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The effect of acute bupropion on sexual motivation and behavior in the female rat

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Abstract

Recent clinical studies have suggested that the atypical antidepressant, bupropion (Wellbutrin), may stimulate sexual desire in women. Two experiments were conducted, testing the effect of acute bupropion administration on the sexual motivation and copulatory behavior of female rats. In the first experiment, 63 sexually-experienced, female Long–Evans rats were tested in a runway for their motivation to approach an empty goalbox, a nonestrous female, and an adult male. Both latency to approach and time spent in close proximity to the targets were used as dependent variables. Subjects were tested in both a nonestrous (OVX) and estrous (OVX+15 μg estradiol+500 μg progesterone) state, and following administration of 0.0, 7.5, or 15 mg/kg bupropion hydrochloride (subcutaneous, 45 min prior to testing). Results indicated that pre-treatment with ovarian hormones significantly increased the sexual motivation of the subjects. Bupropion treatment had no significant effect, either stimulatory or inhibitory, on subjects' socio-sexual motivation.

In the second experiment, 60 female subjects were paired with an adult male for a thirty-minute copulatory test. Subjects were tested under one of three hormonal conditions: nonestrous (no hormones), 15 μg estradiol, or 15 μg estradiol+500 μg progesterone. Subjects were also pre-treated with either physiological saline or 15 mg/kg bupropion. Results indicated that while hormonal administration had a strong effect on female sexual behavior, bupropion treatment did not significantly affect either lordosis or the emission of hop-darts. Males paired with bupropion-treated females successfully achieved a greater number of ejaculations and demonstrated significantly shortened post-ejaculatory intervals. It is possible that bupropion treatment enhanced female attractiveness.

Keywords: Bupropion; Wellbutrin; Sexual motivation; Estradiol; Progesterone; Receptivity; Proceptivity; Hypoactive sexual desire; Runway; Preclinical

1. Introduction

The past several years have witnessed growing interest among clinicians and researchers in the potential for biochemical enhancement of human sexual desire, particularly in women (Agmo et al., 2004; Pfaus et al., 2004; Fourcroy, 2003). Up to one-tenth of adult men and one-third of adult women in the US suffer from inhibited sexual desire associated with marked distress or interpersonal difficulty (Basson et al., 2005; Laumann et al., 1999; Rosen, 2000; Warnock, 2002). Loss of interest in sexual activity may occur due to a medical or psychiatric condition, drug treatment, or abrupt change in internal hormonal milieu — such as major depressive disorder (Cyranowski et al., 2004; Williams and Reynolds, 2006), treatment with selective serotonin reuptake inhibitors (SSRI's; Baldwin, 2004; Clayton, 2002), and the initiation of menopause (Leiblum et al., 2006). To date, no pharmacological treatment for hypoactive sexual desire has been approved. A testosterone-delivery patch, which demonstrated significant efficacy in postmenopausal women, failed to receive FDA approval due to concerns over potential long-term health consequences (Moynihan, 2004). Recent pre-clinical experiments suggest that melanocortin receptor agonists may enhance female sexual desire (Pfaus et al., 2004; Rossler et al., 2006), but as of yet no clinical studies on these promising compounds have been completed.

Numerous clinical reports have suggested that the atypical antidepressant, bupropion (Wellbutrin), may have a positive impact on sexual desire (for a review, see Ginzburg et al., 2005). In comparison to SSRI's, bupropion is associated with a significantly lower incidence of sexual dysfunction as a side-effect of treatment (Clayton et al., 2002; Kavoussi et al., 1997;

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Nieuwstraten & Dolovich, 2001; Segraves et al., 2000). In addition, bupropion may alleviate some of the sexual dysfunction associated with major clinical depression (Thase et al., 2006). Some studies have shown that bupropion can effectively serve as an "antidote" for SSRI-induced sexual dysfunction, with adjunctive or substitute treatment significantly increasing sexual desire (Clayton et al., 2004; Gitlin et al., 2002; Zisook et al., 2006; but see DeBattistia et al., 2005; Masand et al., 2001). Others have examined whether bupropion might be an effective treatment for Hypoactive Sexual Desire Disorder (HSDD) of unknown origin. Crenshaw et al. (1987) noted a gradual but significant therapeutic effect of bupropion in a placebo-controlled, double-blind study of men and women diagnosed with psychosexual dysfunction. Segraves et al. (2001, 2004) examined the therapeutic potential of bupropion SR (sustained release) in premenopausal, nondepressed women diagnosed with HSDD. A small, but statistically significant positive effect of bupropion on both libido and orgasm was noted in both studies. No papers have reported a substantial, positive impact of bupropion on sexual desire or capacity in "normal," non-clinical samples. Bupropion may only reverse or alleviate conditions in which an individual suffers from a pre-existing state of reduced libido. Furthermore, we are not aware of any published preclinical reports documenting a pro-sexual effect of bupropion in a non-human sample.

Bupropion is an indirect dopamine and norepinephrine agonist, although its precise synaptic mechanism of action remains unclear (Ascher et al., 1995; Foley et al., 2006). Acute administration of bupropion (10–100 mg/kg) induces an increase of synaptic dopamine within rat striatum, nucleus accumbens, hypothalamus, hippocampus, and prefrontal cortex (Hasegawa et al., 2005; Li et al., 2002; Nielsen et al., 1986; Nomikos et al., 1989; Piacentini et al., 2003), and inhibits the firing rate of noradrenergic cells in the locus coeruleus (Cooper et al., 1994). In contrast, bupropion has no significant effect on serotonin (Cooper et al., 1994; Piacentini et al., 2003). It is this absence of induced serotonergic activity that primarily differentiates bupropion from the majority of antidepressants, particularly the SSRI's. Serotonin agonists tend to inhibit sexual function, an effect that may be mediated through $5HT_{2A}$ receptors (Bishop et al., 2006). Bupropion's negligible impact on serotonin presumably explains why it does not cause sexual dysfunction.

Bupropion's ability to enhance dopaminergic and noradrenergic transmission serves as a mechanistic hypothesis for its postulated pro-sexual effects. Dopamine has long been recognized as an important signal of sexual incentive-motivational processes and a stimulatory agent of male sexual motivation (Bitran and Hull, 1987; Everitt, 1990; Hull et al., 1999; Lopez and Ettenberg, 2001, 2000; Melis and Argiolis, 1995; Pfaus and Everitt, 1995; Pfaus and Phillips, 1991; Wilson, 1993; but see Paredes and Agmo, 2004). Dopamine's role in female sexual desire is less clear, although recent findings suggest that it facilitates copulatory behavior in female rats as well (Becker et al., 2001; Jenkins and Becker, 2003). Norepinephrine agonists may also enhance sexual desire, although their anxiogenic properties can inhibit sexual function at higher doses (Clark et al., 1984; Viitamaa et al., 2006).

We and others have argued that preclinical models of human sexual desire should focus predominantly on pre-copulatory behaviors that reflect underlying appetitive processes (Agmo et al., 2004; Lopez et al., 1999; Pfaus et al., 2003). Our laboratory has developed a runway methodology that allows for the assessment of incentive-motivation in male and female rats, does not require reinforcement training, and does not present subjects with more than one stimulus target at the same time. Using this model, we have previously demonstrated that sexually-inexperienced male rats are inherently attracted to estrous female cues (Lopez et al., 1999), that sexual experience enhances the incentive value of these cues (Lopez and Ettenberg, 2000), and that direct dopamine receptor antagonists significantly reduce sexual motivation (Lopez and Ettenberg, 2001, 2000). Agmo et al. (2004) have previously criticized use of approach latency as a motivational variable, arguing that it is particularly sensitive to motoric disruption associated with many pharmacological agents. To address this in the current study, we have incorporated proximity time as a second motivational variable that is less dependent upon the motoric capacity of the subject and is utilized in partner preference methodologies (Agmo et al., 2004).

We conducted two experiments assessing the effect of acute bupropion administration on sexual motivation and behavior in female rats. The first experiment examined bupropion's effect on socio-sexual motivation in the runway. Female subjects were tested under both nonestrous (ovariectomized) and estrous conditions (induced via administration of estradiol and progesterone). Hormone treatment was hypothesized to significantly increase sexual motivation, as has been previously demonstrated (e.g. Clark et al., 2004; Meyerson and Lindstrom, 1973). This hormonal manipulation, in addition to validating the sensitivity of our model, would also provide a useful comparison to the effects of bupropion. The second experiment tested the effect of bupropion on female receptivity, proceptivity, and attractiveness (Beach, 1976) in a standard non-paced mating test.

2. Methods

2.1. Subjects

Animals were obtained from Taconic Farms, Inc. (Germantown, NY) and Charles River Laboratories (Wilmington, MA). A total of 63 ovariectomized (OVX) female, Long–Evans rats served as subjects and were 75 days old at the start of testing. Females were ovariectomized at Taconic and Charles River 1 week prior to arrival in our laboratory. Ten sexually-experienced, adult, male Long–Evans rats (130–160 days old) served as sexual partners during copulatory tests. Two sexually-experienced, adult, male Long Evans rats (130–160 days old) served as goalbox targets within the runway apparatus to induce sexual motivation in subjects. Two adult, OVX female Long–Evans rats (100–130 days old) also served as goalbox targets to induce social motivation.

Males were individually housed in plastic tubs within a secure, temperature-controlled (23±2 °C) vivarium. Females

were housed in pairs within the same vivarium but not in close proximity to the males. Food and water were provided ad libitum throughout the study. Animals were maintained under a reverse 12:12 light–dark schedule (lights on 22:00–10:00 h). Animals were handled daily by experimenters for 5–7 days prior to any behavioral testing. The care and use of animals, and all aspects of the experimental protocol, were reviewed and approved by the campus IACUC (Institutional Animal Care and Use Committee) for compliance with the National Institute's of Health *Guide for the Care and Use of Laboratory Animals*.

2.2. Inducing behavioral estrus

Subjects' sexual motivation and behavior was assessed in both a nonestrous and estrous state. "Nonestrous" refers to an OVX female not given any hormonal priming. "Estrous" refers to an OVX female given subcutaneous (SC) administration of 15 μg estradiol benzoate (EB; in 0.1 ml sesame oil) 48 h prior to behavioral testing and 500 μg of progesterone (P; in 0.1 ml propylene glycol) 5 h before testing. Steroid hormones were purchased from Sigma-Aldrich (St. Louis, MO).

2.3. Apparatus

Copulatory tests took place within four cylindrical Plexiglas arenas (53 cm diameter × 60 cm height). Motivational testing took place within two identical straight-arm runways consisting of a startbox (25 × 25 × 20 cm), an alley (160 × 10 × 20 cm), and a cylindrical Plexiglas goalbox (50 cm diameter × 30 cm height). Fig. 1 depicts a line-drawing and photograph of the runway apparatus. Removable Plexiglas doors were located between the startbox and alley and between the alley and goalbox. Within the goalbox, a removable Plexiglas partition divided the arena into two semicircular halves. Thirty-five 1-cm diameter holes drilled into the partition allowed air to pass between the two sides of the goalbox. This partition prevented tactile contact between subject and target during motivational testing, although visual, auditory, and olfactory cues were accessible.

Three infrared photocell emitter-detector sensor pairs were placed within the apparatus to detect subject motion. Sensor #1 was located just outside the startbox and was triggered when the subject entered the alley. Sensor #2 was located within the goalbox (15 cm from the entry) and was triggered when the subject's entire body was within the goalbox. These two sensor pairs were linked to an electronic timer that recorded "run time." This timer started when the subject triggered sensor #1 and stopped when the animal triggered sensor #2. Sensor #3, located within the alley (25 cm from the goalbox entry), became active only after an initial goalbox entry. Sensor #2 and #3 allowed for measurement of subject "proximity time." A second electronic timer started when the subject first entered the goalbox and triggered sensor #2. If the subject left the goalbox and triggered sensor #3, the timer stopped. If the subject re-entered the goalbox and triggered sensor #2, the time would start again. This continued for a period of 3 min, following the initial entry of the subject into the goalbox.

This apparatus is comparable to that used successfully by Ettenberg and colleagues in their analysis of the motivating impact of food (Chausmer and Ettenberg, 1997; Ettenberg and Camp, 1986a; Horvitz and Ettenberg, 1989), water (Ettenberg

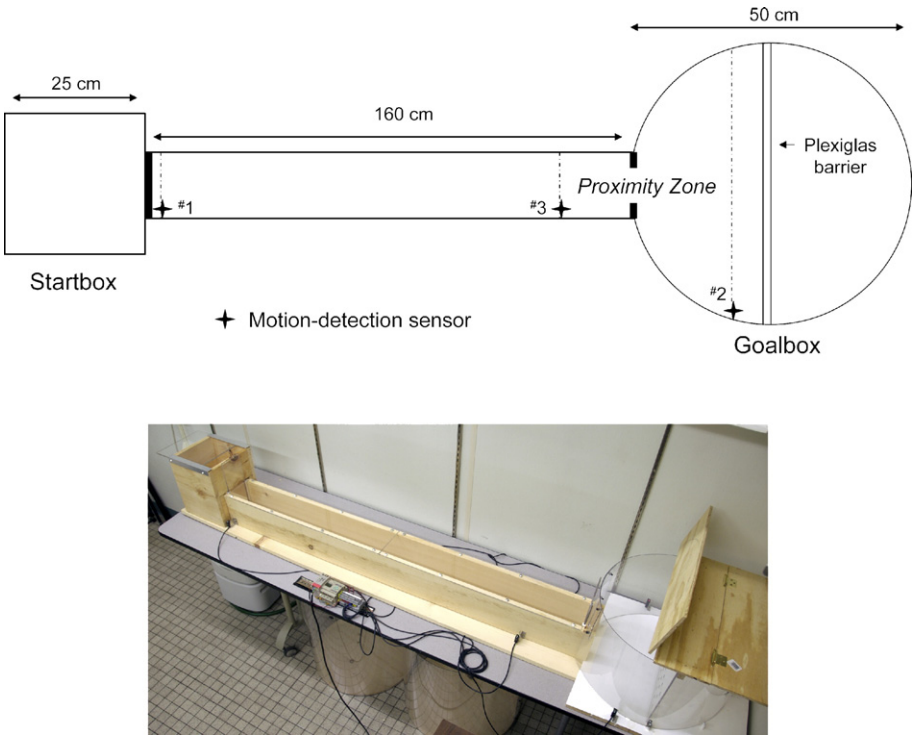

Fig. 1. The runway apparatus used to assess socio-sexual motivation in Experiment #1. Sensors #1 and #2 allowed for the measurement of run time, while Sensors #2 and #3 allowed for the measurement of proximity time.

and Camp, 1986b; Ettenberg and Horvitz, 1990), various drugs of abuse (Ettenberg and Bernardi, 2006; Ettenberg and Geist, 1993; Guzman and Ettenberg, 2004; Knackstedt and Ettenberg, 2005; McFarland and Ettenberg, 1995, 1997), and primary and secondary sexual incentives (Lopez and Ettenberg, 2001, 2000; Lopez et al., 1999).

2.4. Procedure

2.4.1. Socio-sexual experience

Following several days of handling and habituation to the vivarium environment, female subjects were given a single sexual experience with an adult male conspecific while in an estrous state, and a single social experience with a male while in a nonestrous state. Sexual and social testing occurred 2 days apart. Both males and females were habituated to the copulatory arenas on two separate seven-minute sessions, prior to testing. All testing occurred under near-dark conditions, during the dark portion of the animals' photoperiods.

For sexual experience, females were given appropriate hormonal treatment to induce behavioral estrus (see above). They were then paired with a single sexually-experienced male in a copulatory arena until the male ejaculated or 15 min passed. If a male did not ejaculate within 15 min, another male was substituted and testing recommenced. All females successfully received a single ejaculation under these test conditions. Experimenters recorded the time to ejaculation (ejaculation latency), as well as the number of intromissions the male performed prior to ejaculation. The median ejaculation latency during sexual tests was 235 s (with a standard deviation of 189 s), and the median number of intromissions experienced by each female subject was 11 (with a standard deviation of 4.6). After the male had ejaculated, both male and female were returned to the vivarium.

For social experience, the females were kept in a nonestrous state but were again paired with a single sexually-experienced male in a copulatory arena. They remained in the arena for an equivalent amount of time that passed during their sexual experience. Males frequently attempted to mount these females but rarely succeeded in achieving an intromission (the median number of intromissions was 0, with a standard deviation of 1.4).

2.4.2. Experiment #1: effect of acute bupropion on socio-sexual motivation

All runway testing took place under red-light illumination during the 2nd third of the dark phase of the animals' photoperiod. Following socio-sexual experience, all subjects were allowed to individually explore and habituate to the empty runway apparatus for 10 min on two consecutive days. Baseline testing then commenced. Over the next 6 days, subjects were tested for their motivation to approach and maintain close proximity to one of the three different goalbox targets: an empty goalbox, an OVX (nonestrous) female, or an adult male. Subjects were tested in a nonestrous state throughout the baseline phase. On any given day, all subjects ran for the same target in the goalbox; only one trial per day per subject was conducted. Thus, subjects' ran for each goalbox target twice during the baseline phase. The order of goalbox targets was randomly determined.

Prior to a day's trials, the assigned target (if a female or male conspecific) was confined within the goalbox for a period of 2 min. The partition was then introduced into the goalbox with the target placed on the side farthest from the goalbox entrance. A female subject was placed into the goalbox on the opposite side of the partition from the target for 2 min. The subject was then quickly removed from the goalbox and immediately placed within the startbox. After 10 s, the two removable doors were lifted, and the subject was allowed to traverse the alley and re-enter the goalbox. "Run time" was defined as the amount of time (in seconds) it took the subject to enter the goalbox after leaving the startbox. Presumably, a lower run time indicates greater incentive-motivation. "Proximity time" assessed the subject's desire to stay in close physical proximity to the goalbox target and was defined as the total amount of time the subject spent in the goalbox following initial entry, for a period of 3 min. A higher proximity time indicates greater incentive-motivation. After this three-minute period expired, the subject was removed from the runway and returned to the vivarium. The runway was quickly wiped down to remove any urine or feces left by the subject prior to initiating the next trial. This procedure was repeated until all animals were tested. The order of subjects run was kept constant throughout the experiment. The entire runway apparatus was cleaned with a 10% ethanol solution at the end of each day's trials.

Following completion of the baseline phase, subjects were divided into six experimental groups such that mean baseline run times and proximity times were approximately equal between groups. Subjects were then re-tested in the runway for their motivation to approach the same three goalbox targets (empty, female, male) under one of two different hormonal conditions and one of three different drug conditions. Subjects in three of the groups continued to be tested in a nonestrous state and were administered vehicle injections of 0.1 ml sesame oil and 0.1 propylene glycol, 48 and 5 h prior to testing, respectively. Subjects in the other three groups were tested after behavioral estrus was induced via sequential administration of EB and P (see above). Within each hormonal condition, there were three drug conditions. Subjects received either vehicle (physiological saline, 0.9%) or bupropion hydrochloride (SBH Medical, Worthington, OH) administered subcutaneously 45 min prior to testing within the runway. Two different doses of bupropion, 7.5 mg/kg and 15 mg/kg, were used. These doses were chosen based upon previous research indicating that they only modesty impact locomotor behavior (Nielsen et al., 1986; Redolat et al., 2005), while increasing noradrenergic and dopaminergic activity within subcortical regions associated with sexual behavior (Hasegawa et al., 2005; Nielsen et al., 1986; Nomikos et al., 1989; but see Li et al., 2002). All injections were administered in a volume of 1 ml/kg.

Subjects ran a single experimental trial for each goalbox target. These trials were, by necessity, 4 days apart due to the induction of behavioral estrus in half the subjects. Such a treatment regimen requires that at least 3 days separate test

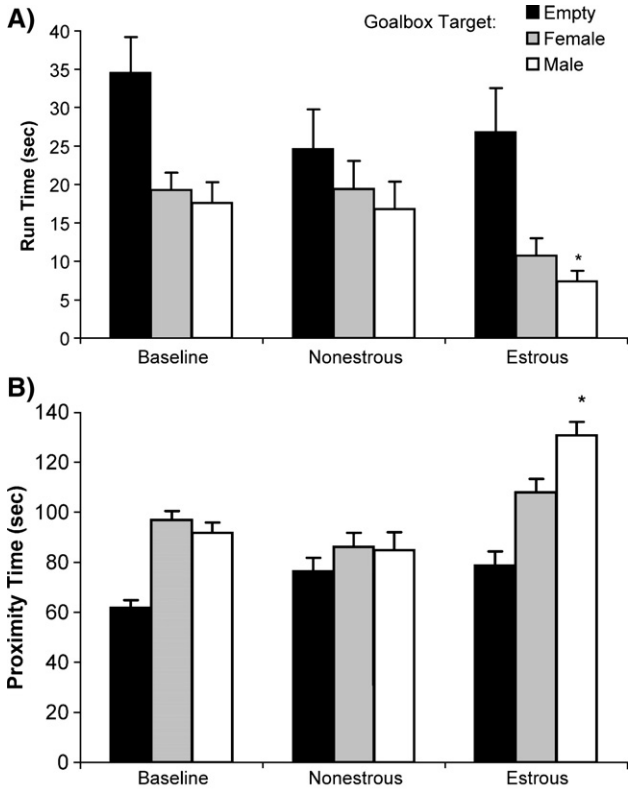

Fig. 2. The effect of hormonal treatment on run time (A) and proximity time (B) for the three goalbox targets. Times are expressed as mean (±SEM) seconds. Lower run times and higher proximity times indicate greater motivation. "Baseline" represents the mean for all 63 subjects, tested under nonestrous, non-drugged conditions. During the experimental phase, subjects were divided into two hormonal conditions: nonestrous (n=32) and estrous (n=31). "Nonestrous" and "Estrous" represent each respective group's socio-sexual motivation during the experimental trials. Drug conditions (0.0, 7.5, and 15 mg/kg bupropion) are collapsed within each hormonal group. Paired-sample *t*-tests compared each subject's baseline performance to their performance under experimental conditions. * indicates a significant increase in motivation from baseline.

periods, mimicking the natural estrous cycle of the female rat. On the second day after each experimental trial, subjects were tested in the runway for their motivation to approach an empty goalbox under nonestrous, non-drugged conditions. The trials provided subjects with a "baseline-like" experience during the experimental phase, and allowed us to determine whether subject behavior was being significantly modified by successive drug treatments.

2.4.3. Experiment #2: effects of bupropion on female receptivity, proceptivity & attractiveness

Sixty out of the original 63 subject females (randomly selected) participated in a second experiment, assessing the effect of acute bupropion administration on female copulatory behavior. These 60 subjects were divided into 6 groups ($n=10$ each), such that each group contained an equal mix of subjects from the six experimental conditions of the first experiment. This allowed us to partially control for previous exposure to bupropion treatment. Subjects that had previously been assigned to nonestrous experimental groups in Experiment #1 were given two successive priming regimens of estradiol benzoate and progesterone to reinstate hormonal sensitivity.

Subjects were tested in one of three hormonal states: OVX (nonestrous), OVX+EB, or OVX+EB+P. Hormonal dosages and timing of administration were the same as in Experiment #1. Subjects were also given either 15 mg/kg bupropion hydrochloride or a vehicle injection of physiological saline (0.9%) 45 min prior to behavioral testing. We opted to use different experimental conditions than in Experiment #1 because of a desire to test the specific hypothesis that bupropion would interact with estradiol pre-treatment, resulting in full behavioral estrus and the emission of proceptive behaviors (which are largely dependent upon progesterone).

Behavioral tests consisted of a 30-minute session in which the female subject was placed with a sexually-experienced adult male within one of the cylindrical copulatory arenas. Ten sexually-experienced, adult Long–Evans males were used as copulatory partners. These same 10 partners were paired with each of the experimental female groups, thus controlling for potential differences in male responsiveness. On any given day, 10 copulatory tests were conducted so that each male only engaged in one thirty-minute test per 24-hour period. Copulatory arenas were cleaned with a 10% ethanol solution between tests.

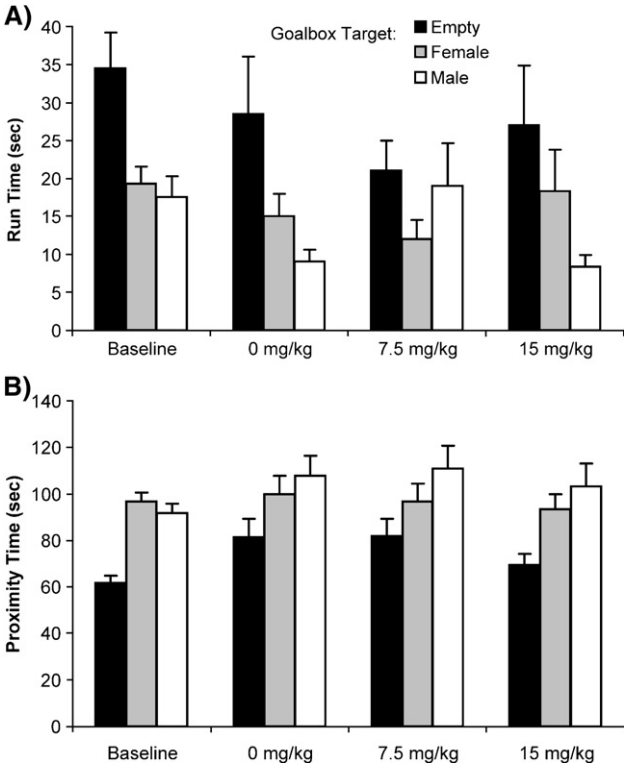

Fig. 3. The effect of bupropion treatment on run time (A) and proximity time (B) for the three goalbox targets. Times are expressed as mean (±SEM) seconds. Baseline represents the mean for all 63 subjects. During the experimental phase, subjects were divided into three drug conditions: 0 mg/kg (n=22), 7.5 mg/kg (n=20), and 15 mg/kg (n=21). Hormonal conditions (nonestrous and estrous) are collapsed within each drug group. Analyses revealed no significant effect of drug treatment on motivation to approach and maintain close proximity to any of the goalbox targets.

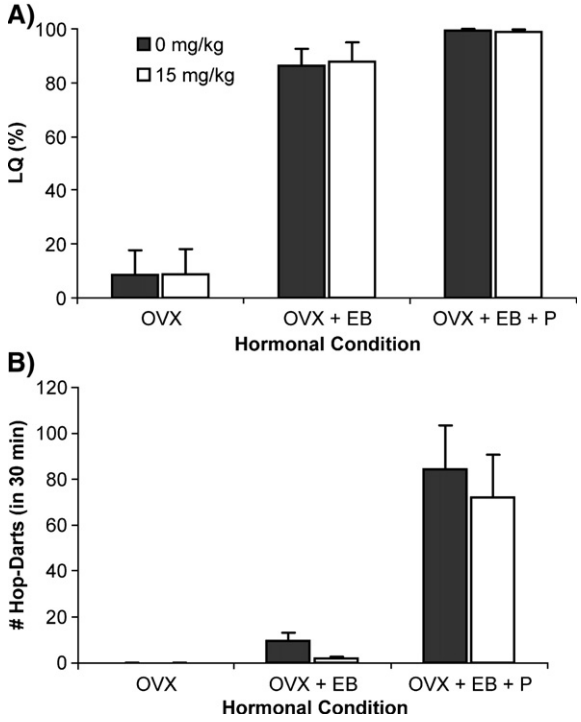

Fig. 4. The effect of hormone and bupropion treatment on female receptivity (A) and proceptivity (B) during a 30-miniute non-paced copulatory test. Subjects were tested under one of three hormone conditions (OVX, OVX+15 μg estradiol, or OVX+ 15 μg estradiol+ 500 μg progesterone) and one of two drug conditions (0.0 and 15 mg/kg bupropion). There was n=10 for each experimental group. Analyses revealed a significant effect of hormonal treatment on lordosis quotient and emission of hop-darts, but no effect of bupropion.

Experimenters recorded the following male copulatory behaviors: mount latency (time from initiation of the test to first mount of the female), ejaculation latency (time to first ejaculation), post-ejaculatory interval (time between first ejaculation and next successful mount), number of mounts (conducted during the entire 30-minute session), and number of ejaculations. Analyses of these behaviors would allow us to determine whether males behaved differently towards females in the different experimental conditions based upon changes in their receptivity, proceptivity, and attractiveness. The following female copulatory behaviors were recorded: lordosis quotient (a measure of receptivity) and hop-darts (a measure of proceptive behavior). Lordosis quotient was calculated as the percentage of male mounts that the female responded to with assumption of the lordosis posture. Hop-darts were coded as individual hops and darts, as well as sequential displays, as defined by Tennent, Smith and Davidson (1980). Experimenters were kept blind to the treatment condition of individual subjects throughout this experiment.

3. Results

3.1. Experiment #1

This experiment utilized a 2 (phase: baseline vs. experimental)×3 (goalbox target)×2 (hormonal condition)×3 (drug condition) mixed-factorial design, with hormonal and drug condition serving as between-subject variables. A mixed-factorial analysis of variance (ANOVA) was conducted on both the run time and proximity time data (using an alpha of 0.05). The analysis of subject run time yielded a significant main effect of phase ($F(1,57)=6.92$, $p=0.01$) and goalbox target ($F(2,56)=12.23$, $p<0.001$). There were no significant interactions. Bupropion treatment had no significant effect on subject run times for any of the goalbox targets, regardless of hormonal state. To test our a priori hypothesis that hormonal treatment induces a specific change in sexual motivation, a series of six paired Student's *t*-tests were performed. Subject run times for the three goalbox targets between the baseline and experimental phases were compared. Drug conditions were collapsed within each hormonal condition. A Bonferroni adjustment was made to reduce the probability of Type 1 error, giving an alpha of 0.0083. All *p*-values reported are for two-tailed tests. For subjects tested in a nonestrous state during the experimental phase, there were no significant changes in run time for any of the goalbox targets: empty ($t(31)=1.39$, $p=0.17$), female ($t(31)=0.01$, $p=0.99$), male ($t(31)=0.19$, $p=0.85$). For subjects tested in an estrous state during the experiment phase, there was no significant change in run time for either the empty goalbox ($t(30)=1.10$, $p=0.28$) or the female target ($t(30)=1.89$, $p=0.07$). There was, however, a significant decrease in run time from the baseline to experimental

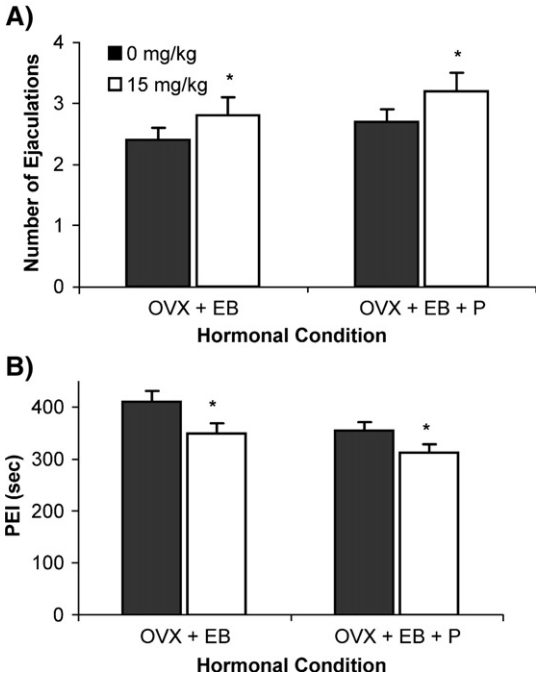

Fig. 5. The effect of hormone and bupropion treatment on male responsiveness to female subjects during a 30-miniute non-paced copulatory test. (A) displays the mean (±SEM) number of ejaculations that male partners achieved during the test, as a function of the hormonal and pharmacological state of their female partners. (B) displays the mean (±SEM) post-ejaculatory interval (in seconds) of males, as a function of the hormonal and pharmacological state of their female partners. Analyses revealed a significant effect of drug, such that when males were paired with bupropion-treated females, they achieved a greater number of ejaculations and initiated copulatory activity sooner after their first ejaculation.

phase for subjects treated with hormones and tested for their motivation to approach a male target ($t(30)=3.06$, $p=0.005$). Fig. 2A displays mean (±SEM) run times for the three goalbox targets both in baseline and as a function of hormonal treatment (collapsing across all drug groups).

Analysis of proximity time yielded a significant main effect of phase ($F(1,57)=9.32$, $p=0.003$) and goalbox target ($F(2,56)=61.00$, $p<0.001$). Bupropion treatment had no significant effect on proximity times for any of the goalbox targets, regardless of hormonal treatment. A three-way interaction between phase, goalbox target, and hormonal condition was significant ($F(2,56)=3.96$, $p=0.022$). Fig. 2B displays mean (±SEM) proximity times for the three goalbox targets both in baseline, and as a function of hormonal treatment (again collapsing across all drug groups). To delineate the nature of the three-way interaction and test our a priori hypothesis that hormonal treatment would affect sexual motivation for a male target, we conducted a series of post-hoc analyses using Tukey's HSD test. For the empty goalbox, there was a main effect of phase but no interaction. Subjects spent more time in the empty goalbox during the experimental phase ($\bar{x}=77.5$ s) than during the baseline phase ($\bar{x}=61.7$ s), regardless of hormonal treatment. For the female target a different pattern emerged, as there was no main effect of phase but a significant interaction between phase and hormone. Subjects tested in a nonestrous condition demonstrated a non-significant decrease in motivation from baseline ($\bar{x}=98.1$ s) to experimental ($\bar{x}=86.0$ s), while subjects tested in an estrous condition showed a non-significant increase in motivation from baseline ($\bar{x}=95.4$ s) to experimental ($\bar{x}=108.0$). For the male target, there was a significant main effect of phase and a significant interaction between phase and hormone. Subjects tested in a nonestrous condition showed no significant change in motivation from baseline ($\bar{x}=93.0$ s) to experimental ($\bar{x}=84.5$), while subjects given hormonal treatment experienced a significant increase in motivation from baseline ($\bar{x}=90.3$ s) to experimental ($\bar{x}=130.8$ s).

As stated earlier, acute bupropion treatment had no significant effect on subject motivation to approach the goalbox targets or maintain close proximity to them. Fig. 3A and B display the mean (±SEM) run times and proximity times, respectively, for subjects as a function of drug treatment (hormonal condition is collapsed within each drug group).

3.2. Experiment #2

Fig. 4A and B display the effects of hormonal treatment and bupropion administration on lordosis and hop-darts, respectively. A 3 (hormonal condition) × 2 (drug dose) ANOVA was conducted on each dependent variable. The analysis of lordosis quotient (LQ) revealed a main effect of hormonal treatment ($F(2,54)=123.4$, $p<0.001$) but no effect of drug treatment or interaction. Post-hoc analysis using the Tukey HSD revealed a significant difference in LQ between OVX subjects and EB primed subjects ($p<0.001$) and between OVX subjects and EB+P primed subjects ($p<0.001$). Estradiol treatment, but not progesterone, significantly influenced receptivity.

The analysis of hop-darts was similar, with a main effect of hormone ($F(2,54)=34.9$, $p<0.001$) but no effect of drug treatment or interaction. Tukey's HSD revealed a significant difference in hop-darts between OVX subjects and EB+P primed subjects ($p<0.001$), as well as between EB primed subjects and EB+P primed subjects ($p<0.001$). Only EB+P treated subjects engaged in a large number of proceptive behaviors.

Nonestrous (OVX) females did not display a significant degree of sexual behavior, regardless of drug treatment. While the males paired with them would periodically attempt to mount them, they did not achieve much success. For this reason, we chose to analyze aspects of male sexual behavior only when they were paired with hormonally-primed females (both EB and EB+P conditions). A 2×2 ANOVA was conducted on the five dependent variables reflecting male copulatory behavior: mount latency (ML), total number of mounts, ejaculation latency (EL), total number of ejaculations, and post-ejaculatory interval (PEI). The analyses of mount latency and ejaculation latency did not yield a significant effect of drug or hormone, or a significant interaction. The analysis of total male mounts yielded a main effect of hormone ($F(1,36)=8.89$, $p=0.005$), whereby males paired with EB+P treated females engaged in a greater number of mounts ($\bar{x}=37.4$) than when paired with EB treated females ($\bar{x}=27.5$).

The analysis of ejaculations yielded a main effect of drug ($F(1,36)=4.643$, $p=0.038$). When paired with females that had received 15 mg/kg bupropion, males achieved a greater number of ejaculations ($\bar{x}=3.0$) than when paired with females receiving vehicle ($\bar{x}=2.5$). The analysis of PEI yielded a significant main effect of both hormone ($F(1,36)=6.94$, $p=0.012$) and drug ($F(1,36)=8.66$, $p=0.006$). When males were paired with bupropion-treated females, they displayed significantly shorter post-ejaculatory intervals ($\bar{x}=331.4$ s) compared to when they were paired with vehicle-treated females ($\bar{x}=382.8$ s). Fig. 5A and B displays the effects of hormonal treatment and bupropion administration on male ejaculations and post-ejaculatory interval, respectively.

4. Discussion

The goal of the current experiments was to assess the effect of acute bupropion administration on various aspects of female rodent sexuality: sexual motivation, receptivity, proceptivity, and attractiveness (Beach, 1976). The first experiment successfully demonstrated the predictive validity of the runway methodology in assessing experimentally-induced changes in female sexual motivation. Hormonal treatment, consisting of supra-physiological doses of estradiol and progesterone, significantly increased female interest in male targets. This enhancement of sexual motivation was manifested in shorter latencies to approach males (run time), as well as greater amounts of time spent in close physical proximity to male targets located on the other side of a Plexiglas barrier (proximity time). That these two variables are behaviorally independent and yet are affected similarly by hormonal treatment, increases our confidence that they reflect underlying incentive–motivational processes. Notably, hormonal treatment did not affect motivation to approach an empty goalbox, which serves as a useful control for alterations in locomotor activity.

The regulation of female sexual motivation in rats by ovarian hormones has been demonstrated previously in numerous experiments (Clark et al., 2004; Edwards and Pfeifle, 1983; McDonald and Meyerson, 1973; Meyerson and Lindstrom, 1973). The adaptive value of such a mechanism is clear: by linking both reproductive potential and sexual desire to the same hormonal system, the probability of successful fertilization is increased. Theoretically, ovarian hormones may increase female sexual motivation through generation of a central motive state that serves to energize behavior and sensitize the individual to sexual-incentives which signal potential mating opportunities (Agmo, 1999; Pfaus, 1999). Ovarian hormones bias the motivational valence of male cues (such as their smell), making them more positive and attractive. The current experimental results are consistent with this theoretical interpretation. It remains unclear how sexual experience modifies sexual motivation in females. We have previously demonstrated that in male rats, sexual experience (even a single ejaculation) enhances the incentive-value of estrous female cues (Lopez et al., 1999). In the current experiment, all subjects were provided with a single non-paced copulatory episode (including several intromissions and an ejaculation from a male partner) prior to behavioral testing. In addition, subjects were paired with a male while in a nonestrous state for an equivalent amount of time. It is possible these experiences influenced subsequent subject behavior in the runway. A rewarding sexual experience may induce a form of "state-dependent learning," such that male incentives arouse sexual motivation on subsequent occasions of behavioral estrus. However, it should be noted that a number of laboratories have argued sexual behavior is only rewarding to females when it is paced (Paredes and Vasquez, 1999; but see Meerts and Clark, 2007). Furthermore, increased sexual motivation during estrus may not be dependent upon prior copulatory experience.

Post-hoc analyses of proximity times revealed that the social motivation of subjects to interact with a female conspecific was mildly affected by hormonal treatment. As can be seen in Figs. 2A and B, estrous subjects ran slightly faster for a female target and spent more time in close proximity to a female, as compared to nonestrous females. In contrast, Matthews et al. (2005) noted that estradiol treatment did not alter the social motivation of female mice trained to emit operant responses for access to another female. It is not clear whether this behavioral change is a by-product of increased sexual motivation or serves an independent function. On a more practical note, inclusion of a social control in preclinical tests of sexual motivation serves an important function. Lack of this condition makes it difficult to determine whether an experimental treatment is influencing sexual motivation independent of a change in social motivation. Partner preference methodologies, in which subjects are concurrently exposed to both a social and sexual target (e.g. Ellingsen and Agmo, 2004), are also susceptible to this confound. They are less likely to detect changes in sexual motivation that may be overwhelmed by alterations in social motivation (and vice-versa). The runway methodology avoids this problem by assessing subject motivation for different incentives in separate trials. The disadvantage to this procedure is that it is more time-intensive.

Bupropion administration, at the doses tested, had no significant effect on female socio-sexual motivation in Experiment #1 and did not alter female receptivity and proceptivity in Experiment #2. These findings support the hypothesis that bupropion, in contrast to many anti-depressants, does not disrupt neurological systems linked to the generation of sexual motivation and behavior. While these results do not support clinical findings documenting a positive impact of bupropion on sexual desire in women (Ginzburg et al., 2005), several caveats should be noted. First, it is possible that higher doses of bupropion would have affected subject motivation and copulatory behavior. However, we did not wish to use doses that induce large increases in ambulation or reward-seeking behavior. Rats will readily self-administer intravenous bupropion (Tella et al., 1997), an effect likely mediated by its ability to elicit dopaminergic release within reward pathways. A dose of 10 mg/kg (IP) has been shown to induce a significant conditioned place preference in rats (Ortmann, 1985), as well as lower reward thresholds assessed via intracranial self-stimulation (Cryan et al., 2003). Furthermore, the dosage range chosen has demonstrated efficacy in standard preclinical tests of antidepressant activity (Cooper et al., 1994; Ripoll et al., 2003).

Second, it is possible that chronic administration of bupropion would have led to significant alterations in socio-sexual motivation. In clinical samples, bupropion typically takes several weeks to show therapeutic efficacy (Crenshaw et al., 1987). A chronic administration paradigm would more accurately model the typical patient scenario. In this study, we chose to administer bupropion acutely as an initial experimental venture. Many preclinical screening methodologies that utilize acute administration are able to detect therapeutic compounds that require chronic administration in humans. For example, acute bupropion has been shown to have a significant effect on behavior in both the Porsolt and tail-suspension tests (Cooper et al., 1994; Ripoll et al., 2003).

The interaction between dose of hormone and dose of bupropion may also have been relevant. It is possible that bupropion could enhance sexual motivation in females treated with lower doses of estradiol and progesterone (or in subjects treated only with estradiol) that do not induce maximal behavioral estrus. This hypothesis is indirectly supported by the recent work of Mani and colleagues (Mani, 2001, 2006; Mani et al., 1994) who have demonstrated that dopamine agonists can mimic the effects of progesterone in facilitating aspects of sexual behavior in female rats.

However, in Experiment #2 we explicitly tested the hypothesis that bupropion might enhance sexual activity in females primed solely with estradiol. Fig. 4A and B indicates that bupropion treatment had no effect on receptivity or proceptivity, regardless of the hormonal state of the female. Subjects that received a combination of EB-priming and 15 mg/kg bupropion did not behave like fully estrous (EB+P) females. This was particularly salient in the case of hop-darts, which presumably serve to increase the sexual desire of the male and may be an indirect reflection of female sexual motivation. Progesterone treatment had a significant effect on the emission of hop-darts, consistent with previous demonstrations (de Jonge et al., 1986; Landau and

Madden, 1983; Tennent et al., 1980). However, females treated with EB+bupropion emitted a mean of 1.8 hop-darts during the copulatory test, indicating that bupropion does not stimulate proceptive displays in estradiol-primed females.

The results from Experiment #2 suggest, however, that bupropion may influence the sexual attractiveness of females. When male studs were paired with bupropion-treated females, they achieved a greater number of ejaculations in the 30-minute session and displayed significantly shorter post-ejaculatory intervals (as seen in Fig. 5A and B). This indicates that males experienced a greater degree of sexual arousal in copulatory tests with treated females. Bupropion may have subtly altered the behavior of the females, making them more active during the post-ejaculatory intervals and stimulating male interest and re-arousal. It is also possible that bupropion enhanced certain incentive properties of the treated females (e.g. pheromone emission). This hypothesis could be tested using an incentive-motivation behavioral model, like the runway, to assess male desire to approach treated and untreated females. Until these findings are explored further, we cannot consider our results conclusive evidence that bupropion enhances female sexual attractiveness.

These experiments have forced us to consider an issue that has remained relatively unexamined in our field: what is the most appropriate preclinical, endocrinological model for women? The hormonal regulation of sexual motivation by gonadal steroids appears to have been preserved throughout most primate species, including humans (Agmo and Ellingsen, 2003; Wallen, 1990; Wallen and Zehr, 2004). This strengthens the external validity of rodent models used to elucidate neurobiological processes that underlie the generation and expression of sexual motivation. However, particular clinical scenarios may require modifications to existing rodent models. Consider a pre-menopausal woman suffering from HSDD of unknown origin. Is the appropriate rodent model a nonestrous or an estrous female? If the woman is experiencing a normal menstrual cycle, the animal model should assess pharmacological efficacy in both nonestrous and estrous females (as does the present research). If we are primarily targeting a post-menopausal patient population, then the most appropriate hormonal model might be an ovariectomized female given low doses of ovarian hormones to stimulate a modest degree of behavioral estrus. Finally, if the loss in sexual desire is associated with a particular psychiatric syndrome then perhaps the animal model should reflect the underlying etiology. Reduced sexual desire associated with depression could be modeled via application of chronic mild stress, for example. More broadly, it seems appropriate for researchers in this field to consider how pharmaceutical agents might interact with endogenous hormones in women, such that their behavioral and psychological effects differ across endocrinological states.

The runway model has proved to be a reliable and valid means of assessing both hormonal and pharmacological effects on sexual motivation in male and female rats. This and similar methodologies will become increasingly relevant as the clinical community and pharmaceutical industry commit more resources towards the development and testing of compounds designed to increase human libido.

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