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# Sniffing a human sex-steroid derived compound affects mood and autonomic arousal in a dose-dependent manner

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**KEYWORDS**
Olfaction; Mood; Autonomic nervous system; Dose-response; Androstadienone; Pheromones

**Summary** The effects of sniffing different concentrations of the human sex-steroid derived compound 4,16-androstadien-3-one (AND) on autonomic nervous system function and mood were measured in 60 subjects. The effects were sex-specific and concentration-dependent. Only high concentrations of AND (0.00625 M) increased positive mood ($p < 0.03$) and decreased negative mood ($p < 0.05$) in women compared to men, and had sympathetic-like effects in women ($p < 0.003$), and parasympathetic-like effects in men ($p < 0.05$). These findings further implicate AND in chemical communication between humans, but pose questions as to the path by which AND is transduced, whether through chemical sensing or transdermal diffusion.


## 1. Introduction

Chemical communication between conspecifics has mostly been documented in insects (Christensen and Hildebrand, 2002; Hansson, 2002) and non-human mammals (Aujard, 1997; Beckman, 2002; Biasi et al., 2001; McClintock, 1998). Sex-specific effects on autonomic nervous system and mood that were induced by sex-steroid derived compounds such as 4,16-androstadien-3-one (AND) have been considered as evidence for similar chemical communication in humans (Bensafi et al., 2003; Grosser et al., 2000; Jacob and McClintock, 2000; Jacob et al., 2001a,b, 2002). AND is the most prevalent androstene in human male secretions (Nixon et al., 1988). The effects of AND vary across studies. In one study, highly diluted AND (0.00025 M) had sympathetic-like effects (decreased skin temperature and increased skin conductance) and maintained positive mood in women (Jacob et al., 2001a). In contrast, in a different study, and at a different molar concentration AND (0.0022 M) was reported to have parasympathetic-like effects (decreases in respiratory and cardiac frequency as well as increased body temperature) and decreased negative feelings in women (Grosser et al., 2000). When tested at a higher concentration, AND had sympathetic-like

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effects in women and parasympathetic-like effects in men (Bensafi et al., 2003). The time course of these effects varied, from 6 min (Jacob and McClintock, 2000), to 30 min (Grosser et al., 2000) and 40 min (Bensafi et al., 2003) to more than 2 h after exposure (Jacob and McClintock, 2000).

The inconsistency in the above reports may reflect various methodological differences such as compound dilution. Dose-dependent effects on autonomic responses and mood are well documented in response to drugs (Greenwald and Stitzer, 2000; Smith et al., 2001), hormones (Buchanan et al., 2001; Fernandez-Guasti and Picazo, 1992) and even tea (caffeine) (Quinlan et al., 2000). To address the possibility that AND effects on autonomic nervous system responses and mood are dose-dependent, we set out to examine the autonomic and mood responses to AND at different concentrations.

## 2. Material and methods

### 2.1. Subjects

Sixty University of California Berkeley undergraduate students (30 women, mean age $20.7 \pm 4.79$; 30 men, mean age $20.2 \pm 3.29$) of mixed ethnic backgrounds participated in this experiment. Exclusion criteria included history of head or nasal passage trauma, history of neurological disease, history of repeated or current sinus infection, chronic use of medication including oral contraceptives, and alcohol, drug, or tobacco abuse. All subjects described themselves as heterosexual. Women's olfactory acuity may vary across the menstrual cycle (Doty et al., 1981; Mair et al., 1978; Pause et al., 1996). We aimed to minimize the variance in this respect by having all women participants begin testing at around the 14th day of their menstrual cycle, counting forward from the first day of menstruation as day 1 to determine the appropriate experimental start date. We acknowledge that this verbal report by subjects is an inaccurate assessment of the menstrual phase in women, but consider it helpful towards minimizing experimental variance.

### 2.2. Compounds

AND was obtained from Steraloids Inc (Newport, RI, USA). For the high concentration (AND-high), 50 mg of AND were dissolved in 30 ml of mineral oil (0.00625 M). For the low concentration (AND-low), 2 mg of AND was dissolved in 30 ml of mineral oil (0.00025 M). Thirty milliliter of mineral oil served as a control condition (Control). All three solutions were put into identical 60 ml opaque jars (4.3 cm in diameter at the opening; 7.5 cm high).

### 2.3. Autonomic nervous system parameters

In previous studies, sex-steroid derived compounds induced autonomic nervous responses related to changes in skin conductance, heart rate, respiratory rate and skin temperature (Bensafi et al., 2003; Grosser et al., 2000; Jacob et al., 2001a). Here, effects on autonomic nervous system function were measured using the following seven parameters that were simultaneously and continuously recorded and displayed during the experiment: skin conductance response (SCR), electrocardiogram (ECG), finger pulse (FP), ear pulse (EP), abdominal respiration (AR), thoracic respiration (TR) and skin temperature (ST). All parameters were sampled and recorded at 1 KHz. Data were converted and amplified via a 16-channel amplifier (PowerLab 16SP, ADInstruments, NSW, Australia), and displayed, stored, reduced, and analyzed with the Chart 4.1.1 software package (ADInstruments, NSW, Australia).

SCR was obtained through two bipolar finger Ag/AgCl electrodes (surface: 1 $cm^2$), placed on the second phalanx of the index and the third digit of the non-dominant hand, attached with Velcro® strap. SCR was measured by applying a 0.5 $\mu A/cm^2$ AC current. The SCR amplifier used was fully isolated with low voltage, 75 Hz ($\sim$40 mV) AC excitation. The derived variables were: (i) during compound exposure, SCR mean (expressed in microsiemens), and (ii) during the ensuing 40 min, the non-specific skin conductance response (NS-SCR), expressed in number of events per minute. NS-SCR has been described as the appropriate SCR measure for continuous non-event-dependent SCR (Dawson et al., 2000). The threshold for an event was a 0.5% deflection from the tracked mean that yielded an average of 3.80 (SD = 5.80) NS-SCR events per minute throughout this experiment.

ECG was obtained through three circular Ag/AgCl conductive adhesive electrodes (0.9 cm diameter). The skin surface was cleaned with alcohol before electrode placement. Electrodes were placed on both the left and the right sides of the abdomen (just under the thoracic cage), and a ground electrode was placed on the left leg. The data were reduced to ECG rate expressed in beats per minute (BPM).

FP and EP were recorded with IR plethysmographs (size: $15 \times 15 \times 6.3$ mm) placed on the fifth finger of the non-dominant hand (FP), and the ear on the side of the non-dominant hand

(EP). These devices used an infrared photoelectric sensor to detect changes in tissue blood volume. They were attached with either a Velcro® strap (for finger), or a clip (for ear). The data were reduced to pulse rate in BPM.

Changes in thoracic (TR) and abdominal (AR) circumference due to respiration were measured using two respiratory belt transducers (30 cm rest length, 10 cm maximum elongation, 4.5 cm in width). They contained a piezo-electric device that responded linearly to changes in length (sensitivity: $4.5 \pm 1$ mV/mm). The data were reduced to abdominal and thoracic respiration rates.

Skin surface temperature (ST) was measured using a small ceramic-encapsulated metal-oxide semiconductor (9.5 mm in length, 2 mm in diameter). The thermistor, designed to operate from 0 to 50 °C was placed directly below the axilla. The data were reduced to skin temperature mean.

## 2.4. Mood ratings

Effects on mood were measured using a 16-item test. Subjects rated how strongly they were experiencing each of 16 different moods on a 9-point scale with 1 corresponding to "not at all" and 9 corresponding to "very strongly". This mood test was devised to tap into mood rather than more transient emotional feelings (Ekman et al., 1980; Levenson et al., 1990). It is well validated and consists of the following variables: afraid, amused, angry, annoyed, anxious, bored, calm, confident, content, contemptuous, disgusted, embarrassed, happy, interested, sad, and stressed. "Sexually aroused" was also added to this test and used as a descriptor.

## 2.5. Procedure

A between-subjects design (Fig. 1) was used such that each subject underwent testing with one of the three compounds (Control, AND-low or AND-high). Participants were randomly assigned to each sub-group.

All testing was performed in a temperature and humidity controlled, stainless steel coated, $11 \times 8$ foot room equipped with HEPA and carbon filtration. This room was designed specifically for olfactory experiments and prevents odor contamination across conditions. Subjects were left alone in the room during the experiment, and activity in the room was continuously monitored from the adjacent control room via a one-way mirror and video monitor. A same-sex experimenter completed all interactions with participants except compound presentation, which was performed by an opposite sex experimenter. This experimenter-to-subject relationship was consistently maintained following the suggestion in Jacob et al. (Jacob et al., 2001a) of increased response under these conditions. Presentation of the mood test, video clips, compound sampling instructions, and recording of autonomic nervous system data, were all time-locked through one central computer.

After completing a demographics questionnaire and providing written informed consent, subjects were taken into the testing room and seated in front of a computer monitor. A keypad was positioned in front of them and they were instructed to answer the questions that would appear on the monitor after the experimenter had left the room. At this point the first baseline mood test was administered via the monitor. Upon completion of the baseline test, the experimenter re-entered the room and fitted the autonomic nervous system recording equipment to the subject. Once autonomic nervous system measures stabilized, recording was then initiated to obtain a 5-min psychophysiological baseline. During this time, participants watched a video of the ocean that is commonly employed for its non-arousing contents (Piferi et al., 2000). This baseline recording was followed by the second administration of the mood test. Next, an opposite-sex experimenter entered the room and held the appropriate experimental jar under the participant's nose for

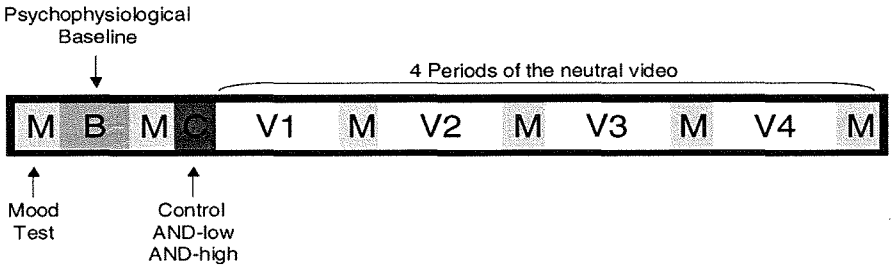


**Fig. 1.** Experimental design. Each subject was tested with one of the three compounds (Control, AND-low and AND-high). M corresponds to mood test, B to baseline, C to compound presentation, and V1 through V4 to the ensuing four 10-min epochs of recording.

each of six sniffs that were timed and cued by computer-generated digitized voice instructions. The digitized voice prompted the subject to sniff at a tone following a countdown (e.g., "three, two, one, sniff"). After each sniff, subjects rated compound intensity, pleasantness and familiarity on a 1–9 point scale presented on the monitor. There was no verbal interaction between experimenters and subjects during compound presentation. The interval between each trial was 30 s. The experimenter then left the room and participants watched a nature video. In order (i) to normalize the environment and rid it of physiologically and psychologically arousing events other than compound presentation, and (ii) to test the effects of AND over time, the nature video was chosen and edited for emotional neutrality and divided into four consecutive 10-min segments (V1 through V4). Subjects had to answer the mood scale again in between each segment. After completion of the last mood scale, the experimenter entered the room and disconnected all autonomic nervous system recording devices. The total experiment lasted about 90 min (from subject arrival at the lab to subject departure).

## 2.6. Data reduction and analysis

Autonomic nervous system data during compound exposure were analyzed in an event-related design in which a baseline of 15 s preceding compound presentation was subtracting from the 15 s period following compound exposure. Here AR and TR were not analyzed given that participants were asked to sniff the content of the jar, thus inducing artifacts in these two measures. Autonomic nervous system data during the ensuing 40-min were expressed as a change score for each period of interest by subtracting the corresponding baseline value (BAS in Fig. 1) from that period (V1, V2, V3 and V4 in Fig. 1). In order to compare between subjects, all autonomic nervous system data were normalized by subject using their maximum response, and then averaged across subjects for each sub-group.

Mood data were also expressed as change scores for each period of interest by subtracting the baseline value from that period (after V1, V2, V3 and V4). In order to reduce the number of comparisons and to provide a clear picture of the mood effects of the Control, AND-low and AND-high on men and women, the 16 items of the Ekman's scale were entered into a Principal Component Analysis (PCA, with Varimax rotation) and a hierarchical cluster analysis (Pearson distance). The resulting groups were then used in the analysis. Because it was not in the original Ekman inventory, "sexual arousal" was analyzed separately. The PCA revealed primary components "one" and "two" that contrasted three groups of descriptors (Fig. 2a).

An hierarchical ascending cluster analysis (Pearson distance) performed on the 16 descriptors of Ekman's scale further confirmed the existence of three main clusters, corresponding respectively to three groups that we labeled "positive mood" (calm, content, confident, happy, interested and amused), "high arousal negative mood" (contemptuous, embarrassed, afraid, disgusted, angry, anxious, stressed), and "low arousal negative mood" (sad, annoyed and bored) (Fig.2b).

In order to test for sex differences following exposure to each compound (Control, AND-low, and AND-high) during the neutral video (V1 to V4), ANOVAs were performed for each autonomic nervous system measure (NS-SCR, ST, ECG, EP, FP, TR

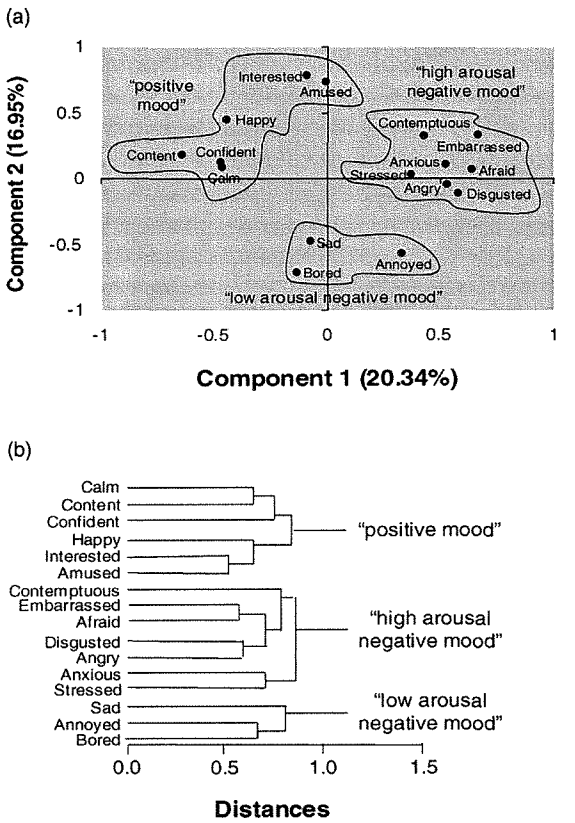


**Fig. 2.** (a) Principal Component Analysis (PCA) performed on the 16 mood descriptors. Components 1 (explaining 20.34% of the total variance) and 2 (explaining 16.95% of the total variance) opposed a group of positive moods to two different groups of negative moods; (b) the hierarchical ascending clustering (Pearson distance) confirmed the existence of three main clusters that we labeled "positive mood", "high arousal negative mood", and "low arousal negative mood".

and AR) and each mood category (''positive mood'', ''high arousal negative mood'', ''low arousal negative mood'' and ''sexual arousal'') including sex (men and women) as a between factor, and time (V1, V2, V3 and V4) as a within factor, separately for the Control, AND-low and AND-high.

## 3. Results

### 3.1. During compound presentation

#### 3.1.1. Compound ratings

To ask whether the compounds differed significantly in perceived intensity, pleasantness, and familiarity during compound presentation, each estimate was entered into an individual ANOVA with sex and compounds as between factors. No sex effect or sex-by-compounds interactions were observed for intensity estimations.

A significant effect of compound was observed for intensity ratings ($F[2, 54] = 7.219$, $p < 0.002$), reflecting that AND-high ($4.25 \pm 1.49$) was rated as more intense than AND-low ($2.92 \pm 1.14$; $t(38) = 3.158$, $p < 0.004$) and the Control ($2.82 \pm 1.25$; $t(38) = 3.276$, $p < 0.003$), but no differences were observed between AND-low and the Control ($t(38) = 0.265$, NS) (Fig. 3). No significant sex and compound effects, or sex-by-compounds interactions were evident for pleasantness and familiarity ratings ($p > 0.05$ in all cases).

#### 3.1.2. Effects on autonomic nervous system function

To ask whether the compounds differently affected autonomic nervous system measures in men and women, each parameter was entered into a separate ANOVA with sex as a between factor for each compound. No significant sex effects were observed for any of the autonomic nervous system measures whatever the compound ($p > 0.05$ in all cases). In other words, the Control, AND-low and AND-high did not differently affect autonomic nervous system function in men and women during compound presentation.

### 3.2. Post-compound presentation

#### 3.2.1. Effects on mood

Following exposure to the Control or AND-low, no significant sex effects, or sex-by-time interactions were observed for any of the mood categories ($p > 0.05$ in all cases) (Fig. 4a and b). Following exposure to AND-high, significant sex effects were observed for ''positive mood'' (women: $0.43 \pm 1.01$; men: $-0.65 \pm 1.03$; $F[1, 54] = 5.603$, $p < 0.03$) and ''high arousal negative mood'' (women: $-0.27 \pm 0.62$; men: $0.36 \pm 0.71$; $F[1, 54] = 4.446$, $p < 0.05$). No significant sex, or sex-by-time interactions were observed for the remaining mood categories ($p > 0.05$ in all cases) (Fig. 4c). In other words, following exposure to AND-high, but not to the Control or AND-low, ''positive mood'' was increased and ''high arousal negative mood'' decreased in women in comparison to men.

#### 3.2.2. Effects on autonomic nervous system function

Following exposure to the Control or AND-low, no significant sex effects, or sex-by-time interactions were observed for any of the autonomic nervous system parameters ($p > 0.05$ in all cases) (Fig. 5a and b). Following exposure to AND-high, significant sex effects were observed for NS-SCR (women: $0.189 \pm 0.29$; men: $-0.352 \pm 0.39$; $F[1, 54] = 12.257$, $p < 0.003$) and ST (women: $0.006 \pm 0.006$; men: $0.012 \pm 0.007$; $F[1, 54] = 4.873$, $p < 0.05$).

Moreover, a significant sex-by-time interaction was observed for ST ($F[3, 54] = 3.555$, $p < 0.03$) reflecting that following exposure to AND-high, ST was significantly increased in men compared to women after V3 (women: $0.006 \pm 0.002$; men: $0.014 \pm 0.003$; $t(18) = 2.314$, $p < 0.04$) and V4 (women: $0.006 \pm 0.003$; men: $0.015 \pm 0.003$; $t(18) = 2.176$, $p < 0.05$). No significant sex, or sex-by-time interactions were observed for the remaining autonomic nervous system parameter ($p > 0.05$ in all cases) (Fig. 5c). In other words, following exposure to AND-high, but not to the Control or AND-low, skin conductance was

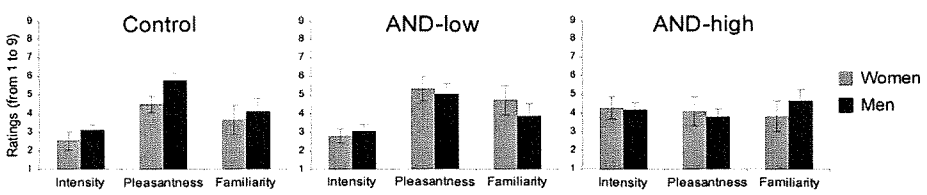


**Fig. 3.** Means (m) and standard errors (se) of intensity, pleasantness and familiarity ratings of the Control, AND-low and AND-high in women and men. No sex differences were observed for intensity, pleasantness and familiarity ratings whatever the compound (Control, AND-low and AND-high).

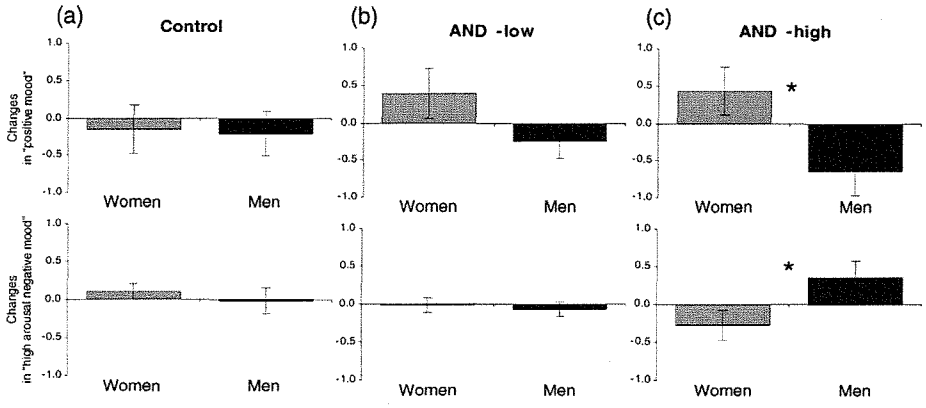


**Fig. 4.** Means and standard errors of differences in "positive mood" (top figures) and "high arousal negative mood" (bottom figures) in men and women following exposure to the Control (a), to AND-low (b), and to AND-high (c). Following sniffing AND-high, "positive mood" was significantly increased and "high arousal negative mood" significantly decreased in women compared to men. * corresponds to a $p < 0.05$. Change scores correspond to differences between the mood values (from 1 to 9) during the video minus the mood values (from 1 to 9) during baseline.

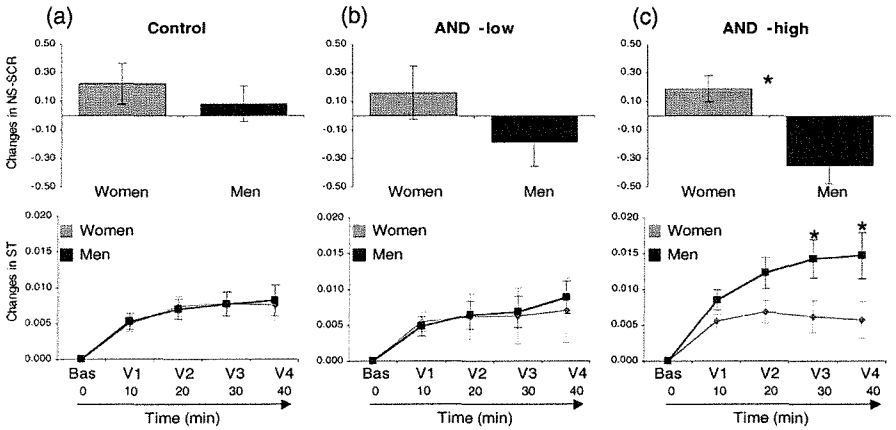


**Fig. 5.** Means and standard errors of changes in NS-SCR (expressed in number of events per minute, top figures) and ST mean (expressed in degree Celsius, bottom figures) in men and women for the Control (a), AND-low (b), and AND-high (c). Data are presented as a function of time (from Baseline to V4) for ST mean. Following exposure to AND-high, NS-SCR changes were significantly increased in women compared to men. By contrast, following exposure to AND-high, ST mean changes were significantly increased in men compared to women, especially, after V3, and V4. * corresponds to a $p < 0.05$. Data are normalized by subject using their maximum response, and then averaged across subjects for each sub-group.

increased in women relative to men, and ST was increased in men in comparison to women, especially 30–40 min after exposure.

## 4. Discussion

In the present study, we set out to test for dose-dependence in autonomic and mood responses following sniffing AND. The effects of AND were in agreement with most previous studies (Bensafi et al., 2003; Jacob and McClintock, 2000; Jacob et al., 2001a; Jacob et al., 2002), and were dose-dependent. Whereas the low concentration AND had no effects on mood and autonomic responses, the high concentration affected both mood and autonomic responses in a sex-specific manner. High concentration AND had sympathetic-like effects in women and parasympathetic-like effects in men, an effect that increased in magnitude over time following exposure.

This overall pattern is consistent with our previous results (Bensafi et al., 2003) and the results of Jacob et al. (Jacob and McClintock, 2000), but

inconsistent with the results of Grosser et al. (Grosser et al., 2000) where AND induced parasympathetic-like effects in women. Here, sympathetic-like effects were reflected in changes in electrodermal response whereas parasympathetic-like effects were reflected in changes in ST. Whereas electrodermal activity is considered a very sensitive psychophysiological index of changes in autonomic sympathetic arousal (Critchley, 2002; Lang et al., 1993; Bensafi et al., 2002a), ST is usually used as a good parasympathetic nervous system biomarker (Jacob et al., 2001a,b). In contrast, measures such as heart rate and respiration activity that did not reveal an effect in the current study, are measures susceptible to increased modulation by more cognitive factors such as stimulus' familiarity and/or pleasantness (Lang et al., 1993; Bensafi et al., 2002b; Soussignan et al., 1997, 1999).

Paralleling the effects on autonomic responses, AND increased positive mood and decreased negative mood in women only. These results are in general agreement with those of Jacob et al. (Jacob and McClintock, 2000) and Grosser et al. (Grosser et al., 2000) where AND maintained positive mood, and reduced negative mood in women, respectively.

Although the low concentration used here was equal to that used by Jacob et al. (0.00025 M), this concentration failed to induce the responses that were induced in the Jacob et al. study, and by the high concentration here. This difference between the present results and results of Jacob et al. (Jacob and McClintock, 2000) may be attributed to various methodological variables, and specifically method of exposure. Whereas Jacob et al. used continuous exposure through application of the compound to the subjects' upper lip, here we used transient exposure through only six sniffs. Considering that this methodological difference would lead to significantly greater overall exposure in the Jacob study versus this study, it is likely that this difference is sufficient to explain the difference in results. Furthermore, by making specific predictions, Jacob et al. were able to use single *t*-tests in their analysis. Here, we conducted our initial analysis with conservative mixed-ANOVAs. However, applying single *t*-tests similar to those of Jacob et al. to the current results indicated that low concentration AND increased ''positive mood'' in women relative to men 10 min ($t(18) = 1.819$, $p < 0.05$) and 40 min ($t(18) = 1.833$, $p < 0.05$) after exposure. There were no effects of the Control using this test ($p > 0.05$ in all cases). Thus, the reduced effects of the low concentration AND in the current study do not contradict the results of Jacob et al.

One may ask by what route did AND affect autonomic function and mood in the current study. In non-human mammals, chemical communication between conspecifics is partly mediated through the vomeronasal organ (VNO) (Aujard, 1997; Beckman, 2002; Berghard et al., 1996; Biasi et al., 2001; Brennan and Keverne, 1997; Dulac and Axel, 1998; Johns, 1980; Keverne, 2002; Leinders-Zufall et al., 2000; Wysocki, 1979; Zhou and Moss, 1997). VNO receptor neuron responses are dose-dependent, and remain narrowly tuned across concentration ranges (Leinders-Zufall et al., 2000). Monti-Bloch and colleagues have suggested that the effects of AND are mediated via a human VNO (Berliner et al., 1996; Grosser et al., 2000; Monti-Bloch et al., 1998a ,b; Monti-Bloch and Grosser, 1991; Monti-Bloch et al., 1994). Other studies, however, doubt the existence of a functional human VNO (Knecht et al., 2001; Trotier et al., 2000), and have also questioned the methodology used by Monti-Bloch, Grosser, and colleagues (Meredith, 2001). The current results did not directly address the path by which AND affected autonomic function and mood, but may be considered as supportive of a concern raised in previous studies. Specifically, AND naturally occurs in men and women at about 98 and 36 ng/100 ml of blood plasma, respectively (Brooksbank et al., 1972), and its concentration in male axillary hair is estimated to be in picomolar proportion to total axillary hair weight (Nixon et al., 1988) (but see Nixon et al., 1988; Preti et al., 1987). Thus, the concentration of AND that was necessary to affect autonomic function and mood following transient exposure in this study (0.00625 M) was far greater than reported endogenous levels. This may be considered as supportive of the possibility that AND was not acting through chemical sensing (either VNO or the main olfactory system) per se, but rather was directly absorbed into the bloodstream and acting pharmacologically. Furthermore, some may consider the current long time-course of response as additional evidence for a transdermal rather than a chemical sensing pathway of action for AND. That said, a cascade that has a long time course, may nevertheless be set in motion by a brief chemical signal. Thus, the time course alone is not sufficient argument against a chemical sensing path. Furthermore, the effective dosages of transdermal nasally delivered sex-steroids ranges from 0.008 to 0.064 M (Cicinelli et al., 1991a, b; Devissaguet et al., 1999; Gompel et al., 2000; Hermens et al., 1992; Wattanakumtornkul et al., 2003), which is far greater than the concentrations of AND used here (0.00025 and 0.00625 M in mineral oil). Thus, we

conclude that a transdermal path of action for AND in the current study is unlikely, but nevertheless, not ruled out.

One may ask how the finding of dose-dependence reflects on the possible role of AND in human chemical communication. Behavioral effects of chemical signals are narrowly tuned and dose-dependent. For example, the mammary pheromone 2-methylbut-2-enal is the only component in rabbits milk that induces significant increases in neonatal searching–grasping behavior, and it does this in a dose-dependent manner (Schaal et al., 2003). In line with this, pheromonal dose-dependent effects were observed in others species from insects to mammals (Dolzer et al., 2003; Franklin and Gregoir, 2001; Han and Chen, 2002; Kaissling, 1996; Zhou and Moss, 1997). In this regard, the dose-dependence seen in the current study is consistent with a role for AND in human chemical communication.

Ordinary odorants not derived from bodily secretions can also affect autonomic function and mood in humans (Alaoui-Ismaili et al., 1997; Bensafi et al., 2002a; Brauchli et al., 1995; Graham et al., 2000; Lehrner et al., 2000), but we know of no such case where the effects are opposite in men and women, nor do we know of dose-dependence in these effects. That such sex-specificity exists in the effects of AND further implicates this compound as a meaningful signal in communication between humans, and may also point to a specific role related to reproduction, an area of behavior long implicated in human chemical communication. For example, in 1971 Martha McClintock observed that the menstrual cycles of women who were roommates in dormitories, but with no previous social contact, became synchronized over time (McClintock, 1971). Later, Stern and McClintock (1998) found that contact with sweat alone, without social interaction, was sufficient to alter the timing and the length of the menstrual cycle in other women. Given that a similar phenomenon occurs in mice, and is considered as pheromonal in that species (Weller, 1998), Stern and McClintock argued that their results describe a pheromonal effect in humans. More recently, Preti et al. (in press) observed that human axillary male extracts contain primer and modulator compounds that affect mood and pulsatile secretion of luteinizing hormones in women. Given that AND modulates mood (Bensafi et al., 2003; Grosser et al., 2000; Jacob et al., 2001a, 2002; Jacob and McClintock, 2000), and induces specific brain activation (Jacob et al., 2001b; Savic et al., 2001) and autonomic nervous system responses (Bensafi et al., 2003) in women, it is tempting to speculate that AND was one of the active compounds in the male axillary extracts used by Preti et al. This speculation, however, must be treated with caution in light of some contradicting findings regarding the presence of AND in male axillary extracts (Nixon et al., 1988; Preti et al., 1987). In conclusion, the present results show that AND, a sex-steroid derived compound, induces dose-dependent and gender-specific effects on both mood and autonomic nervous system responses, and may play a role in chemical communication between humans.

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