertebrates and invertebrates are pheromones (see definition below).

Lately, the notion of human pheromones has attracted considerable attention from scientists and laymen alike. The present thesis explores the behav-

ioral and psychophysiological effects of exposure to a putative human pheromone, 4, 16androstadien-3-one (androstadienone).

Pheromones

Hormones, circulating chemicals that control the action of certain cells were a unified term until 1932 when the entomologist Bethe (1932) suggested a distinction between endohormones and ectohormones. The first term described hormones secreted within the body and the latter defined hormones excreted outside the body. This division of hormones was redefined almost fifty years ago when Karlson and Lüscher (1959) introduced the term pheromones, derived from the two Greek words *pherein* (to transfer) and *hormon* (to excite). The term was introduced to distinguish chemosignals in insects with special and unique functions, such as regulating social functions, from common odors. The first and still universally accepted¹ definition of pheromones is:

“... substances which 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 behaviour or a developmental process.” (Karlson & Lüscher, 1959).

Pheromones are ubiquitous among phyla (Albone & Natynczuk, 1992). Pheromonal effects have been well documented in species ranging from the small yeast cell (Hicks & Herskowitz, 1976) to the significantly larger Asian elephant (Rasmussen & Schulte, 1998). In some form or another, most species, when thoroughly investigated, seem to possess pheromonal communication.

The classification of pheromones is traditionally divided into three classes applied over phyla; *releaser*, *priming*, and *signaling* pheromones. These classes are broadly based on their functions, systems affected, and working time span. Although minor alterations have been made during the years, these three main classes have been stable and applied to all species. Lately, a fourth class has been proposed: *modulator pheromones*. As reviewed below, modulator pheromones are thought of as being a class that acts predominantly in humans and in interplay with the social surrounding.

¹ However, in a subsequent article, Karlson and Butenandt (1959) defined pheromones as “... substances that are secreted by an animal to the outside and cause a specific reaction in a receiving individual of the same species, e.g., a release of certain behavior or a determination of physiologic development.”

Releaser pheromones

Releaser pheromones have a rapid onset, varying from seconds to minutes, which elicits a stereotypic response (Wilson & Bossert, 1963). Although well documented among insects, reports of mammalian releaser pheromones in the literature are scarce. The most renowned example of a mammalian releaser pheromone is the pig pheromone 5α -androst-16-en-3-one (androstenone). The boar snorts masticated saliva containing androstenone onto the sow and then proceeds to stimulate her haunch causing the sow to freeze in a mating stance allowing the boar to mount her (Melrose, Reed, & Patterson, 1971). This response (lordosis) is so strong that the sow will elicit the response even in the absence of a boar, allowing breeders to provoke the response with mere an aerosol spray containing androstenone. More recently, Schaal and colleagues (2003) managed to isolate one of the few known single mammalian pheromonal compounds. In a series of well controlled experiments, nipple secretions from lactating rabbits were analyzed and behavioral responses to the individual compounds were studied in pups. A specific component in the nipple secretion, 2-methylbut-2-enal (2MB2), elicited a strong sucking response in the puppy rabbit, hence qualifying as a mammalian releaser pheromone. Although a large commercial market for human releaser pheromones already exists, no peer-reviewed data reporting pheromones that would classify as releaser pheromones have been documented in either humans or Old World monkeys.

Priming pheromones

Priming pheromones act over a longer time span than releaser pheromones, typically hours to days (Preti & Wysocki, 1999). A large amount of evidence in favor of primer pheromones exists in the literature. Most of these effects induce reproductive alterations in rodents such as timing of puberty, onset of estrus, regulation of gonadal hormones in both sexes, and length of ovarian cycle (Bronson & Desjardins, 1974; McClintock, 1978; Vandenberg, 1969; Whitten, Bronson, & Greenstein, 1968). One of the best known effects of priming pheromones is the so-called Bruce-effect where the pregnant female mouse will induce a spontaneous abortion when exposed to the mere odor of an unknown male (Bruce, 1959). As will be reviewed below, several reports of effects in both humans (McClintock, 1971; Preti, Wysocki, Barnhart, Sondheimer, & Leyden, 2003; Russell, Switz, & Thompson, 1980; Stern & McClintock, 1998) and Old World primates (Wallis, 1989) that mimic priming pheromones have been reported in the literature.

Signaling pheromones

Signaling pheromones convey messages from a sender to a receiver. This class of pheromones can convey strikingly different and complex information ranging from sender's sexual maturation to complex social hierarchies, e.g. the domestic dog's urine that can convey information about the sender's social status (Doty & Dunbar, 1974).

Several species use signaling pheromones as an important mate selection tool (Johnston, 1998). The major histocompatibility complex (MHC) is an immunologically important group of genes that regulates the discrimination of self/non-self within the immune system. The MHC has been demonstrated to be a good determinant of genetic similarity between two individuals (Klein, 1986). Rodents have the ability to discriminate minute differences in MHC composition found in body odor, allowing them to identify relatives from non-relatives (Beauchamp & Yamazaki, 2003; Eggert, Muller-Ruchholtz, & Ferstl, 1998; Hepper & Cleland, 1998; Mateo & Johnston, 2000, 2003; Yamazaki, Beauchamp, Curran, Bard, & Boyse, 2000). This ability is used in their selection of mating partners where evidence suggests that highest preference is for mating partners that are dissimilar in their genetic composition (Beauchamp & Yamazaki, 2003; Yamazaki, Beauchamp, Bard, Boyse, & Thomas, 1993; Yamazaki et al., 2000). As reviewed below, it has been suggested that humans also possess this ability (Jacob, McClintock, Zelano, & Ober, 2002; Ober et al., 1997; Wedekind & Furi, 1997; Wedekind, Seebeck, Bettens, & Paepke, 1995).

Modulator pheromones

Recently, a new class of pheromonal compounds was suggested: the modulator pheromones (Jacob & McClintock, 2000; McClintock, 2000). Like signaling pheromones, they do not have an immediate effect on behavior. However, modulator pheromones do more than simply convey information about the sender. Modulator pheromones elicit stereotypical responses within a given context or situational meaning. If the three previously mentioned classes can be sorted accordingly to their behavioral strength with releaser pheromones eliciting the strongest and most imminent effect, signaling pheromones the weakest, modulator pheromones can then be seen as an intermediate class with respect to its behavioral effects. Modulator pheromones have been defined as:

“Modulator pheromones modulate ongoing behavior or a psychological reaction to a particular context, without triggering specific behavior or thoughts. They change stimulus sensitivity, salience, and sensory-motor integration.” (McClintock, 2003)

As will be reviewed below, a specific compound, androstadienone, has been suggested as a putative human modulator pheromone.

Potential receptor systems

One issue related to, but not a prerequisite for, the existence of human pheromones is the presence of a unique pheromonal receptor organ in humans. There are numerous examples of involvement of a specialized receptor organ in pheromonal perception and detection in the animal literature (Johnston, 1998; Meredith, 1998; Pfeiffer & Johnston, 1994; Smith et al., 2001; Tirindelli, Mucignat-Caretta, & Ryba, 1998; Wysocki & Lepri, 1991). However, the existence of a functional pheromonal receptor organ in humans has been widely disputed.

Below I will review and comment on some of the potential human pheromone receptor organs mentioned in the literature.

The Nasopalatine duct and the Nervous Terminalis

The Nasopalatine duct is a bilateral structure residing around 2 to 8 mm from the nasal floor and around 19 to 28 mm anterior to the opening of the nares (Jacob et al., 2000; Knecht et al., 2003). Via two small canals that converge into one before the intervention into the oral cavity, a direct connection between the oral and nasal cavities exists (Knecht et al., 2005). The function of this structure might be to facilitate molecule transportation between the two cavities. Even though the anatomical structure of the Nasopalatine duct have been known for more than a hundred year, little is known about the functionality. In the animal kingdom, one of the few examples of functionality is the male elephant's use of his trunk to bypass his long snout by transfer female urine to the bilateral Nasopalatine ducts in his mouth (Rasmussen & Schulte, 1998). In humans, although speculated about, no evidence of functionality exists.

The respiratory mucosa in the nasal cavity is intervened with free nerve endings from the terminal nerve, the function of which little is known. Studies have shown that terminal nerve fibers originate from the olfactory placode from where they traverse over the septum thru the cribriform plate and project to the forebrain (Pearson, Sauter, & Herrin, 1964). Moreover, the terminalis system contains luteinizing hormone releasing hormone (LHRH) and synapse in the hypothalamus (Schwanzel-Fukuda et al., 1996). Interestingly, as reviewed below, the hypothalamus has recently been implicated as part of a potential network that processes putative pheromones in the human brain (Jacob, Kinnunen, Metz, Cooper, & McClintock, 2001; Savic, Berglund, Gulyas, & Roland, 2001; Savic, Berglund, & Lindstrom, 2005). Little evidence exist today that indicates that the terminal nerve act as a human

pheromonal receptor system, however, no studies up to date have actively examined the role of this nerve in pheromonal communication.

The Vomeronasal organ

The functionality, and even existence, of the human vomeronasal organ (VNO) is a disputed topic in the scientific literature (cf. Meredith, 2001). The frequency of at least one visible unilateral VNO in humans varies in the literature from reports as high as 91 percent to a mere 46 percent in all individuals (Jacob et al., 2000; Knecht, Kuhnau, Huttenbrink, Witt, & Hummel, 2001; Stensaas, Lavker, Monti-Bloch, Grosser, & Berliner, 1991; Trotier et al., 2000; Zbar et al., 2000). The VNO is commonly described as a small orifice with a diameter of 1-2.5 mm (Trotier et al., 2000) that exhibits a yellow-brownish pigmentation, located around 2.7 cm anterior to the nares and 0.9 cm above the nasal floor (Knecht et al., 2001). Inside the orifice, a blind ended duct-like structure projects into the septum with a length of between 2 to 23 mm (Abolmaali et al., 2001; Trotier et al., 2000; Witt, Georgiewa, Knecht, & Hummel, 2002). The human VNO shows a pseudoepithelium and histochemical properties that are clearly different from the nearby respiratory epithelium (Jahnke & Merker, 2000; Witt et al., 2002). However, the fact that the VNO lacks typical neurochemical markers indicates a non-functionality of the epithelium (Trotier et al., 2000; Witt et al., 2002). Interestingly, histological studies in fetuses clearly indicate that nerve connections between the elongated microvillar cells in the VNO and the brain exist (Bhatnagar & Smith, 2001; Witt et al., 2002). After week 32 in gestation, the nerve is no longer found in cadavers (Meisami & Bhatnagar, 1998; Trotier et al., 2000; Witt et al., 2002). The nerve of the VNO connects to the accessory olfactory bulb in animals (Brennan, 2001). So far, the accessory bulb or an anatomical equivalent formation has not been found in humans (Meisami & Bhatnagar, 1998).

Evidence for a functional VNO in humans originates almost exclusively from work of the group lead by Monti-Bloch and Berliner (Berliner, Jennings-White, & Lavker, 1991; Berliner, Monti-Bloch, Jennings-White, & Diaz-Sanchez, 1996; Grosser, Monti-Bloch, Jennings-White, & Berliner, 2000; Monti-Bloch, Diaz-Sanchez, Jennings-White, & Berliner, 1998; Monti-Bloch & Grosser, 1991; Monti-Bloch, Jennings-White, Dolberg, & Berliner, 1994). The very first study tentatively reporting that a functional VNO system exists in Man was Monti-Bloch and Berliner's (1991) experiment. By stimulating only the VNO, they found that the steroid compounds 1,3,5(10) 16-estratetraen-3-ol (estratetraenol) and androstadienone raised the recorded potentials in a sex-specific way that did not correspond with an olfactory control stimulus. However, none of the studies mentioned above have successfully been independently replicated (these studies have also been criticized in Preti & Wysocki, 1999).

A recent effort to replicate Monti-Bloch and Berliner's finding that steroids elicit sex-specific electric responses in the VNO indicated that the previously reported effects were most probably mediated by a trigeminal² response in the surrounding mucosa (Thomas Hummel, personal communication). Moreover, genotyping studies have indicated that the putative VNO receptor genes (V1r and V2r) are non-coding in the human genome (Giorgi, Friedman, Trask, & Rouquier, 2000; Zhang & Webb, 2003). The functionality of the human VNO can thus be questioned.

The main olfactory system and VNO misconceptions

Although a majority of the scientific evidence indicates that the VNO in man is a residual organ, a misconception exists in the literature. Several authors base their rejection of pheromonal communication among humans, entirely or partially, on their belief that we do not possess a functional VNO (see among others Giorgi et al., 2000; Zhang & Webb, 2003). This assumption is based on the faulty claim that all pheromonal messages in mammals must be mediated by a vomeronasal system. However, several animals, where the presence of pheromonal communication is undisputed, use solely the main olfactory system to mediate these pheromonal messages (Johnston, 1998). As mentioned previously, a well known behavioral response to a pheromonal stimulation is the lordosis response in the sow when stimulated by the boar pheromone androstenone (Reed, Melrose, & Patterson, 1974). Although pigs have a VNO, the pheromonal response is mediated by the main olfactory system and not via the VNO (Dorries, Adkins-Regan, & Halpern, 1997). Moreover, other species with a documented functional VNO depend either solely on the main olfactory system or on an interaction between inputs from the main and accessory olfactory systems for pheromonal communication (Johnston, 1998). Evidence also exists, both *in vitro* and *in vivo*, that the VNO, besides mediating pheromonal signals in rodents, also mediates normal olfactory information (Meredith, 1991; Sam et al., 2001; Trinh & Storm, 2003). In an effort to investigate whether the VNO possesses the same capacity in humans, we recently measured olfactory threshold with and without the VNO functionally occluded. No differences in threshold for either an endogenous odor or PEA could be detected (Knecht et al., 2003). Up to date, we do not know if the main olfactory system is capable of mediating pheromonal signals also in humans.

The emerging facts about the intricate interplay between the main and the accessory olfactory systems discredit the notion that a functional accessory olfactory system is a necessity for human pheromonal communication to

² The trigeminal system is a part of our pain perception. Among others, the nasal and oral cavities are innervated by the ophthalmic and maxillary branches of the trigeminal nerve that react to chemical irritation and produce percepts such as coldness, warmth, and pungency.

take place. Although beyond the scope of this thesis, the current oversimplified view of the two different chemosensory systems and their roles in mediating both pheromonal and olfactory signals may have to be re-examined.

Potential human pheromonal compounds

Over the years, several compounds have been suggested to be human pheromones. Most of these compounds can be found in human sweat, semen, blood plasma, or in all of the above. They are mainly thought of as being emitted by the glandular system that covers the human skin surface.

Little is known with regard to which glands produce the putative pheromones portrayed below (Wysocki & Preti, 2000). The eccrine glands are the predominant category of glands that are densely distributed over the whole body. They excrete eccrine sweat which is the most copious skin secretion (Stoddart, 1990). The sebaceous glands also appear abundantly over the whole body and little is known about their method of excretion (Gower & Ruparelia, 1993). The glands that have attracted most attention are the apocrine glands due to their increased production at the onset of puberty (Pochi, Strauss, & Downing, 1979). Apocrine glands are mostly distributed over hair covered regions such as the axillae, pubic, areole, and perineal areas (Wysocki & Preti, 2000). When the individual is physically aroused, these glands produce small amounts of a milky liquid that contains fatty acids, proteins, and traces of steroids (cf. Schaal & Porter, 1991).

Putative human pheromonal compounds originate almost exclusively from two major chemical categories, estrogens or androgens (although see Monti-Bloch, Diaz-Sanchez et al., 1998). Compounds and their claimed effects that have been mentioned in the literature as putative human pheromones, belonging to these two categories, will be reviewed below.

Estrogens

Reports that have measured naturally occurring concentrations of estratetraenol in the human body are scarce. However, a report on the occurrence of estratetraenol in the urine of pregnant women exists (Thysen, Elliott, & Katzman, 1968). Studies investigating the behavioral aspect of the steroid estratetraenol also exist and have somewhat disparate results (Bensafi et al., 2003; Jacob & McClintock, 2000; Savic et al., 2001).

The first behavioral data on this endogenous steroid indicated that small amounts of estratetraenol were able to modulate subjective mood ratings in both male and female participants (Jacob & McClintock, 2000). Interestingly, the behavioral responses were sex-specific in that men experienced more negative mood and women more positive mood when stimulated. Data

from the same investigators indicated that estratetraenol had the ability to increase men's and decrease women's skin temperature (Jacob, Hayreh, & McClintock, 2001). However, others have failed to reproduce these effects. Bensafi and colleagues (2003) recently reported that exposure to a supra-threshold concentration of estratetraenol did not effect mood, nor psychophysiology of the participating men and women. As will be reviewed below, this lack of effect could be mediated by the social context of the experimental setup. A recent experiment in our laboratory (Olsson, Lundström, Diamantopoulou, & Esteves, In press) demonstrated that an appropriate social context was a necessity to elicit similar effects to the previous mentioned study by Jacob and colleagues (2000). Moreover, a recent brain imaging study reported activation of the hypothalamus in men, but not women, when they passively smelled suprathreshold concentrations of estratetraenol (Savic et al., 2001). Interestingly, Sobel and colleagues (1999) found greater activation in the anterior medial thalamus and the inferior frontal gyrus areas in men when stimulated with an undetectable concentration of the closely related compound estra-1,3,5(10),16-tetraen-3-yl acetate.

These findings, taken together, produce conflicting views. While Jacob and colleagues (2001; 2000) reported that estratetraenol affects both mood and psychophysiology in a sex-specific way, Bensafi and colleagues (2003) reported the contrary. Moreover, Savic and colleagues (2001) reported a unique activation of the hypothalamus in men whereas Sobel and colleagues (1999) reported activation in larger areas including known olfactory structures. Although the latter comparison is problematic due to a difference in imaging techniques, no clear synthesis of the data is possible.

Androgens

Since the first speculations of the existence of potential human pheromones, androgens have been in the spotlight. Among the very first reports on potential pheromonal effects due to exposure to a single endogenous compound was Cowley and colleagues (1977). They reported that androstenol, when applied onto a surgical face mask, made women rate men more favorably. This initial study set the trend for both the future design and aims of other experiments. Several other studies followed with the aim to determine effects of exposure to different androgens such as androstenone (M. D. Kirk-Smith & Booth, 1980), androstenol (Filsinger, Braun, & Monte, 1990; M. Kirk-Smith, Booth, Carroll, & Davies, 1978), androsterone (Gustavson, Dawson, & Bonett, 1987), and 5- α -androgenst-16-en-3-one (Kovacs et al., 2004). Studies on these androgenic compounds have demonstrated none to minimal effects. Moreover, none of these studies controlled for perceptual awareness of the experimental stimuli. Hence, the reported effects that do exist in the literature could be explained by perceptual differences between the experimental and control stimuli. Besides the behavioral effects men-

tioned above, androstenol has also been suggested as a potential regulator of the menstrual synchrony phenomena that will be reviewed below (Shinohara, Morofushi, Funabashi, Mitsushima, & Kimura, 2000).

To this day, the androgen that has received the most attention in the scientific literature is 5α -androst-16-en-3-one (androstenone). However, attention has not primarily been directed to the compound's prospective pheromonal traits, rather, the focus has been on the compound's interesting psychophysical characteristics. A large part of the population has a specific anosmia³ to the odor of androstenone. Interestingly, the reported levels of specific anosmia to androstenone in the literature range between 2 to 50 percent (Bremner, Mainland, Khan, & Sobel, 2003; Dorries, Schmidt, Beauchamp, & Wysocki, 1989; Hummel, Gollisch, Wildt, & Kobal, 1991; Knecht et al., 2003; Labows & Wysocki, 1984; Pollack et al., 1982; Wang, Chen, & Jacob, 2004; Wysocki & Beauchamp, 1991; Wysocki, Beauchamp, Schmidt, & Dorries, 1987; Wysocki, Dorries, & Beauchamp, 1989). Although the wide range of reported levels is most probably due to a difference in assessment methods and populations, androstenone is unique among compounds with this large rate of specific anosmia. There is still a debate in the literature whether androstenone insensitivity is due to central (Mainland et al., 2002) or peripheral mechanisms (Wang et al., 2004; Yee & Wysocki, 2001, 2002). Interestingly, specific anosmia to androstenone seems to be in part related to genetic factors (Wysocki & Beauchamp, 1984) and the development of the gonadal hormone system (Dorries et al., 1989).

The androgen compound most eligible as a pheromone is the aforementioned substance androstadienone. The reported exposure effects of this compound will be reviewed in more detail below.

Evidence for human pheromones

Releaser pheromones

Humans have well developed cortical structures with a memory system that modulate most stimulus inputs. Our overt responses to signals are thus strongly confounded by past experiences, context, and sensory integration processes. As expected, there is no peer-reviewed study, in humans, that claims that a known endogenous compound would elicit a rapid stereotypical behavioral response, independent of previous associations; the definition of releaser pheromones (Wilson & Bossert, 1963).

³ Specific anosmia is a term that describes a state of insensitivity or lack of percept in the individual to a specific odor whereas no defects in the general sensitivity can be found (Amoore, 1967).

Priming pheromones

The first evidence of a connection between the olfactory and endocrine system was a tentative report by Le Magnen (1952) that demonstrated that menstrual cycle phase had an impact on women's olfactory sensitivity. A phenomenon now firmly established for the olfactory system (Doty, Snyder, Huggins, & Lowry, 1981; but see T. Hummel et al., 1991) as well as our other four senses (cf. Parlee, 1983).

The first tentative evidence of human pheromones was reported as recently as 1971. McClintock (1971) demonstrated that women living in close proximity to each other tended to synchronize their menstrual cycles over time. Although some aspects of the method used have later come into question (see Schank, 2000; Schank, 2002), numerous replications have been made since then (Preti, Cutler, Garcia, Huggins, & Lawley, 1986; Russell et al., 1980; Weller & Weller, 1997; Weller & Weller, 1993; but see Weller & Weller, 1995). The occurrence of menstrual synchrony was first demonstrated among rodents (Whitten, 1959) where the initial understanding was that it was a social occurrence. However, the mechanism was later isolated to olfactory cues and labeled as a phenomenon caused by priming pheromones (Whitten et al., 1968).

Olfactory, and hence potential pheromonal cues, were not demonstrated as mediators of the signal in humans until a tentative study demonstrated that the underarm sweat from donor women, swiped above the upper lip of women, was able to shift the menstrual cycle of the receiver towards the donors (Russell et al., 1980). This discovery was later extended by the demonstrated effect that underarm sweat taken from donors at the peri-ovulatory phase elongates, and when taken from the follicular phase abridge, the receiving woman's menstrual cycle (Stern & McClintock, 1998). As mentioned above, an androgen has been implicated as the active compound. 5α -androstanol (androstanol) decreases the luteinizing hormone (LH) pulse⁴, thus serving as a regulatory compound (Shinohara et al., 2000). Women seem to emit pheromone-like compounds that have the capacity to regulate the menstrual cycle of receiving women in a non-conscious way by regulation of the LH pulse (Shinohara, Morofushi, Funabashi, & Kimura, 2001); hence classifying as evidence of human pheromonal communication akin to the priming pheromones in rodents.

Evidence of male priming pheromones is also reported in the literature. A recent study by Preti and colleagues (2003) demonstrated that male axillary odors modulate women's LH pulse. Moreover, there are reports that exposure to men renders women to experience shorter and more regular menstrual cycles (cf. McClintock, 1971; Stern & McClintock, 1996). Taken to-

⁴ LH is a gonadal hormone that stimulates the release and maturation of the ova in women. The excretion of LH is performed in regular pulses within the major upside down v-shaped distribution curve of LH over the course of a menstrual cycle.

gether, compounds in the sweat of both men and women seem to contain pheromone-like compounds that have the capacity of regulating women's menstrual cycle. These biological signals mimic the primer pheromones demonstrated for other species.

Signaling pheromones

The best example of signaling pheromones in the animal literature is the conveying of chemical signals that enhance reproductive outcome. The use of signaling pheromones related to mate choice has been demonstrated in such diverse species as fish (Milinski et al., 2005; Reusch, Haberli, Aeschlimann, & Milinski, 2001), mice (Yamazaki et al., 1993; Yamazaki et al., 2000), and beetles (Rantala, Jokinen, Kortet, Vainikka, & Suhonen, 2002) to mention a few. Although the detailed genetic basis of this connection between MHC and mate preferences is not well understood, the ongoing strive of each individual to promote its genes in the general gene pool is believed to be the underlying cause (Apanius, Penn, Slev, Ruff, & Potts, 1997). Genetic heterozygosity enhances resistance to infectious diseases (Penn, Damjanovich, & Potts, 2002), lowers the general level of inbreeding in the population (Penn & Potts, 1998), and enhances reproduction success (Potts, Manning, & Wakeland, 1991). These factors all promote the prolonged survival of heterozygotic individuals. The selective pressure also acts prenatally. Rate of spontaneous abortions (Ho et al., 1994; Laitinen, 1993; Weckstein, Patriuzio, Balmaceda, Asch, & Branch, 1991) and fetal implantation success (Porter & Scott, 2000) have been demonstrated in both animals and humans to be somewhat dependent on parental MHC. The evolutionary pressure to develop mechanisms for genetic similarity/dissimilarity judgments of potential mating partners could be hypothesized to be extremely high.

Recent evidence promotes the idea that humans use signaling pheromones in an effort to reach reproductive success. Ober and colleagues (1997) investigated the rate of inbreeding in an isolated religious group and showed that the level of inbreedance was much lower than statistically expected. Moreover, a connection between HLA⁵, mate selection, and reproductive success in the same population was evident (Ober, 1999; Ober, Hyslop, & Hauck, 1999; Weitkamp & Ober, 1999; but see Hedrick & Black, 1997). Related data found that women's hedonic preference of male body odors is dependent on the degree of HLA similarity between the male donor and the female rater (Sandro Carvalho Santos, Augusto Schinemann, Gabardo, & da Graca Bicalho, 2005; Wedekind & Furi, 1997; Wedekind et al., 1995).

⁵ MHC is called HLA (Human leukocyte antigen) in humans. HLA is often also referred to as the 'donator gene' due to its use as determinant of genetic compatibility between individuals before organ transplantation (Klein, 1986).

In animals, the preference for MHC dissimilarity as indicated by a potential mate's individual odor is dependent on inherited alleles of the MHC loci (Gilder & Slater, 1978; Ochoa & Jaffe, 1999). In other words, the animal is not trying to maximize the genetic difference; rather, a balance between already acquired and new alleles is sought for, creating a balance between inbreeding and outbreeding costs (Penn & Potts, 1998). Jacob and colleagues (2002) found that humans also follow this logic of maximizing immunological fitness in their preferences. They demonstrated that the mechanism responsible for a woman's ability to discriminate and select body odors is based on the HLA loci inherited solely from her father. Interestingly, Sandro and colleagues (2005) in the aforementioned study found that the connection between HLA and hedonic preference of body odors was reflected only in the participating women's ratings.

These data, taken together, indicate that inbreedance avoidance and mate choice could be, in part, mediated by a signaling pheromone residing in our body odor given the strong connection between hedonic ratings of body odors and HLA composition. Moreover, this phenomenon seems to be more functional, or better preserved, in women than in men.

Modulator pheromones

As stated above, a new functional class of pheromones was recently suggested (Jacob & McClintock, 2000; McClintock, 2000): the modulator pheromones. Rather than to elicit a stereotypic behavioral response irrespectively of the social surrounding, as in the case of the releaser pheromones, modulator pheromones are thought to elicit stereotypical responses within a given context. An analogue could be how humans interpret humor. A dirty joke told by a stand up comedian during his act can elicit massive laughter every time it is told, however, the very same joke, told in an identical way by the same comedian but in a different context, let us say during a dissertation defense, will only produce dead silence. The pairing with the appropriate social context is thus required to elicit the sought effect.

Studies employing diary-like self-reports as well as behavioral measurements have reported that exposure to undisclosed compound(s)⁶ modulates the participating women's (Friebely & Rako, 2004; McCoy & Pitino, 2002) and men's (Cutler, Friedmann, & McCoy, 1998a) sociosexual behaviors. The participants reported an increase in sexual activities such as petting, kissing, and general affection. However, this line of research performed by Cutler and colleagues has been heavily criticized on several important

⁶ The authors of these articles claim that the identity of the compound(s) used (it is not disclosed whether an identical compound was used to stimulate both men and women in the studies above) is being withheld due to an ongoing patent process and will be disclosed when the patent process is completed.

points. First of all, the identity of the compound(s) has never been disclosed (see note 6 above) rendering analyses regarding the biological origin of the reported effects impossible. Secondly, no adequate stimulus control was employed thus leaving the possibility that the reported effects are due to a perceptual difference between the stimuli rather than the suggested pheromonal effect. Thirdly, inferences of the direction of the reported effects are impossible to draw due to the study design, i.e. whether the carrier subjects or their partners are the mediators of the reported effects. Lastly, Wysocki and Preti (1998) published a commentary to the original findings where they not only pointed out critical statistical errors made by the authors but also criticized their claims of a successful synthesis of the undisclosed pheromonal compounds from human axillary sweat (but see reply in Cutler, Friedmann, & McCoy, 1998b). Although these findings have been widely cited by commercial manufactures of human pheromones, they do not provide compelling evidence of the existence of human modulator pheromones.

As stated above, the compound receiving most attention with regards to the existence of a potential human pheromone is the endogenous steroid androstadienone. In the time period of just a few years, several effects have been reported in the scientific literature. These effects can be divided into three major categories; cortical responses, psychophysiological, and psychological responses to androstadienone exposure. Below, the natural endogenous occurrence of androstadienone and the reported behavioral effects will be reviewed.

Natural occurrence of androstadienone in humans

Androstadienone is a member of the odorous family 16-androstenes and can be found in the peripheral blood plasma of men to the extent of 98 ng / 100 ml blood (Brooksbank, Wilson, & Gustafsson, 1972; Brooksbank, Wilson, & MacSweeney, 1972) and in their axillary secretion with a mean value of 228 pmol / total axillary hair weight (Nixon, Mallet, & Gower, 1988). Interestingly, androstadienone can also be found in women, but in a much smaller concentration (Brooksbank, Wilson, & Gustafsson, 1972).

Male axillae are said to be dominated by coryneform bacteria whilst women's axillae microflora are said to be dominated by micrococceae bacteria (Jackman & Noble, 1983). Although examined only in a few subjects, it has been shown that there is a high correlation between the presence of coryneform bacteria and the amount of androstenone (Gower, Holland, Mallet, Rennie, & Watkins, 1994; Gower & Ruparelia, 1993), a compound believed to be derived from androstadienone. Based on this observation, it has been proposed that androstadienone may be created from androstadienol by axillary coryneform bacteria and later transformed into the more odorous androstenone (Mallet, Holland, Rennie, Watkins, & Gower, 1991; Rennie, Gower, & Holland, 1991). Androstadienone may therefore be a precursor to many of the other 16-androstenes (Gower & Ruparelia, 1993). Moreover,

coryneform bacteria are only present in axillary sweat after the maturity of the apocrine glands that takes place during puberty (Stoddart, 1990). Androstadienone, being a precursor, and transformed by coryneform bacteria suggests that androstadienone is a potential human male pheromone.

Cortical responses to androstadienone exposure

The first report of cortical modulation from exposure to androstadienone was Grosser and colleagues (2000) who reported an increase in alpha cortical activity in the participating women as measured by phasic electroencephalographic (EEG) activity. The authors attributed the reported effects to a hypothalamic induced state of reduced tension. Interestingly, androstadienone exposure in a suprathreshold concentration has been demonstrated to induce a sexually dimorphic response. It has been shown that exposure to the steroid primarily activates the hypothalamus in women and mainly olfactory regions in men (Savic et al., 2001). Although somewhat limited by the spatial resolution of the positron emission tomography (PET) technique used, the results suggested that local maxima activated the anterior-ventral hypothalamus in women. This hypothalamic nucleus is reportedly involved in the sexual activity of monkeys (Oomura, Aou, Koyama, Fujita, & Yoshimatsu, 1988) but also strongly connected to feeding behavior (Takaki, Aou, Oomura, Okada, & Hori, 1992) and the down regulation of food-related transcripts (Lindblom, Haitina, Fredriksson, & Schioth, 2005). Possibly due to hypothalamus' multiple roles, the authors⁷ were not able to replicate their finding in a subsequent study employing contrasts between two different odorants (a pleasant and an unpleasant odorant) and androstadienone in a suprathreshold concentration. Rather than the expected hypothalamic activation in the participating women, regions involved in social recognition and attention were activated.

In a recent study, Savic and colleagues (2005) investigated potential differences and similarities in cortical activity of exposure to a suprathreshold amount of androstadienone between heterosexual and homosexual individuals. The intricate connection between the hypothalamus and sexual activity (Oomura et al., 1988) postulates that sexual orientation should be manifested in some way by activation of this region during exposure to androstadienone (Monti-Bloch, Jennings-White, & Berliner, 1998; Savic, 2002). Indeed, although non-schematic overlap was demonstrated, the activation pattern of the participating homosexual men bared more resemblance to the activation pattern of the heterosexual women than the heterosexual men. Analyses indicated that homosexual men differed only from heterosexual men, not from heterosexual women, when they smelled androstadienone with respect to

⁷ Two out of four listed authors in the aforementioned paper is also listed as authors of the latter paper (Gulyas, Keri, O'Sullivan, Decety, & Roland, 2004). However, note that only six subjects were included in the study.

brain activity. It should be noted that the authors also replicated their previous finding in that the hypothalamus was activated in heterosexual women, but not in heterosexual men, when stimulated by androstadienone.

As will be reviewed below, consistent reported behavioral effects are that exposure to androstadienone modulates mood in women over an extended time period rather than producing releaser-like effects. In an effort to explore potential cumulative effects of a sustained exposure to androstadienone, Jacob and colleagues (2001) exposed women to a peri-threshold amount of androstadienone while measuring their cortical glucose utilization by means of PET. The participating women expressed an increased activation in attention and mood regulating regions when contrasted to the control condition. The authors attributed these effects to the pheromonal properties of androstadienone that focused the participant's attention to the task at hand; a visual tracking task used to focus participant's attention during scanning.

Taken together, these studies imply that androstadienone is processed by a subset of brain regions that are not commonly involved in olfactory processing. However, although limited by the use of tracer and stimulus control, only Jacob and colleagues tried to assess potential effects of a subthreshold exposure. The other aforementioned studies exposed their participants to a suprathreshold concentration and chose not to contrast activation of androstadienone to a chemically similar odorant which limits straightforward conclusions about potential pheromonal characteristics. It is conceivable that the reported effects are due to a difference in activation between steroids and common odorants or a unique effect for musky odors as indicated by others (Boyle, Zatorre, Pause, & Jones-Gotman, 2004; Gottfried, Winston, & Dolan, 2005; Kalmus & Seedburgh, 1975; Koelega & Koster, 1974; Le Magnen, 1952).

Although highly suggestive and supported by the modulation of sexual orientation, definitive evidence of pheromonal properties as deemed by brain imaging techniques requires a controlled non-conscious exposure in contrast to a perceptually and chemically similar odorant.

Psychological and psychophysiological responses to androstadienone

The most consistent effect of exposure to androstadienone has been its ability to modulate self-reported mood variables (Bensafi, Brown, Khan, Levenson, & Sobel, 2004; Bensafi, Tsutsui, Khan, Levenson, & Sobel, 2004; Grosser et al., 2000; Jacob, Garcia, Hayreh, & McClintock, 2002; Jacob, Hayreh et al., 2001; Jacob & McClintock, 2000). Jacob and McClintock (2000) published the very first report that exposure to androstadienone could modulate women's self-reported mood. In two consecutive experiments, they demonstrated that androstadienone, masked by a clove odor, changed the participating women's mood. Shortly thereafter, the Monti-Bloch group published the aforementioned report with similar findings (Grosser et al., 2000).

Given the notion that androstadienone might be a human male pheromone, Jacob and colleagues (2001) recently reported interesting findings in support of that idea. Only in the presence of a man did androstadienone exposure induce any measurable effects in the psychophysical responses. The participating women exhibited a decrease in their skin temperature and an increase in their skin conductance, indicating an activation of the sympathetic nervous system. No detectable effects were found when tested by a female experimenter. Thus, although no effects were apparent on mood, it seems like an appropriate context is a necessity, or a catalyst, for androstadienone exposure to induce behavioral effects in women. Two studies from the Sobel group might shed some light over the need for a social context. Bensafi and colleagues (2003) initially reported that women did not experience alteration of mood when exposed to a suprathreshold concentration of androstadienone in an environment without any contextual or other stimulating cues present. However, when the authors in a subsequent experiment induced contextual cues in form of arousing video clips, the participating women expressed an increase in positive mood (Bensafi, Brown et al., 2004).

The discussions regarding the existence of human pheromones have mainly focused on the existence of pheromone that signal, or regulate signals, related to mating or other direct sexual activities. The majority of the behavioral findings up to date have, however, not directly been related to the sexual sphere. Only one androstadienone related finding in the literature can be directly linked to mate choice. Cornwell and colleagues (2004) recently reported a significant correlation between how women rate the odor of androstadienone for pleasantness and their preference for a face with stereotypical masculine traits as a longtime partner. Although the ecological validity of these findings can be brought into question, the finding is interesting in the suggested connection between perceived valence and behavior.

To conclude, several studies have demonstrated relatively coherent results indicating that androstadienone seems to foremost modulate women's mood in a positive manner. This effect seems to be dependent on the contextual situation. However, these findings maybe limited in that only suprathreshold and masked stimuli were used. Moreover, no study has investigated whether the findings are dependent on a conscious awareness of the experimental compound. This raises the question whether the observable effects are mediated by conscious perception of the odor, leading to an influence of subject's responses, which and in turn limits any conclusions about potential pheromonal effects and their mechanisms.

Aims of the thesis

The most robust evidence that humans use social chemosignals as means of communication comes from the demonstration that women's menstrual cycle can be altered by the underarm odor of other women (Russell et al., 1980; Stern & McClintock, 1998). Since these seminal studies, the quest has been to identify potential pheromonal compounds in man. Androstadienone has recently been implicated in human chemical communication by a range of indicative studies. However, as reviewed above, the question of whether the previously demonstrated effects are due to a conscious discrimination between the experimental odorants has not been addressed. Moreover, no effects on specific mood have been reported; specific mood that can be linked to testable corresponding behavior.

The over-reaching aim of this thesis was to explore whether androstadienone functions as a human modulator pheromone in the absence of a conscious awareness of the stimuli. This general question was subdivided into four research questions which were addressed in four separate empirical studies. Below, I will address these specific aims in more details. To avoid redundancy, the specific aims of each paper and experiment will be described in more detail later.

Specific aims

The over-arching aim of this thesis was subdivided into four specific aims that are described below under each sub-header. Briefly, Paper I sought to establish the absolute threshold and sensitivity distribution of androstadienone and whether androstadienone has a detectable level of trigeminal irritants. In Paper II, the question of whether the early processing of androstadienone differed from that of perceptually similar odorants was answered. Based on the results of Paper I, potential modulation of mood by exposure to a subthreshold amount of androstadienone was explored in Paper III. Lastly, Paper IV investigated whether the consistent mood effects reported in Paper III were dependent on the social context and whether the exposure also modulated behavior in correspondence to the mood changes observed.

Conscious awareness and perceptual distribution

The question of conscious awareness should be a central aspect of studies addressing potential effects of a putative pheromone. The well developed human neo-cortex places considerable methodological constraints not necessary in experiments with insects or lower mammals. Human's well developed memory system modulates most stimulus inputs so that our overt response to a signal is confounded by past experiences. Studies have demonstrated that the conscious awareness of a common odor has the capacity to modulate overt behavior (see among others Baron, 1988; Knasko, 1995).

Therefore, to enable conclusions of whether effects are caused by conscious detection of the stimuli or not, subthreshold exposure is of methodological importance.

No studies have established the absolute threshold for androstadienone or explored its other psychophysical characteristics. Therefore, as a framework for further studies, the relevant stimulus properties such as absolute threshold, trigeminal factor, and sensitivity distribution of androstadienone were explored.

Differences in early cortical processing

Cortical activation of androstadienone is known to differ from that of common odors (Jacob, Kinnunen et al., 2001; Savic et al., 2001; Savic et al., 2005). The most consistent effect reported is that the hypothalamus is activated in women when exposed to androstadienone. However, no studies have explored whether androstadienone is processed temporally in a different way than other, perceptually similar, common odors. If androstadienone is a human social chemosignal, it could be postulated that the early cortical processing is different than for perceptual similar odorants. Neuroimaging techniques were therefore used to seek understanding of the early processes of androstadienone processing, contrasted with that of perceptually similar odorants.

Effects on mood and behavior

To date, only non-specific mood effects based on aggregated scales have been demonstrated with respect to androstadienone exposure. Moreover, no studies have assessed, using standard psychophysical testing, whether the reported effects were caused by conscious awareness of the stimulus or not.

By utilizing the results from prior experiments (Paper I), effects of a subthreshold exposure to androstadienone were explored in several experiments. This allowed us to draw conclusions regarding whether androstadienone modulates women's mood also in the absence of a conscious awareness of the stimulus. Moreover, in Paper IV, effects on a corresponding behavior (sustained attention) to the mood effects discovered in previous experiments, together with attraction ratings, were also investigated.

Contextual effects on mood and behavior

Androstadienone has been suggested to be a human modulator pheromone. As such, androstadienone should elicit stronger effects in appropriate contexts. Several examples exist in both the mammalian and insect literature indicating that the context is an important, and sometimes necessary, component for pheromone mediated responses. It can be postulated that among the strongest contextual cues in pheromonal communication is the presence of a potential sender of the pheromonal compound in question.

To explore potential influence of contextual cues for androstadienone to exert effects on mood and behavior, women were exposed to a subthreshold amount of androstadienone with either a man or a women present during the experiment. Effects on mood and sustained attention were assessed.

Empirical studies

To enhance readability, statistical references and detailed accounts of the methods used have been excluded from this brief summary of the empirical studies. The interested reader is referred to the full length articles that appear in the Appendix.

A general note about the methods used in the papers presented below; in all experiments, participants were often giving their responses by the means of visual analogue scales (VAS) without subdivisions. This method was selected due to the ease of administration, the high reliability (Fahndrich & Linden, 1982; Folstein & Luria, 1973), and its known ability to measure also small changes in responses (Monk, 1989). It should further be noted that all participants included in the studies had a functional sense of smell as deemed by pre-screening. All individuals with either total or specific anosmia to the odorants in question were not included in the studies portrayed here.

Paper I – Conscious awareness

Individual Differences in Sensitivity to the Odor of 4, 16-Androstadien-3-one

General aims

An interesting question is whether putative human pheromones exert their effects due to conscious experience of the exposure or not. It has clearly been demonstrated that consciously perceived odorants, not considered as potential pheromones, can modulate behavior (see among others Baron, 1988; Knasko, 1995). An important methodological aspect of studies aiming at exploring potential pheromonal effects of compounds is the conscious discrimination between the experimental and the control stimuli. To explore the psychophysical characteristics and to set the frame for future studies on potential behavioral effects of exposure to androstadienone, three experiments were conducted, investigating different psychophysical aspects of the odorant. In Experiment I, the absolute threshold of androstadienone was determined. Experiment II sought to investigate the sensory distribution of

androstadienone sensitivity in the population. Finally, Experiment III investigated whether androstadienone activated the trigeminal system.

Experiment I

Aim

The aim of Experiment I was to determine the absolute threshold in the population for the two steroids androstadienone and estratetraenol.

Summary of methods

Absolute olfactory sensitivities for androstadienone and estratetraenol, diluted in propylene glycol, were assessed in 42 participants (22 women). Five concentrations (with a 2.5-increase of liquid concentration; androstadienone: 76 - 3000 μM ; estratetraenol: 192 - 7500 μM) and one blank stimulus were presented in separate sessions using the method of constant stimuli with a three-alternative, forced-choice design (Gescheider, 1985). The stimulus range was selected based on the results from a pilot study. Polypropylene squeeze bottles with pop-up spouts were used to present 15ml of each stimulus. After each individual trial, the participants were asked to rate the confidence in their choice on a VAS.

The proportion correct responses were calculated for each participant and concentration. A logarithmic function was fitted to the group data and a 66.7% proportion correct threshold was determined, yielding an absolute threshold value for the group.

Main results

The absolute threshold for androstadienone was 211 μM , expressed as concentration in solution (see Figure 1). An absolute threshold for estratetraenol was not possible to determine since no reliable detection of the highest concentration used in this study was demonstrated by any of the participants. A disproportional number of participants were able to detect the lowest concentration.

Participants' confidence judgments in this experiment were well calibrated with their actual performance. Hence, conscious experience and behavioral discrimination concurred in this task.

Conclusions

The absolute threshold for androstadienone was found to be considerably lower than previously reported by Koelega and Köster (1974). This discrepancy between thresholds is most probably due to the difference in methods employed. As Koelega and Köster themselves pointed out, their method of choice was not suited for determining absolute thresholds.

Estratetraenol in the concentrations used here was not reliably detected by any of the participants. The absolute threshold for estratetraenol therefore, most probably, lies above the highest concentration used in this experiment; 7500 μ M.

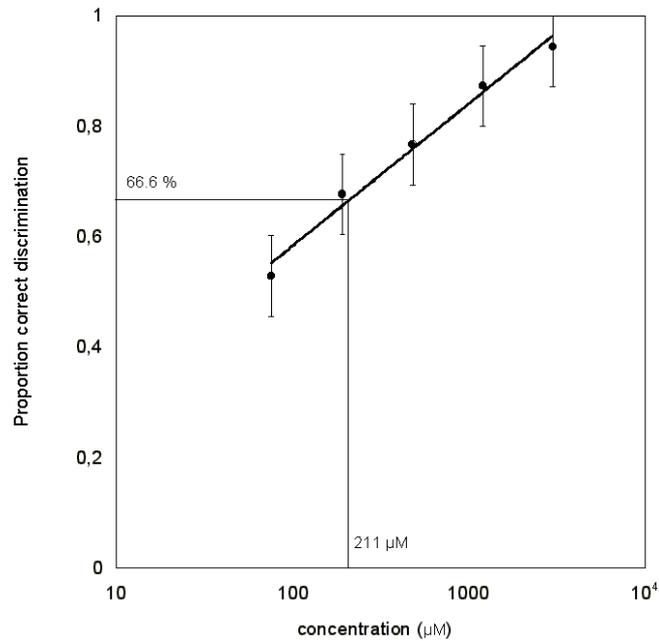


Figure 1. Relationship between proportion correct responses and androstadienone stimulus concentration in micromolar concentrations. Error bars represent *SEM*

Experiment II

Aims

A few participants in Experiment I demonstrated a remarkable capacity to accurately detect androstadienone even in the lowest concentration used. The data distribution suggested a bimodal sensitivity distribution in the population to androstadienone.

The aims of Experiment II were twofold. The first aim was to determine the sensitivity distribution of androstadienone in the population. The second aim was to compare individual sensitivity to androstadienone to that of phenyl ethyl alcohol (PEA). This was done to determine whether individuals with a high sensitivity to androstadienone expressed a high olfactory sensitivity in general.

Summary of methods

Individual thresholds for androstadienone and PEA were determined in 100 participants (58 women). Thresholds for both androstadienone and PEA were determined by the ascending staircase method with a three-alternative, forced-choice procedure (Gescheider, 1985). Sixteen concentrations of each compound were presented in a 2-fold increase of liquid concentration (androstadienone: 0.091 – 3000 μM ; PEA: 16.3 μM – 0.54 M), diluted in propylene glycol. Androstadienone was presented by polypropylene squeeze bottles with pop-up spouts and PEA with the Sniffin' Sticks (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). For both odorants, the test ended after the seventh reversal of the staircase and the mean of the last four reversals was used as an estimate of the individuals' threshold.

A statistical test for bimodality, the DIP intensity test (Giacomelli, Wiener, Kruskal, Pomeranz, & Loud, 1971), was used in order to test the significance of the possible bimodal sensitivity distribution of androstadienone. The DIP intensity test is a measure of the mean spacing between points in the gap divided by the dispersion of the data.

Main results

The sensitivity distribution of androstadienone, but not PEA, was bimodal as evident by the DIP intensity test (see Figures 2A and 2B). The sensitivity distribution for androstadienone consisted of two modes with one mode consisting of highly sensitive individuals. The correlation between individual thresholds for the two compounds was near zero, a seldom seen phenomenon in olfaction. Correlations of individual thresholds between other odorants were generally high (Cain & Gent, 1991). Women expressed a nominally higher sensitivity for androstadienone, but not for PEA, than men.

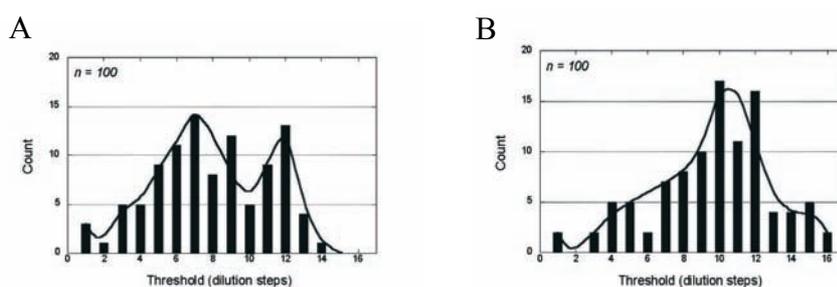


Figure 2. (A) Sensitivity distribution for androstadienone expressed in counts per dilution step. The solid line is a smoothed function. Note the anti-mode at dilution step 10. (B) Sensitivity distribution for PEA expressed in count per dilution step. The solid line is a smoothed function.

One might argue that the bimodal distribution is mediated by the tendency for a difference in sensitivity between men and women. However, as Figure 3 indicates, women are not solely mediating this effect. Rather, the highest scores are produced by men.

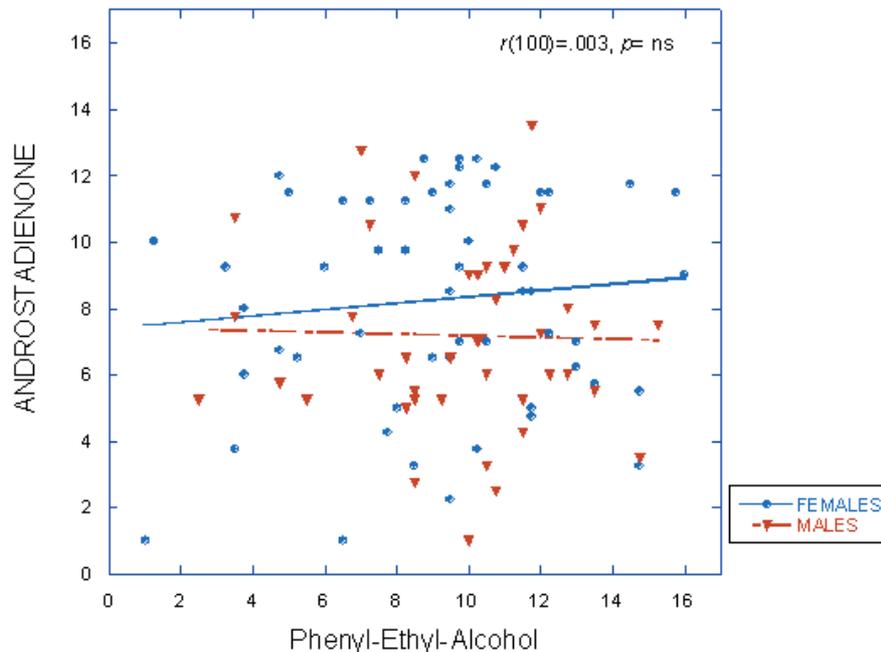


Figure 3. Distribution of individual thresholds for the two odorants divided between the participating men and women. The correlation statistics given in figure represents the whole sample while regression lines are presented for each sex separately. Values on axes represent dilution steps.

Conclusions

The sensitivity distribution for androstadienone was bimodal with one mode consisting of highly sensitive individuals; ‘supersmellers’. This bimodal distribution was not due to a skewness of general sensitivity in the sample as evident by the apparent lack of correlation between odorants.

Experiment III

Aim

The demonstrated bimodal distribution, with one group as more sensitive, has been reported previously for odorants with evident trigeminal components (Lison, Blondheim, & Melmed, 1980; Odeigah, 1994). The possibility therefore arises that the bimodal distribution, also in this case, could be at-

tributed to an interaction between the olfactory and the trigeminal sense rather than the olfactory sense alone.

The aims of Experiment III were to determine whether androstadienone in the highest concentration used in the two previous experiments has detectable trigeminal irritants. Further, potential difference in trigeminal sensitivity between the normal group and the supersmellers was assessed.

Summary of method

Twenty participants (10 women) were recruited from the sample in Experiment 3, 10 who were classified to have a normal threshold for androstadienone and 10 that were labeled as supersmellers. Correct lateralization of intranasal stimuli is believed to be due to trigeminal chemoreception based on the fact that neither feedback, nor training, enhances performance above chance level (Radil & Wysocki, 1998; Wysocki, Cowart, & Radil, 2003). This disparity between the olfactory and trigeminal system makes it possible to use lateralization judgments as a mean to assess the trigeminal impact of an odor (Berg, Hummel, Huang, & Doty, 1998). Ability to correctly make laterality judgments for stimulation of 3000 μ M androstadienone were assessed by means of a hand-held device producing a total of 40 stimulus presentations, 20 to each nostril, in a random order.

Main results and conclusions

The participants were not able to correctly assess which nostril was being stimulated by androstadienone. This implies that androstadienone in the highest concentration used in the two previous experiments did not activate the trigeminal system. Further, there was no difference in performance between the supersmellers and the normal group implying that the previously demonstrated bimodal distribution was not caused by a heightened trigeminal sensitivity in a subset of the sample.

General conclusions

Androstadienone possesses psychophysical characteristics that render the odorant unique. The sensitivity distribution of androstadienone is bimodal with a subpopulation consisting of highly sensitive individuals. This bimodal distribution is not due to trigeminal irritants since the highest concentration used in these studies did not elicit a trigeminal reaction as deemed by a laterality task. Although not significant, the overall results hold at hand that women are nominally more sensitive to the odor of androstadienone than men. The lack of correlation between androstadienone and PEA sensitivity implies a difference in processing. However, whether this is unique for androstadienone or due to other properties (such as its musky odor) is not clear.

An important methodological issue when investigating behavioral responses to putative pheromonal compounds is the notion of subthreshold

exposure of the experimental solution. Experiment I demonstrates that the absolute threshold in the population for the odor of androstadienone is 211 μM . However, not included in the original article (Lundström, Hummel, & Olsson, 2003) but of interest in the light of recent findings is the question of what is the calculated absolute threshold with supersmellers excluded from the analyses. A re-analysis of the data from Experiment I with supersmellers⁸ excluded gives at hand that the absolute threshold increase to 300 μM .

Paper II – Differences in Early Cortical Processing

A Putative Social Chemosignal Elicits Faster Cortical Responses than Perceptually Similar Odorants

Aim

Evolutionarily relevant visual stimulus are processed by a subsystem to the main visual system rendering the processing faster and more automatic (Lang, Davis, & Ohman, 2000; Ohman, Flykt, & Esteves, 2001; Ohman, Lundqvist, & Esteves, 2001). Pheromones could be stipulated to be of high evolutionary importance. Potential human pheromones would therefore be processed differentially by the brain when compared to other compounds. The aim of Paper II was to test the hypothesis that the human brain would process androstadienone faster than other odorants with perceptually matched intensity and hedonic characteristics.

Summary of methods

Chemosensory event-related potentials (ERP) for androstadienone, androstenone, and hydrogen sulfide (H_2S) were recorded in 15 right-handed heterosexual women at the three midline positions; Fz, Cz, and Pz. Androstenone was selected as a control odorant due to its similar perceptual characteristics to androstadienone, the fact that it is an endogenous compound, and the lack of reported pheromonal effects in the literature. H_2S was selected due its wide use in the human olfactory ERP literature, lack of reported trigeminal irritation (Kobal & Hummel, 1998), for being an endogenous compound, and for being typical rated as having an unpleasant odor as do the two androgens. All participants were tested by a 31 year old male experimenter and underwent a series of screening tests prior the experiment including a test of gen-

⁸ For the sake of this analyze, I define supersmellers as participants that were clearly able to discriminate the lowest concentration used in Experiment 1. They all had at least 8 out of 9 correct discrimination responses for the lowest concentration given (76 μM) which represent a binominal probability of .001 and .00005, respectively. Further, they correctly detected all presentations of the other, higher, concentrations.

eral olfactory function, a discrimination test of the two androgens, an otorhinolaryngological examination, and handedness test.

Odorants were delivered by an olfactometer with a total of monorhinal 20 stimulus presentations for each odorant. Stimulations were grouped in blocks of four per odorant with a 40 s inter-stimulus interval between each individual stimulus; each with a 250 ms long stimulus duration. Between stimulations, participants performed a tracking task. Directly after each stimulus, the tracking task was briefly interrupted and the participants had to rate the stimulus intensity on a computerized VAS. At the end of the recordings, each odorant was presented once again and the participants had to rate their hedonic value, individually, on an adapted VAS. Recordings were averaged off-line separately for each recording site and ERP peaks were defined as P1, N1, and P3. Mean base-to-peak amplitudes, peak-to-peak amplitudes, and peak latencies were assessed.

Main results

There were no significant differences in participants' intensity or hedonic ratings between the three odorants indicating that the three odorants were perceived as iso-intense and of a similar hedonic tone.

There were large differences between odorants with respect to their peak latencies. Androstadienone was processed significantly faster than both androstenone and H₂S in the P1 and P3 peaks. There was also a statistical tendency for androstadienone to be processed faster than androstenone and H₂S also in the N1 peak. There were no differences between androstenone and H₂S in any of the peaks in respect to latencies (see Figure 4).

Regarding amplitudes, there were no significant differences in base-to-peak amplitudes nor where there any significant differences in peak-to-peak amplitudes between odorants for any of the peaks.

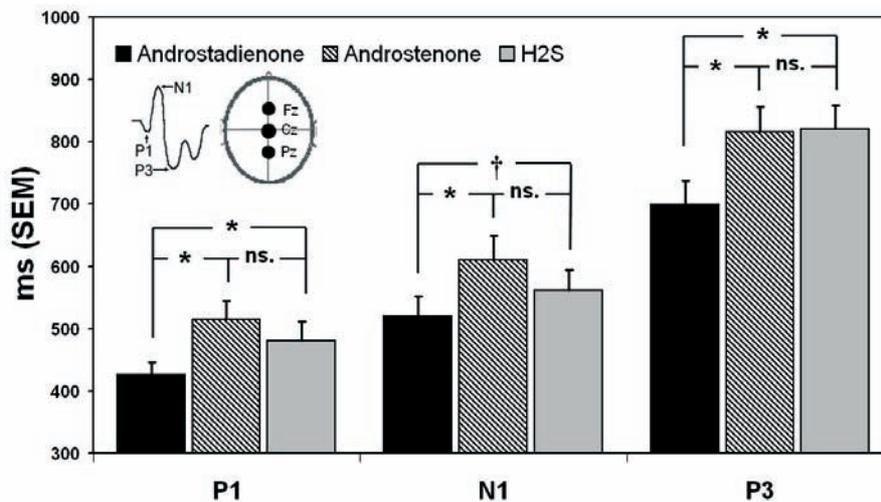


Figure 4. Mean (\pm SEM) latencies of the averaged means of the Fz, Cz, and Pz electrodes separated by ERP components. In the figure, * denotes a significant difference ($p < .05$) and † denotes a statistical tendency ($p < .10$) as deemed by post-hoc tests with Bonferroni corrections. Cartoon indicates ERP components and electrode positions.

General conclusions

Although rated as iso-intense and as having a similar hedonic tone, androstadienone was processed faster by the brain than both androstenone and H₂S. The perceptual similarity among these odorants was supported by the lack of differences in amplitudes between the three odorants.

The large differences between androstadienone and the two control odorant's latencies in the late positive component indicates that androstadienone receives more rapid and more automatic processing as previously demonstrated for visual processing (Kramer, Strayer, & Buckley, 1991).

Savic and colleagues (2001) recently suggested that a separate neuronal pathway could be the mediating mechanism behind the sex-specific results akin to the pathway previously demonstrated in old-world monkeys (Takagi, 1989; Tazawa, Onoda, & Takagi, 1987) and in human visual processing (Morris, Ohman, & Dolan, 1999; Sahraie et al., 1997). This large difference in processing speed between perceptually similar odorants has not previously been reported and supports the hypothesis that androstadienone is processed differently by the cortex than the two other odorants, possibly by a neural subsystem to the main olfactory system.

Paper III – Effects on Mood

Psychological Effects of Subthreshold Exposure to the Putative Human Pheromone 4, 16-androstadien-3-one

General aims

Few, if any, reports on the behavioral effects of potential human pheromones have been replicated. Previous studies on potential effects of androstadienone have all used aggregated mood scales producing larger emotional spectra. None have explored potential differences between specific mood variables. Moreover, no studies have thoroughly controlled for participants' ability to discriminate between the experimental and control stimuli. The general aim of Paper III was to explore potential effects of androstadienone exposure on specific states of mood when conscious discrimination between the experimental and control stimuli was rigorously controlled for. A further aim was to assess the replicability of potential effects.

Experiment I

Aim

The aim of Experiment I was to assess potential effects of androstadienone exposure on the mood of women when the conscious awareness of the stimuli was rigorously controlled for.

Summary of method

Thirty-eight women participated in an experiment that was of a double-blind, between-groups design. They were randomly assigned to either the experimental or the control group. The experimental group was exposed to 250 μ M of androstadienone masked by eugenol and the control group to the mere diluent (mineral oil) with an identical odor mask. All participants were naive to the experiment's main hypotheses and the identity of all stimuli involved. The general design of the experiments is depicted in Figure 5.

To measure potential psychological effects of androstadienone, we administered a test battery consisting of two different psychometric tests and a questionnaire consisting of eight adjectives: *social*, *open*, *relaxed*, *heavy*, *focused*, *sensual*, *energetic*, and *irritated*. The participants gave their response on a VAS. The psychometric tests were the State Trait Anxiety Inventory-State (STAI-S) and the State Trait Anxiety Inventory-Trait (STAI-T). The STAI is a valid measure of anxiety, as STAI-S is measuring situational anxiety and STAI-T a more underlying, or trait, anxiety (Spielberger, Gorsuch, & Lushene, 1970).

In order to assess whether control and test substances were discriminable, a three-alternative forced-choice discrimination test was administered. The

discrimination test consisted of nine trials in which the participants were presented three glass jars in randomized order and were then asked to point out the odd one. In the experimental session, the odd jar contained the same solution as the experimental solution, while the other two were identical to the control solution. In the control session, all three jars contained the control solution.

All participants were tested by the same male experimenter that stayed in their direct vicinity throughout the whole experiment. Three ml of the solution was applied to a cotton swab which was used to apply the solution on to the skin area between the upper lip and the nostrils. The participants were then instructed to rest for 20 minutes while they were entertained by a non arousing movie clip. Mood was assessed both before the discrimination test and directly after the resting period.

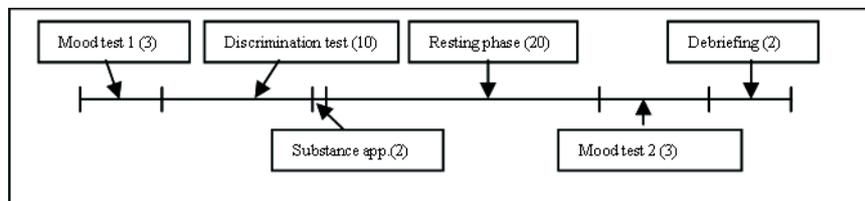


Figure 5. Experimental procedure and elapsed time for different experimental blocks. Numbers in parentheses denote time in minutes.

Main results

Exposure to androstadienone modulated participant's mood in only one of the mood scales. Participants in the experimental group felt more focused⁹ after being exposed to androstadienone than those exposed to the control odor. No other effects were found. Initial analyses indicated that this effect could not be explained by a conscious awareness of the experimental stimulus. Neither the experimental group, nor the control group, differed statistically from the expected chance level which indicates that participants were not able to reliably discriminate between the experimental and control solutions. Two individuals in the experimental group were, however, able to discriminate between the solutions. Additional analyses showed that the mood results did not change when they were removed from the analyses. Their potential perception was clearly not responsible for the group effect.

Conclusions Experiment I

The results of Experiment I demonstrated that women, when exposed to a subthreshold amount of androstadienone, felt more focused. Androstadienone thus seems to activate an attention related mechanism; this observation

⁹ The word *focused* in Swedish (*fokuserad*) relates to a stage of being attentative rather than being focused at a single object or individual.

is consistent with the notion of androstadienone as a modulator pheromone. These effects were present even when conscious awareness was rigorously controlled for.

Experiment II

Aim

The aim of Experiment II was to further investigate mood effects and to replicate the finding in Experiment I indicating that women feel more focused when exposed to androstadienone.

Summary of method

Experiment II included 40 women (three of which were excluded due to missing values) that participated in a double-blind, within-groups designed experiment that was counterbalanced for order of treatment and time of day for the two experimental sessions. All sessions were run by the same experimenter, a 26-year-old male, which differed from Experiment I. Participants were instructed and tested in the same way as in Experiment I with a few exceptions. These were that propylene glycol was used as carrier instead of mineral oil, the women were tested on day 12-14 (peri-ovulation) in their menstrual cycle, and instead of viewing a movie clip, they this time browsed through travel magazines (see Figure 5).

Main results

As in Experiment I, women again felt more focused when exposed to androstadienone in comparison with control. Moreover, as in Experiment I, four individuals were in a side-by-side comparison able to detect a difference between experimental and control condition. However, removal of these four individuals did not alter the mood effects.

Test-retest analyses

A test-retest analysis of the two experiments demonstrated a high correlation between the results obtained in Experiment I with Experiment II. This indicated a high replicability in the effects even though experimenters and carrier solution differed between experiments.

General conclusions

Consistent effects were observed across experiments in that androstadienone exposure enhanced the feeling of being focused in women. Moreover, the finding was not dependent of menstrual phase since effects were identical in both experiments and not dependent on participant's menstrual cycle phase.

As reported in Paper I, a few participants demonstrated such a high sensitivity to the odor of androstadienone that despite the strong odor mask used to hide the minute amounts of androstadienone, they were clearly able to discriminate between the experimental and control stimuli. However, conscious awareness did not mediate the effects reported above. The effects occur also when androstadienone detection is rigorously controlled for.

Paper IV – Contextual effects

Subthreshold Amounts of Social Odorant Affect Mood, But Not Behavior, in Heterosexual Women When Tested By a Male, But Not a Female, Experimenter

Aims

The results from Paper III suggest that androstadienone activates attention related mechanisms in exposed women. Moreover, many reported pheromonal effects in mammals need pairing with some form of ecological valid contextual cue (cf. Izard, 1983; Johnston, 1998). The aims of Study IV were to further investigate whether exposure to a subthreshold amount of androstadienone would modulate actual attention performance as deemed by a task tapping sustained attention. Further, to test whether potential behavioral effects of exposure to androstadienone would require being paired with an ecologically valid contextual cue, two experimenters of opposite sex were employed. Lastly, studies using sweat derived compounds have indicated that they are able to alter viewers' perception of faces (Cornwell et al., 2004). To test whether androstadienone can modulate women's percept of male faces the participating women rated perceived attractiveness of pictures of unknown males.

Summary of methods

Thirty-seven heterosexual women that were naïve to the main hypotheses participated in an experiment with a double-blind, within-groups design, counterbalanced for treatment order. Participants were tested across the menstrual cycle with an even distribution between phases. In the experimental condition, the participating women were stimulated with 250 μ M androstadienone which was diluted in the carrier solution propylene glycol and masked with a strong odor of clove. In the control condition, the participants were only stimulated with the carrier solution and odor mask. Moreover, as in Paper III, conscious awareness of the stimulus was controlled by a psychophysical discrimination test.

To measure if exposure to androstadienone could modulate women's level of sustained attention, a computerized attention task was constructed. The task consisted of adjusting the position of a smaller square inside a constantly moving larger square at all times for twenty minutes with the means of a joystick.

A questionnaire consisting of ten adjectives (*social, open, relaxed, focused, sensual, energetic, happy, heavy, irritated, and down*) was employed to measure alteration of mood. The applicability of the adjectives to their current mood was rated by the participants on a VAS that ranged from 'not at all' to 'extremely'. Participants' responses on the mood scales were then subjected to a hierarchical cluster analysis with squared Euclidian distance. The analyses yielded one cluster with the seven positive directed scales (*social, open, relaxed, focused, sensual, energetic, and happy*), denoted 'positive mood', and another with the three negative directed scales (*heavy, irritated, and down*), denoted 'negative mood'.

Modulation of the autonomic nervous system (ANS) was recoded by measuring finger pulse and skin temperature on their non-dominant hand. To assess effects on general psychophysiological arousal, FP and ST were equally weighted in respect to each variable's direction of effect and combined into a general psychophysiological index.

Participants provided attraction ratings of 20 different pictures of males, viewed from the shoulders up with the gaze facing the camera, at the end of the experiment. Ratings of attractiveness and the latencies of their response were measured.

All participants were tested in two seemingly identical sessions by either a female (age 28) or a male experimenter (age 30) with one day in-between and on the same time of the day to minimize effects caused by potential differences in circadian rhythm. For a general overview of the experimental paradigm (see Figure 6).

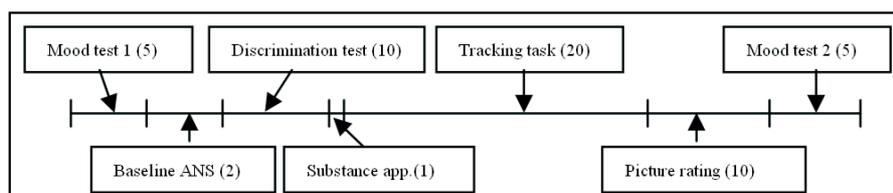


Figure 6. Experimental procedure and elapsed time for different experimental blocks. Numbers in parentheses denote time in minutes.

Main results

The participating women felt more positive and a tendency to feel less negative mood when exposed to androstadienone. Also in this experiment, androstadienone exposure made women feel more focused.

One of the hypotheses was that an experimenter of the opposite sex (i.e. a male) would be a necessity to facilitate effects due to androstadienone exposure. Interaction analyses revealed that this was the case. Only in the presence of a male experimenter did the participating women experience exposure induced effects on mood in that they felt significantly more positive and less negative emotions. When tested by a same-sex experimenter (i.e., a woman) exposure to androstadienone had virtually no effects at all (see Figures 7A and 7B).

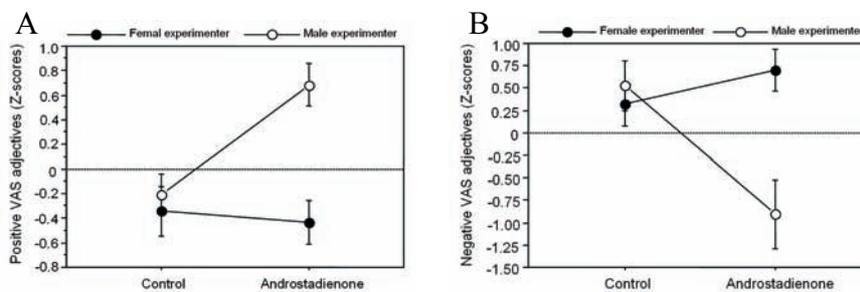


Figure 7. A) Effect of exposure to androstadienone on the positive mood scales expressed as Z scores. B) Effect of exposure to androstadienone on the negative mood scales expressed as Z scores. Filled circles indicate participants tested by a female experimenter and open circles indicate participants tested by a male experimenter. Error bars denote SEM.

Contradictory to our hypothesis, androstadienone did not enhance attention performance. Although the nominal values indicated an enhanced performance during the androstadienone conditions in comparisons with the control, and a similar nominal enhancement during the presence of a male experimenter, no significant effects were demonstrated. Moreover, we were not able to replicate the previously demonstrated effects by others on face perception.

Interestingly, although there was no main effect of exposure on the participating women's general psychophysiological arousal, interaction analyses indicated that the presence of a man increased, and the presence of a women decreased, psychophysical arousal (see Figure 8).

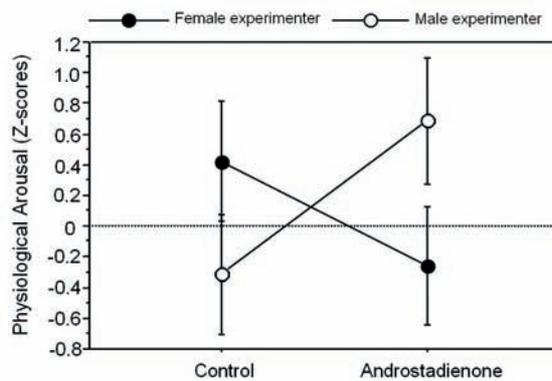


Figure 8. Interaction effect between sex of experimenter and exposure type on the general psychophysiological arousal index expressed as Z scores. Filled circles indicate participants tested by a female experimenter and open circles indicate participants tested by a male experimenter. Error bars denote SEM.

As in the previous experiments, a few participants could consciously detect the minute amounts of androstadienone in the experimental solution when paired with the control stimuli. These two individuals were in this study removed from the analyses altogether to ascertain that all effects were caused without conscious awareness of the presence of androstadienone. The remaining participants could not discriminate between the two experimental solutions as deemed by the discrimination tests.

General conclusions

Women reported an increase in overall positive mood and a decrease in overall negative mood while exposed to androstadienone even when conscious awareness was controlled for. However, changes in mood and general arousal were evident only when there was a man present in the room during testing.

Although for the third time replicated, that exposure to androstadienone induced an increase in self reported activation of the attention system in women, assessed here as increases in the feeling of being focused, no effects on their sustained attention performance or attraction ratings were found.

General Discussion

The general discussion is divided into three major parts. First, each of the four specific aims of the thesis will be discussed and tentative conclusions will be made. Then, a general discussion of human pheromones that ends with a conclusion for the main aim of the thesis. Finally, methodological questions will be discussed.

Conscious awareness and threshold distributions

Of particular interest to Papers III and IV in this thesis was the ability to present stimuli in such a concentration that conscious awareness of the stimuli was prevented. For that, the absolute threshold of androstadienone was determined in Paper I. The threshold was 211 μM for the whole sample and 300 μM when the hypersensitive group, the so-called ‘supersmellers’, described in Paper I (Experiment II) was excluded. The threshold obtained in Experiment I of Paper I differed from the previously reported threshold (Koelega & Koster, 1974). The previous threshold was, however, obtained in a different demographic sample with a method not suitable for determining an absolute threshold. Moreover, the average of repeated threshold testing in each individual was used; all these are variables known to produce disparate olfactory thresholds (see discussion in Dalton, Doolittle, & Breslin, 2002; Koelega & Koster, 1974; Rabin & Cain, 1986). Although a direct comparison of obtained threshold measures between these two studies is not possible, interesting similarities do exist as I will review below.

Are there sex-related sensitivity differences?

The nominal tendency for women to have a lower threshold for androstadienone than men, in Experiment I and II in Paper I, is supported by findings reported by Koelega and Köster (1974). The authors concluded that women are more sensitive to androstadienone than men. Interestingly, this finding seems to be extended to most androgens tested to date (Dorries et al., 1989; Koelega & Koster, 1974; Le Magnen, 1952; Wysocki, Pierce, & Gilbert, 1991), whereas other differences in olfactory capabilities are mostly limited to tasks involving lexical abilities (Larsson, Finkel, & Pedersen, 2000; Oberg, Larsson, & Bäckman, 2002; but see Lundström & Hummel, In

press). It could be hypothesized that the ongoing exposure to androgens that men, in particular, are subject to causes a desensitization over time. This theory finds some support in that the onset of puberty also marks the onset of an increase in both male androgen production and male individuals with a specific anosmia to androstenone (Dorries et al., 1989) and androstadienone (Hummel, Krone, Lundström, & Bartsch, 2005). On the other hand, increased exposure to androstenone in people with a specific anosmia to the compound can induce sensitization. This phenomenon seems to, at least for women, be extended to other odors as well (Dalton et al., 2002). Whether the underlying mechanism is centrally or peripherally mediated is debated (Dalton, 2000; Dalton et al., 2002; Diamond, Dalton, Doolittle, & Breslin, 2005; Mainland et al., 2002; Wang et al., 2004; Yee & Wysocki, 2001, 2002).

To conclude, a sex difference in sensitivity to the odor of androstadienone is plausible. However, the difference is small and has been demonstrated to have weak power.

Why a bimodal sensitivity distribution?

The sensitivity distribution for androstadienone was determined to be bimodal. A few individuals were, as indicated by Experiment I in Paper I, highly sensitive to the odor of androstadienone; this sensitivity that was not mediated by the trigeminal system (Experiment III, Paper I). The biological explanation for this finding is not clear. An interesting question is whether the difference is innate or exposure related. It can be hypothesized that an innate factor would be related to a difference in actively coding receptors. Alternatively, the difference in the amount of exposure separating these two groups can be a likely explanation as well. Future research using a combination of measures investigating receptor activation, genotyping, and psychophysical testing is necessary to solve this larger question of which mechanisms modulate individual differences in olfactory sensitivity.

An interesting finding in Experiment II of Paper I was the lack of correlation between thresholds for PEA and androstadienone. This low correlation between a musky odorant (specific anosmia excluded) and other non-musky odorants has previously been demonstrated (Kalmus & Seedburgh, 1975; Knecht et al., 2003; Koelega & Koster, 1974) whereas correlations between non-musky odors generally are high (Cain & Gent, 1991; Kobal et al., 2001). The notion that there is a general difference in sensitivity related processing between androstadienone and PEA was recently supported. We found that fertile women were more sensitive to androstadienone than PEA, while women using oral contraceptives, a non-fertile hormonal state similar to early pregnancy, were more sensitive to PEA than androstadienone (Lundström, McClintock, & Olsson, *In press*). These results taken together

suggest that androstadienone, compared to other odors, is processed differently by our olfactory system.

Difference in early cortical processing

The odor of androstadienone is primarily processed by brain regions other than those commonly associated with odor processing (Jacob, Kinnunen et al., 2001; Savic et al., 2001; Savic et al., 2005). This finding is congruent with the notion that androstadienone is a human pheromone. However, whether this difference is due to a compound specific effect or other properties, which could be shared with other musky odorants (Boyle et al., 2004; Kalmus & Seedburgh, 1975; Koelega & Koster, 1974; Le Magnen, 1952), has not yet been established. In Paper II, we therefore tested whether the early cortical processing of androstadienone was different than two perceptually similar odorants.

Androstadienone was processed faster than both the structurally dissimilar H₂S and the structurally similar androstenone whereas there were no differences in the intensity of the recorded activity. For the first time, tentative evidence for an odor-specific difference in the early stage of odor processing has been demonstrated. This supports and extends the previously reported findings in several ways as will be reviewed below.

Does the difference in processing suggest odor specificity?

Although odorants are rated as similar in both intensity and hedonic tone, other differences may still exist such as differences in quality (Laing, Eddy, & Best, 1994). Androstadienone and androstenone are both commonly described as similar in quality with a musky and/or urine-like odor whereas H₂S is commonly described as resembling rotten eggs. We found no differences between androstenone and H₂S in any of our measures. However, androstadienone was processed significantly faster than both the two control odorants indicating that the differences demonstrated here are independent of odor quality, intensity or hedonic valence.

Differences in speed of processing between odorants have been hypothesized to be dependent on the disparity in mucosa transduction. In short, this theory postulates that odorants binding at similar receptors are similarly transduced and hence are processed similarly (Laing, Eddy, Francis, & Stephens, 1994). One might argue that little is known about whether androstadienone and androstenone bind at similar receptor sites, however, it has been suggested, and shown, that chemically similar odorants bind at same receptors sites (cf. Schild & Restrepo, 1998). Here, androstadienone was processed more than 100 ms faster than both the chemically similar odorant androstenone and the chemically dissimilar odorant H₂S. Thus,

based on their chemical structures and the large temporal difference, this suggests that the demonstrated difference in speed of processing is not mediated by a disparity in mucosa transduction. By controlling for hedonic valence, perceived intensity, chemical structure, and by using one musky and one non-musky control odorant, we conclude that androstadienone is processed faster than comparative odorants.

Is androstadienone processed by a neuronal subsystem?

Savic and colleagues recently speculated that androstadienone is processed by a neuronal subsystem other than the main olfactory system, akin to the subsystem previously demonstrated for Old world monkeys (Takagi, 1989; Takaki et al., 1992; Tazawa et al., 1987). Takazawa and colleagues (1987) argued that such a subsystem would project directly to the hypothalamus from the olfactory bulb rather than following the path of the main olfactory system. Interestingly, this seems to be supported in that androstadienone primarily activates the hypothalamus of exposed women (Savic et al., 2001; Savic et al., 2005) and in that a pheromonal pathway in mice projects to the medial hypothalamus¹⁰ (Mori et al., 2005). Moreover, as evident in Paper IV, exposure to androstadienone activates the ANS which is primarily regulated by the hypothalamus (Andreassi, 2000). Similar subsystems have interestingly been demonstrated in other sensory modalities for evolutionary relevant stimuli. In vision, a similar separate circuitry has previously been shown to exist using behavioral (Ohman, Flykt et al., 2001; Ohman, Lundqvist et al., 2001; Zihl & von Cramon, 1979), imaging (Morris et al., 1999; Sahraie et al., 1997), and lesion studies (Tomaiuolo, Ptito, Marzi, Paus, & Ptito, 1997). Evolutionarily relevant stimuli are processed by a separate subcortical pathway, rendering a faster and more automatic processing than non-relevant stimuli (Morris et al., 1999; Ohman & Mineka, 2001). If in some sense androstadienone is a human pheromone, its evolutionary relevance should be evident. As for evolutionary relevant visual stimuli, it can therefore be hypothesized that androstadienone is processed by a similar subcortical subsystem of the main olfactory pathway as previously demonstrated in Old world monkeys. However, further studies employing connectivity analyses are needed before final conclusion can be made.

¹⁰ Compare this finding with that of Savic and colleagues (2001) described in detail above.

Effects on mood and behavior

Does androstadienone modulate women's mood?

In Paper III and Paper IV, three consecutive experiments demonstrated that exposure to androstadienone supports attention related mechanisms rather than enhancing mood variables indiscriminably. Women, when exposed to androstadienone, experience a heightened feeling of being focused. The replicability over experiments indicates a robust effect. Moreover, in Paper IV, exposure to androstadienone rendered the participating women to report an increase in positive and a tendency towards a decrease in negative emotions.

To conclude, the collective data has clearly demonstrated that exposure to androstadienone modulates women's mood. For future studies, it should be noted that exposure to androstadienone in the typical experiment prevented mood from deterioration rather than produced an enhancement from baseline.

Does androstadienone modulate ongoing behavior?

A definitive proof that androstadienone is a functional human pheromone would be to demonstrate a direct impact on overt behavior. In Paper IV, we further explored whether the modulation of subjective attention also manifested itself in an enhancement of attention-related performance. However, although the participating women reported an increase in attention, no significant change in performance on the sustained attention task was observed. Whether the lack of significant effect is related to the task at hand or whether it is indicative of an inability of androstadienone to modulate attention-related behavioral responses is not a possible distinction to make. Although Jacob and colleagues (2001) reported that a similar visual tracking task induced increased activation in attention and vision-related cortical regions, we can not conclude from Paper IV that androstadienone has the ability to modulate an ongoing attention related behavior.

Cornwell and colleagues (2004) recently reported that women's hedonic ratings of androstadienone correlated with attractiveness ratings of pictures in a sex-specific manner¹¹. In opposition to this, we could not find any effects of exposure to androstadienone on either attractiveness ratings or their response times (Paper IV). Interestingly, we recently measured whether the response times in a visual search task involving semi-nude pictures of men and women would be modulated by exposure to androstadienone (Lundström, Ohman, & Olsson, 2005). No effects of androstadienone exposure were seen on the participating men's or women's reaction time.

¹¹ Interestingly, this finding was not observed when subjects were exposed to the related substance androstenone; the same odorant that was used in Paper II in this thesis.

Tasks with an underlying sexual nature that uses reaction time as a measure could be argued to be ill fitted to measure potential pheromonal responses in humans. In the light of the presented data, there is, I would argue, no ecological relevance for potential pheromones to enhance the speed of mate choice processes. On the contrary, it could be stipulated that rather than modulating the speed of mate choice in humans, pheromones should modulate the accuracy of the search process and correctness of the choice. The latter two variables could be considered to be of higher ecological importance than speed.

To conclude, no exposure-related effects on any of the behavioral measures: sustained attention task, attraction ratings, and their response times could be found.

Are the reported effects due to a conscious awareness?

A factor often addressed, but seldom controlled for in the literature concerns the notion of conscious discrimination between the putative pheromone in question and the control. Pheromones do not have to be unconsciously presented to fit the traditional definition. In fact, it is well documented in the animal literature that some pheromonal effects are mediated by a detectable odor source (Dorries et al., 1997). However, the functions of the well developed human neo-cortex make dissociations between effects exerted by common odors and those exerted by potential pheromones difficult if conscious awareness occurs. To rule out that participants are able to consciously discriminate between the experimental and control stimulus thus becomes an important methodological issue.

Previously, two different methods have been used in the literature in order to control for perceptual differences between control and test stimuli. These are comparison of retrospective verbal descriptors (Jacob, Garcia et al., 2002; Jacob, Hayreh et al., 2001; Jacob & McClintock, 2000) and comparison of intensity and hedonic differences (Bensafi, Brown et al., 2004; Bensafi et al., 2003; Bensafi, Tsutsui et al., 2004; Gulyas et al., 2004; Savic et al., 2001; Savic et al., 2005). Problems arise with both these methods. Verbal discrimination puts high demands on memory and accuracy of verbal descriptors (White, 1998). Of similar concern is that quality discrimination, even between iso-intense stimuli, can evoke stimulus-related memory effects. Therefore, if the aim of the study is to present stimuli that cannot be readily discriminated by the participants, a discrimination test where participants are asked to make a direct comparison between the experimental and the control stimulus is recommended. In both Paper III and IV, we presented a perithreshold concentration of androstadienone, masked with a strong odor. We further assessed participants' ability to discriminate using a standardized psychophysical discrimination test. This extra step allowed us to conclude

that the effects reported were not due to a conscious awareness of the experimental stimuli.

Contextual effects on mood and behavior

Pairing the stimulus with a valid contextual cue is essential for many of the pheromonal effects demonstrated in both the mammalian and insect literature (cf. Beauchamp, Doty, Moulton, & Mugford, 1979; Beauchamp, Doty, Moulton, & Mugford, 1976; Katz & Shorey, 1979). It has previously been suggested that contextual information is of importance for androstadienone to exert an effect (Bensafi, Brown et al., 2004; Jacob, Hayreh et al., 2001). In Paper IV, we explored whether the demonstrated effects were context dependent. We postulated that the presence of a potential sender of the stimuli would be a valid ecological context. By using experimenters of different sex, we were able to vary the contextual situation. When a same-sex experimenter was present, no effects on mood and psychophysiology were found. However, the presence of a male experimenter significantly modulated the participating women's mood and psychophysiology when paired with androstadienone exposure. No effects were found on the attention performance.

The possible conclusions that can be drawn from this study are somewhat limited in that only one experimenter of each sex was used. Differences could be attributed to a difference in personality or physical appearance rather than their sex alone. However, Jacob and colleagues (2001) have previously demonstrated that an experimenter of opposite sex affects women's psychophysiology when stimulated with androstadienone. Experiments with systematic variations of ecologically valid contextual cues are needed to finally reveal the importance of appropriate contexts for androstadienone related effects to take place.

To conclude, exposure to non-detectable amounts of androstadienone was able to modulate the participating women's mood and psychophysiology, but only in the presence of a male experimenter; this pattern of results corresponds well with the definition of a modulator pheromone.

The existence of human pheromones

The general aim of this thesis was to investigate whether the endogenous steroid androstadienone is a human modulator pheromone. It was demonstrated that the early processing of androstadienone is vastly different from that of two perceptually similar odorants of which one was chemically similar. Moreover, a subthreshold amount of androstadienone modulated women's mood, in particular in that they felt more focused; this effect was replicated in three consecutive experiments. These mood effects, as well as

the modulation of women psychophysiological arousal, were only observed when paired with a relevant contextual cue in the form of the presence of an individual of the opposite sex. However, no effects were found on a task tapping an overt behavior potentially related to the observed mood effects. In the light of these results, one could ask is androstadienone a human modulator pheromone or not? Before this question is further addressed, let us revisit an ongoing debate in the literature.

Re-defining the definition of pheromone

The debate whether human pheromones exist or not has been raging since the first notion of human pheromones. The first definition of pheromones was originally used for insects but has since also been used also for higher order animals. The original author broadened the use of pheromones in a subsequent article (Karlson & Butenandt, 1959) in which he states:

“According to our definition, pheromones function as chemical messenger among individuals. /.../ the mechanism of olfactory acting pheromones is clearly understood. They are highly active stimulants which affect the central nervous system via the chemical sense.”

The spread in the use of the label pheromone is somewhat problematic. The mammalian brain is more evolved than the common insects and as such, simple behavior programs are not as easily triggered by external stimuli only. The question is what then constitutes the difference between effects elicited by common odors and pheromones? It has been proposed that five additional requirements should be amended to the definition of a pheromone (Beauchamp et al., 1976). These are *a*) species specificity, *b*) elicit a well defined behavior or endocrine function, *c*) be dependent on a large degree of genetic programming, *d*) consist of one or a few compounds, and *e*) produce a unique behavioral or endocrine response not demonstrated by other similar stimuli. These addendums were suggested to enable distinctions between olfactory and pheromonal responses. However, these additional requirements for mammalian pheromones have been criticized in that, if applied to insects, many compounds already labeled as pheromones have to be reconsidered. Recent findings have indicated that pheromones among insects are often dependent on contextual cues and sometimes enhance rather than release a unique response, consist of a complex mixture, elicit behavioral responses across species, and require paired association (i.e. learning).

Two main problems arise when overly strict definition criteria are employed. The first problem is of a more theoretical nature in that most chemical signals defined as pheromones to date will be indeterminate chemical signals that elicit responses not fit to be defined as olfactory. An olfactory component has by definition an odor, hence its name. However, several of

these aforementioned compounds elicit their effects also in the absence of an olfactory percept. The second is more practical in nature. By defining a phenomenon with a specific and detailed set of criteria, new and novel findings might not fit into these strict criteria which unable the findings to be put in its right biological context. Definitions which are too strict will create the need for new, even more specific, definitions; potentially leading to too specific definitions appertain to only a single compound. Thus, although it might strictly speaking be impossible to keep a strict definition of a behavioral term, such as pheromones, constant over all phyla, the use of a unified term might be an end in itself.

A new definition of human pheromones

Although no definitive and undisputed proof of human pheromones has been reported, several highly suggestive studies do exist. In the light of the collective evidence in the literature, few, if any, would argue that humans do not use social chemosignals in any form, in any situation. This renders the heated debate on the existence of human pheromones, although important in itself, more of a semantic character. However, what should the demonstrated effects be termed if not pheromonal?

Several suggestions have been put forth such as semiochemicals, ecto-hormones, vomeropherins, to mention only a few. I argue that the use of the term “pheromone” is still appropriate. The word and its definition (although not agreed upon in detail) are well known among scientist and the layman alike. Moreover, the word has an attraction in itself that promotes the field in a way that no other word can do. Instead of inventing yet another specific term for human pheromones, I argue that a new definition should be applied. This will allow a continuous use of the term pheromones. When referred to effects in mammals, I suggest this new definition of a pheromone should be used.

Pheromones are single chemicals or a well defined mixture of chemicals capable of acting in ecologically relevant amounts. They are isolated in, and emitted by, an individual of the same species as the receiver. They serve a biological function and elicit a well defined neuroendocrine or psychological response.

One might argue that the use of separate definitions of pheromones for different species renders the term pheromone useless. However, only the notion of “a psychological response” is incongruent with previously demonstrated pheromonal effects in insects and mammals alike. I argue that the human cortex might have evolved beyond the point where simple external stimuli are capable of mediating automatic behavioral responses but not beyond the point where the same stimuli might be able to steer a behavior in a certain direction by modulation of an ongoing psychological process. The inclusion

of “definitive behaviour” in any definition of a human pheromone might thus exclude the possibility of its existence if defined as a change of overt behavior.

Although not included in the new definition of mammalian pheromones suggested above, the notion of conscious awareness is a question of great methodological importance. I argue that in order to separate an effect created by a cognitive influence of an odor stimuli from a true pheromonal response in humans; the experimental stimuli should be presented below the concentration that is consciously detectable or be thoroughly masked.

By using the definition suggested above, investigating whether compounds are potential human pheromones will be more straightforward and the difference between consciously mediated and automatic processes will be better understood.

Is androstadienone a human modulator pheromone?

According to the definition, modulator pheromones should elicit stereotypical responses within a given context or situational meaning. We have here demonstrated that exposure to a non-detectable amount of androstadienone induces heightened attention in the participating women in that they feel more focused over time. This effect is stable between experiments and is dependent on the social context. Moreover, the large difference in processing speed of androstadienone, in comparison to other perceptually similar odorants, supports the notion that attention mechanisms are affected. In Paper II, the greatest difference between androstadienone and the two other odorants was demonstrated for the P3 latency. Interestingly, studies have demonstrated that latencies of the late component are reduced when subjects perform automatic processing of stimuli (Hoffman, Simons, & Houck, 1983; Kramer, Schneider, Fisk, & Donchin, 1986; Kramer et al., 1991). Consequently, it has been suggested that this phenomenon reflects an automatic attention response (Kok, 1997). This large difference in processing speed between androstadienone and the two control odorants, as reflected in response latencies for the late positive component observed here, may indicate that androstadienone receives more rapid and more automatic processing. Recent imaging data support this notion in that androstadienone, when compared to a common odor, induced an increased activity in areas previously known to code for sustained attention (Lundström, Gerber et al., 2005). In my view, it is thus conceivable that androstadienone may act via modulation of attention-related networks. If so, androstadienone would act as an enhancer of attention to relevant stimuli for the individual.

A non-detectable amount of androstadienone has reliably been demonstrated to elicit a well defined psychological response in that women feel more focused. Moreover, this effect was dependent on the contextual situation. By utilizing the above proposed definition of pheromones, androstadie-

none meets the definition's requirements. However, one might ask what the biological function of this demonstrated response is.

It may be reasonable to postulate that potential human pheromones act through an interaction with basic physiological and mood processes. As demonstrated in this thesis and by others, exposure to androstadienone modulates the ANS (Bensafi, Brown et al., 2004; Bensafi et al., 2003) and alters basic mood processes in women (Jacob, Hayreh et al., 2001; Jacob & McClintock, 2000). This may lead to a more subtle change in higher cognitive processes, such as attention, which in turn might act to guide our behavior in certain contexts. The presence of a man in the immediate surrounding may thus elicit an activation of attention related systems, i.e. the basic biological function is not to sexually attract women to the man emitting the signal. Rather, the function may be to facilitate the evaluation process that others have postulated as driven by genetic compatibility factors (Jacob, McClintock et al., 2002; Penton-Voak et al., 2001; Perrett et al., 1998; Rikowski & Grammer, 1999; Scheib, Gangestad, & Thornhill, 1999; Wedekind & Furi, 1997; Wedekind et al., 1995).

To conclude, androstadienone seems to elicit effects very much similar, if not identical, to effects expected from a human modulator pheromone. In light of these findings and with the use of the new definition, I argue that androstadienone is a human modulator pheromone.

Methodological questions

Why investigate potential effects in women only?

I have in this thesis decided to focus on what potential effects androstadienone exerts on mood and behavior in women. Several reasons lie behind this decision. As reviewed above, the most frequent and strongest effects attributed to androstadienone exposure have been documented in women. Studies investigating mood effects in both men and women generally report no (Jacob, Hayreh et al., 2001) or a differential effect for the male participants (Bensafi, Tsutsui et al., 2004; Jacob & McClintock, 2000). However, Bensafi and colleagues (2004) do report sex-independent mood effects to arousing stimuli. Similar findings have been observed for both ANS responses and cortical activity (Bensafi, Brown et al., 2004; Bensafi et al., 2003; Bensafi, Tsutsui et al., 2004; Jacob, Hayreh et al., 2001; Savic et al., 2001; Savic et al., 2005). Based on this information, no clear conclusions as to whether androstadienone affects primarily women or men can be made. However, the most consistent effects reported in the literature are that androstadienone exposure in women induces positive mood and activates their sympathetic nervous system.

In Darwin's (1874) introduction to the book on sexual selection "The Descent of Man and Selection in Relation to Sex", he makes the statement "*It is his show, but it is her choice*". Indeed, in most animals, from fruit flies to elephants, females pick the male with which they will mate. Interestingly, as reported above, it seems like that the HLA driven preferences of body odor are only evident in women (Sandro Carvalho Santos et al., 2005). Moreover, although possibly due to an uneven distribution of attention, most reported biological manifestations of potential pheromonal effects in humans have been attributed to women (cf. McClintock, 2003).

Lastly, androstadienone is found almost exclusively in male plasma and excretions (Brooksbank, Cunningham, & Wilson, 1969; Brooksbank, Wilson, & Gustafsson, 1972; Brooksbank, Wilson, & MacSweeney, 1972; Nixon et al., 1988). In the rare occasions when androstadienone is detected in women, other androgen irregularities occur in their excretions (Brooksbank, personal communication). Although it is conceivable that androstadienone could serve as a potential information mediator between men, the likelihood is less than its claimed function as a between sexes signal. The existence of intra-male pheromones has been demonstrated among rodents in that an olfactory cue mediates aggression (Mucignat-Caretta, Cavaggioni, & Caretta, 2004). However, evidence for similar function in other species is scarce.

Therefore, to enable maximization of power in the study designs and to adhere to the logic portrayed above, we find it defensible to have directed our initial efforts to investigate potential effects of androstadienone in women only.

How were the androstadienone concentrations selected?

Two different concentrations have been used in the behavioral studies of this thesis (Papers II, III, and IV). The high concentration used in Paper II was mainly selected due to the fact that odors need to be presented in a suprathreshold concentration in order for recordable ERPs to appear. Moreover, a pilot study indicated that the selected concentration was iso-intense to the two control odorants used. The concentration used in Papers III and IV was partly selected based on previous studies thus making direct comparisons possible. More importantly, Paper I demonstrated that the general threshold was 300 μM after excluding the supersmellers. By using a concentration of 250 μM that was masked with a strong odor of clove, we could present indiscriminable experimental and control solutions.

One might argue that the concentrations used in studies on potential pheromonal effects of androstadienone up to date (ranging from 250 μM to crystalline form) have been too high to be ecologically valid concentrations. This is a most interesting question. Karlson and Lüscher (1959) write in their original article where they coin and define the term pheromones that "The principle of minute amounts holds." Indeed, they were later proven correct in

that mammalian pheromone receptors have been demonstrated as being among the most sensitive in the neuronal repertoire. The detection threshold for pheromones in some species is as low as 10^{-11} M. Interestingly, these neurons do not seem to exhibit a dose-dependent response (Leinders-Zufall et al., 2000).

Only one study has investigated potential dose-dependent effects. Bensafi and colleagues (2004) investigated effects on mood and psychophysiology of two concentrations; 250 μ M and 6250 μ M. Both mood and psychophysiology were significantly affected by the higher concentration whereas only minor effects were observed for the lower. This contradicts previous results presented by others using the lower concentration (Jacob, Garcia et al., 2002; Jacob, Hayreh et al., 2001; Jacob & McClintock, 2000; Lundström, Gonçalves, Esteves, & Olsson, 2003) but raises important questions. Is it a possibility that some of the demonstrated effects could have been strictly pharmacological in nature? Indeed, the naturally occurring levels are far below the level of the concentration used to date. However, the stimulus presentation method used in Papers III and IV has been demonstrated to deliver amounts of the actual compound, i.e. which is retained in the fluid placed above the upper lip, near the naturally occurring levels (Jacob & McClintock, 2000).

In an initial pilot experiment from our group using concentrations near natural occurring levels of androstadienone (< 1 μ M), exposure only elicited minor effects. Unfortunately, no attention related variables were measured (Lundström, Olsson, & Larsson, 2000). Although, concentrations of the actual compound presented in Papers III and IV seems to be very close to natural occurring levels, as verified by Jacob and McClintock (2000), it is my recommendation that future studies should investigate whether the results presented above are replicable with a stimulus concentration close to concentrations naturally emitted by individuals.

Concluding remarks

The chemoreceptive capacity of living organism is hypothesized to have developed in the earliest organism on earth since chemoreception allowed the organism to respond to substances without necessarily internalizing them (Hildebrand, 1995; Stoddart, 1990). Most, not to say all species that have been thoroughly examined have exhibited pheromonal communication. Indeed, the pheromonal system in most species is well developed and fine-tuned to detect even very small concentrations of potential pheromones in their surrounding.

We have demonstrated that exposure to a non-detectable amount of androstadienone induces heightened attention in the participating women in that they feel more focused over time. This effect is stable between experi-

ments and is dependent on the social context. Moreover, the sensory distribution of olfactory sensitivity for androstadienone may be unique among odors in its bimodal distribution with one highly sensitive group that is independent of trigeminal sensitivity.

No effects on overt behavior were demonstrated which suggests that androstadienone cannot yet be classified as a pheromone according to the classical definition coined by Karlson and Lüscher (1959). However, the effects elicited by androstadienone are unique among odors. If we follow the original definition, which was defined to classify certain insect behaviors, these effects will be left without a conceptual classification.

I argue that the term 'pheromone' need to be re-defined in accordance with the definition suggested above. Given this new definition, androstadienone should be viewed as a human pheromone. In the light of what has been presented above, I suggest that potential human pheromones act through an interaction with basic physiological and psychological processes. This leads to a more subtle change of higher cognitive processes, such as attention or social cognition, which in turn might act to guide our behavior in certain social context.

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