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Gender and gonadal hormone effects in the olfactory bulbectomy animal model of depression

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Abstract

Major depressive disorder (MDD) affects women to a greater extent then men; however, the few studies that have examined the role of gender in an animal model of depression have shown inconsistent results. The purpose of the present study was to determine if the gonadal hormone milieu of the animal modulated behavioral changes following olfactory bulbectomy (OBX), a well-documented animal model of depression. Body weight, sucrose preference levels and open-field activity levels were measured once a week for a period of 2 weeks in gonadally intact and gonadectomized male and female rats. Following these baseline measurements, animals underwent either OBX or sham surgery. Body weight, sucrose preference and activity levels were assessed for 4 weeks post-OBX surgery. OBX-gonadectomized animals exhibited higher activity levels than OBX gonadally intact and control animals. This effect of gonadectomy was more robust in males. OBX-females (both intact and gonadectomized) exhibited significantly lower sucrose preference levels than OBX-males (both intact and gonadectomized) and control animals. These results suggest that the gonadal hormone milieu of the animal plays a role in modulating sucrose preference and activity levels following OBX.

Keywords: Olfactory bulbectomy; Depression; Sex differences; Anhedonia

Major depressive disorder (MDD) is a debilitating illness that affects about 5% of the population. While the etiology and mechanisms of this disorder are not completely understood, the ratio of women suffering from MDD compared to men is about 2:1 [29,30,36,43,56]. A significant contributor to this sexually dimorphic ratio may be that women may have earlier onset of depressive episodes and a greater number of recurrent depressive episodes than men [9,29,30,34]. While a variety of social and economic factors may play a role in this gender difference, the fact that this female predominance in MDD is not observed in prepubertal or postmenopausal subjects supports a biological component [9,20,43].

The greater prevalence of MDD in women does not appear to be due to postpartum depression, since the onset of depressive symptomatology following birth accounts only for a small portion of the total cases of MDD [43]. While it is not clear whether gender differences in MDD can be explained by changes in affect across the menstrual cycle (i.e., premenstrual dysphoric disorder (PMDD)) the behavioral changes associated with PMDD are reported to be vegetative in nature (i.e., increased sleep, decreased activity) [21,43]. These vegetative changes are more common in atypical MDD and do not explain the gender differences in MDD where the behavioral changes are more agitated in nature (i.e., decreased sleep, increased activity). Evidence for depression symptomatology during menopause is still under debate [43].

One method to investigate the possible biological mechanisms of this gender difference in MDD is an effective animal model of depression, such as the learned helplessness or chronic mild stress models [14,18,38,41]. Many of the studies using animal models of depression have shown inconsistent differences between males and females. Using the Porsolt swim test, female rats have been reported to have either longer or shorter immobile times [42] as compared to male rats. Following exposure to acute restraint stress, male

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rats show a greater suppression in open-field activity and a significant increase in fecal boli output compared to females, whereas food intake is significantly suppressed in both sexes [28]. However, following chronic restraint stress a switch in the behavioral patterns between male and female rats is observed. Specifically, following chronic restraint stress male rats exhibit open-field activity levels that are similar to controls males, while female rats show a suppression in open-field activity levels compared to control females [28]. Following exposure to shocks that produce learned helplessness (i.e., 60–80 footshocks), male rats performed more poorly, compared to female rats, on an active avoidance task [22].

Two core symptoms for the diagnosis of MDD in humans are depressed mood and a decrease in pleasure (i.e., anhedonia). Since a depressed mood is difficult to measure in animals, anhedonia becomes an important measure in determining the validity of animal models of depression [14,40]. While it is unknown if either restraint stress or the Porsolt swim stress produces an anhedonic state, prior research has suggested that both learned helplessness and chronic mild stress can produce an anhedonic state [39,57,59,60]. While learned helplessness can attenuate responding for intracranial self-stimulation, a measure of anhedonia [60,61] in male rats, no studies have yet compared males and females in regards to anhedonia following learned helplessness. However, the behavioral data suggests that female rats are less severely affected by exposure to learned helplessness-producing shocks than male rats [22]. Following exposure to chronic mild stress no gender differences in sucrose intake, a measure of anhedonia, were reported [14]. Thus, it appears that an animal model of depression that adequately reflects the gender difference observed in humans, especially in regards to anhedonia, has not yet been developed.

The role of the gonadal hormones in relation to animal models of depression also demonstrate inconsistent results. Kennett et al. [28] reported that gonadectomy has no effect on behavioral changes following chronic stress exposure. However, Bernardi et al. [6,7] report that both ovariectomy and orchidectomy decrease struggling times, as tested by the tail-suspension test. These decreases in struggling times are attenuated by either antidepressant treatment or gonadal hormonal replacement [6,7].

Another well-described animal model of depression is induced by olfactory bulbectomy (OBX). In males, destruction of the olfactory bulbs causes a wide variety of behavioral, neurochemical and hormonal changes including increased open-field activity levels, decreased weight gain, decreased rapid eye movement sleep, poor performance on passive avoidance tasks, and poor performance on the Morris water maze [27]. Also, decreased serotonin (5-HT) and noradrenalin (NA) levels within forebrain and limbic regions [27,48,53], increased 5-HT and NA receptor binding within forebrain and limbic regions [23,25,27,48,53] and increased corticosterone (CORT) levels have all been reported following OBX [12,27]. OBX also results in alterations in immunocological functioning similar to those seen in individuals suffering from MDD [48]. A variety of these behavioral, neurochemical and hormonal changes following OBX are similar to the changes observed during MDD. In addition, the behavioral changes following OBX are reversed only after chronic antidepressant treatment, which is similar to human MDD [27]. Therefore, the purpose of this study is to test the hypothesis that the gonadal hormone milieu of an animal affects behavioral responding following OBX. Changes in body weight, sucrose preference and open-field activity levels were examined before and 4 weeks following OBX in intact and gonadectomized (GNX) male and female rats.

1. Materials and methods

1.1. Subjects

Male and female Long–Evans hooded rats (Harlan Sprague–Dawley, Indianapolis, IN) were housed singly with food and water available ad libitum. The animals were kept on a 12/12 h light/dark cycle, lights on at 7:00 am, with behavioral testing occurring in the early part of the light phase (0900–1200 hours). Animals were housed in an AAALAC-approved animal colony room and all procedures were approved by the University of South Carolina Animal Care and Use Committee.

1.2. Handling

Twenty-four hours after arrival to the colony, all animals were handled daily by gently holding the animal for a period of 3 min. Two weeks after arrival to the colony the animals were handling-habituated daily to the procedures used for decapitation. This process included weighing, placement in the guillotine and return to the home cage. During these handling periods, body weight was measured and the estrous cycle of gonadally intact females was determined using daily vaginal smears. Intact females were randomly tested across the estrous cycle. At the time of sacrifice, visual inspection of the gonads in males and uterine weights in females were analyzed to determine the effectiveness of gonadectomy and to verify the stage of estrous in intact females. Visual inspection of the olfactory cavities was also conducted at the time of sacrifice.

1.3. Sucrose preference

Twenty-four hours following arrival to the colony, a second water bottle containing a 1% sucrose solution was added to the animals' home cages in addition to the bottle containing tap water. Both the tap water and the sucrose solution were available ad libitum throughout the length of the experiment. The bottles were weighed daily to record the amount of water and sucrose consumed, and a sucrose preference score was calculated by using the following formula: % preference=(sucrose intake/total intake) $\times$ 100.

1.4. Surgeries

One week following arrival, animals were either sham-operated or gonadectomized (GNX) under ketamine (10 mg/kg, s.c.) and halothane (3% in oxygen as needed) anesthesia. Gonads were removed through a single ventral incision. Animals were allowed 3 days to recover before open-field testing was conducted. One week following gonadectomy, animals were sham-operated or olfactory bulbectomized. Animals were anesthetized using a xylazine/ketamine combination (10 mg/kg xylazine (i.p.)/70 mg/kg of ketamine (i.p.)) and then placed in a stereotaxic apparatus. Following the scalp incision, a hole was drilled through the skull and dura mater 6 mm anterior to bregma directly on the midline, with a 5-mm dental trephine bit attached to a dental drill. The olfactory bulbs were visualized and excised using suction. Once the olfactory bulbs were removed, the cavity was filled with gel foam and the piece of skull was reattached using dental cement. Animals were treated with topical antibiotic (nitrofurazone) and the area was closed using sutures. Animals were then placed on a heating pad, allowed to regain consciousness, and given a 1 mg/kg injection of nalbuphinal (s.c.). Animals were allowed 6 days of recovery before resuming behavioral testing. Animals that did not have complete removal of the olfactory bulbs or had significant damage to the frontal cortex, as visually assessed post-sacrifice, were omitted from the data analysis. Eight groups were tested: male sham (n=8), male OBX (n=6), orchidectomized (ORCH) sham (n=6), OBX-ORCH (n=7), female sham (n=8), female OBX (n=7), ovariectomized (OVX) sham (n=6), OBX–OVX (n=7).

1.5. Apparatus and test procedure

Once a week animals were tested in an open-field apparatus constructed of black plexiglass and measuring 76 $\times$ 76 $\times$ 46 cm. The interior of the field was further divided by white lines into 25 squares measuring 15 $\times$ 15 cm. Light levels in the center of the open-field were 16 fc. The animals were placed into the center of the open-field and allowed to explore freely for 5 min. Behavior was videotaped using a video camera suspended 6 ft above the center of the maze. The video tapes were scored at a later date by an experimenter who was blind to the treatment conditions of the animals. The behaviors of interest were the number of lines crossed and fecal boli counts. A line crossing was defined as all four paws crossing over the line. Immediately after exposure to the open-field, the animals were returned to their home cages. Animals were tested once a week for a period of 6 weeks. This resulted in two pre-OBX time points that were used as baseline measures and four post-OBX time points that were considered tests.

Week 1: Sucrose preference baseline test 1
+ Open-field baseline test 1
+ GNX or sham surgery followed by 3 days recovery
Week 2: Sucrose preference baseline test 2
+ Open-field baseline test 2
+ OBX or sham surgery followed by 6 days recovery
Week 3: Post-OBX test 1
Open-field + Sucrose preference
Week 4: Post-OBX test 2
Open-field + Sucrose preference
Week 5: Post-OBX test 3
Open-field + Sucrose preference
Week 6: Post-OBX test 4
Open-field + Sucrose preference

1.6. Statistics

The influences of sex (male vs. female), gonadectomy (intact vs. gonadectomized), OBX condition (sham vs. OBX) and time (baseline, test 1, test 2, test 3, test 4) on body weight, open-field activity, and sucrose preference were compared by a mixed design measures three-way analysis of variance (ANOVA; sex, gonadectomy and OBX as the between-subject factors and time as the within-subject factor). The baseline measures used were obtained from the second week of testing (i.e., post-gonadectomy). Both the sucrose preference and body weight data were measured once a week so that the results would be comparable to previous work investigating sucrose preference and body weight, in animal models of depression [14,27,40]. The Tukey test was used as the post hoc test. A significant main effect of sex was detected during baseline open-field testing. Since this main effect of sex did not interact with any of the other variables, a change score was calculated using the formula: % change=((test_n – base-baseline)/baseline) $\times$ 100.

2. Results

2.1. Body weight

As seen in Fig. 1, body weight increased across the time points tested. This was supported by a main effect of time ($F_{4,184}$=389.9, p=0.001). A significant sex$\times$gonadectomy$\times$time interaction was detected ($F_{4,184}$=16.07, p=0.001). The Tukey post hoc test showed that this

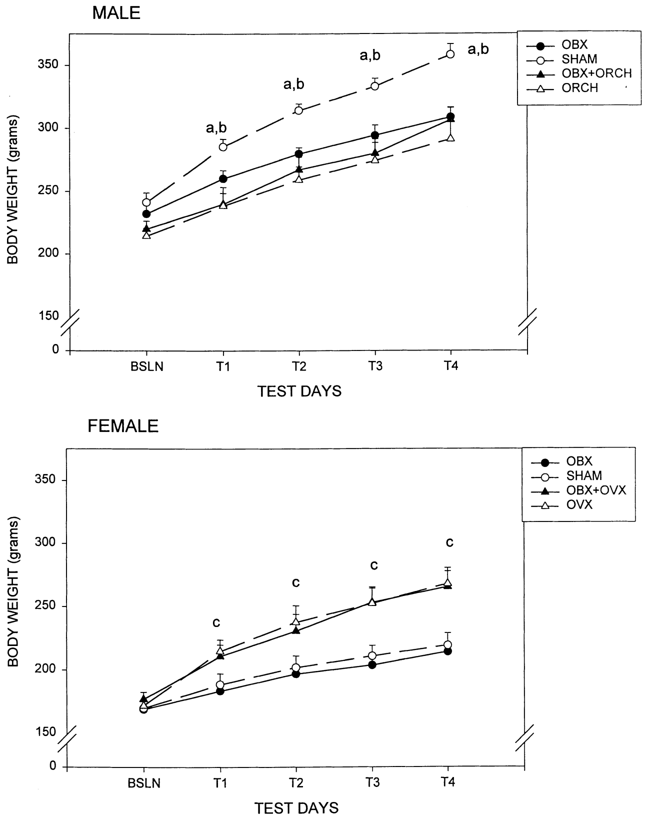

Fig. 1. Each data point represents mean body weight (± SEM) measured during the 5-week experimental period, across the different gonadal hormone conditions (intact male (n = 6–8), ORCH male (n = 6–7), intact female (n = 7–8), OVX female (n = 6–7)). Animals underwent either olfactory bulbectomy (OBX: dark symbols) or sham surgery (sham: open symbols). (a) Males (both intact and ORCH) weighed more than females (both intact and OVX) and, across the 4 weeks post-OBX ($p < 0.05$). (b) ORCH males weighed less than intact males, across the 4 weeks post-OBX ($p < 0.05$). (c) OVX females weighed more than intact females ($p < 0.05$). The baseline data presented is from the second week of testing (i.e., post-gonadectomy).

interaction resulted from the fact that intact males weighed significantly more than all other hormone groups tested across the 4 weeks post-OBX. Both ORCH males and OVX females weighed significantly more than intact females across the 4 weeks post-OBX ($p < 0.05$). In addition, ORCH males weighed significantly more than OVX females 2 and 4 weeks post-OBX ($p < 0.05$). No effect of OBX on body weight was detected. No effect of OBX on the estrous cycle was detected; this finding replicates previous work showing no effect of OBX on the estrous cycle in adult female rats [35].

2.2. Open-field

As seen in Fig. 2, gonadectomized OBX animals had greater activity levels than sham controls. One week following OBX a significant main effect of OBX ($F_{1,42}$=5.7, p=0.02) was detected. A Tukey post hoc test demonstrated that OBX animals showed significantly greater activity levels than sham controls ($p < 0.05$). In addition, 2 weeks post-OBX a significant gonadectomy × OBX interaction ($F_{1,42}$=3.9, p=0.05) was detected. A Tukey post hoc test demonstrated that OBX-gonadectomized animals showed significantly greater activity levels than the sham controls ($p < 0.05$). Analysis of the fecal boli, presented in Fig. 3, detected a significant main effect of OBX ($F_{1,35}$=4.34, p = 0.044) 1 week following OBX, and a significant gonadectomy × OBX ($F_{1,35}$=5.7, p=0.021) interaction at 4 weeks post-OBX. Tukey post hoc tests showed that at 1 week post-OBX, OBX animals had significantly greater fecal boli counts than sham control animals (p<0.05). At 4 weeks post-OBX, OBX gonadectomized animals had significantly greater fecal boli counts than sham controls (p<0.05).

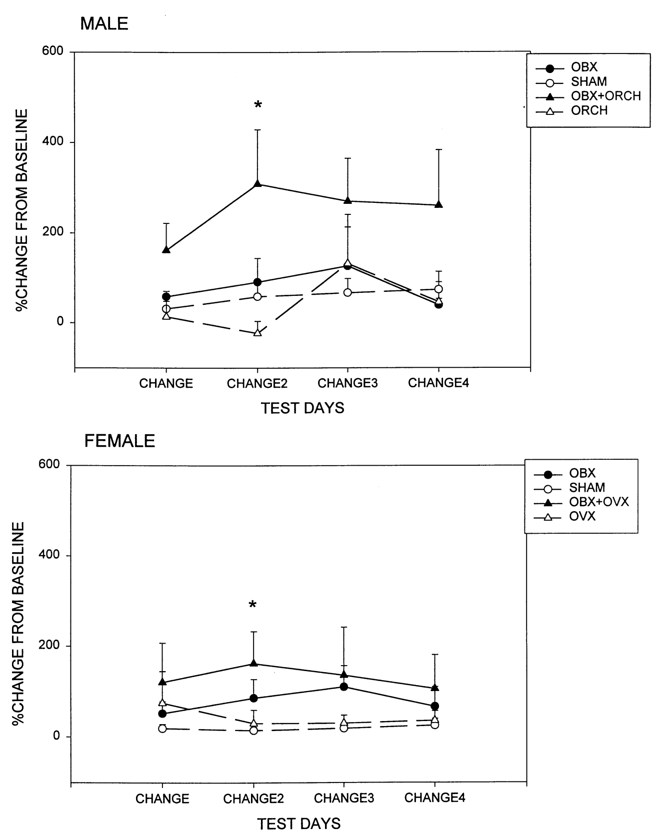

Fig. 2. Each data point represents the mean percent change from baseline scores (± SEM) measured during a 5-min exposure to the open-field apparatus during the 5-week experimental period, across the different gonadal hormone conditions (intact male (n = 6–8), ORCH male (n = 6–7), intact female (n = 7–8), OVX female (n = 6–7)). Animals underwent either olfactory bulbectomy (OBX: dark symbols) or sham surgery (sham: open symbols). * Two weeks following OBX, OBX-gonadectomized animals had significantly higher activity levels than the sham controls ($p < 0.05$). The baseline data presented is from the second week of testing (i.e., post-gonadectomy).

2.3. Sucrose preference

As seen in Fig. 4, OBX resulted in a decrease in sucrose preference levels which was most robust in female (i.e., both intact and gonadectomized) animals. A significant main effect of OBX was detected 1 week following OBX surgery ($F_{1,47}$=6.9, p=0.011). Post hoc tests demonstrated that OBX animals had significantly lower sucrose preference levels than sham animals. A significant sex × OBX interaction was detected 2 and 4 weeks following OBX, OBX. Tukey post hoc tests demonstrated that 2 weeks following OBX females (i.e., both intact and gonadectomized) had significantly lower sucrose preference levels than sham controls ($p < 0.05$). At 4 weeks post-OBX, OBX females had significantly lower sucrose levels than the other groups tested ($p < 0.05$). Analysis of total fluid consumption demonstrated no significant effect of sex, gonadectomy, or OBX (data not shown).

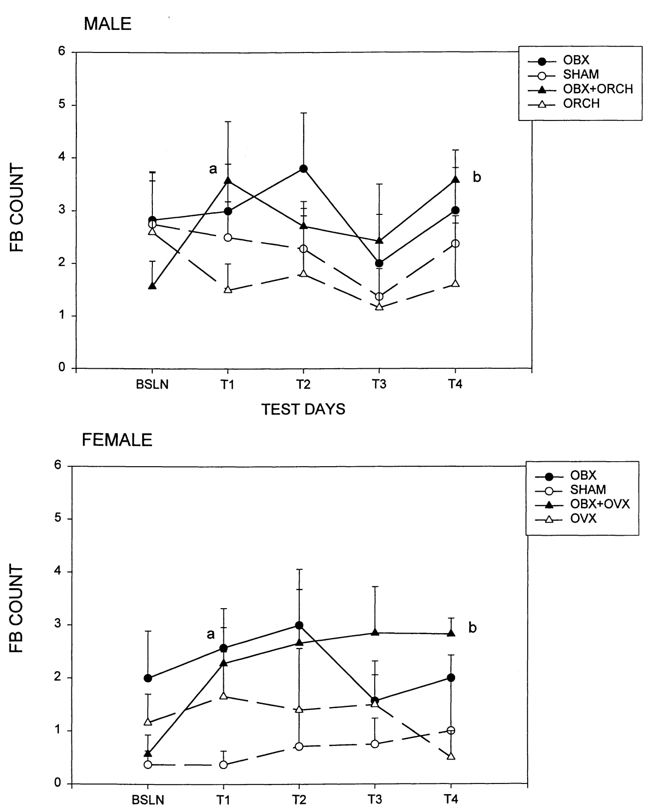

Fig. 3. Each data point represents the mean fecal boli count (±SEM) measured during a 5-min exposure to the open-field apparatus during the 5-week experimental period, across the different gonadal hormone conditions (intact male (n = 6–8), ORCH male (n = 6–7), intact female (n = 7–8), OVX female (n = 6–7)). Animals underwent either olfactory bulbectomy (OBX: dark symbols) or sham surgery (sham: open symbols). (a) At 1 week post-OBX, OBX animals had significantly higher fecal boli counts than their sham controls ($p < 0.05$). (b) At 4 weeks post-OBX, OBX-gonadectomized animals had significantly higher fecal boli counts than their sham controls ($p < 0.05$). The baseline data presented is from the second week of testing (i.e., post-gonadectomy). No effect of gender was observed.

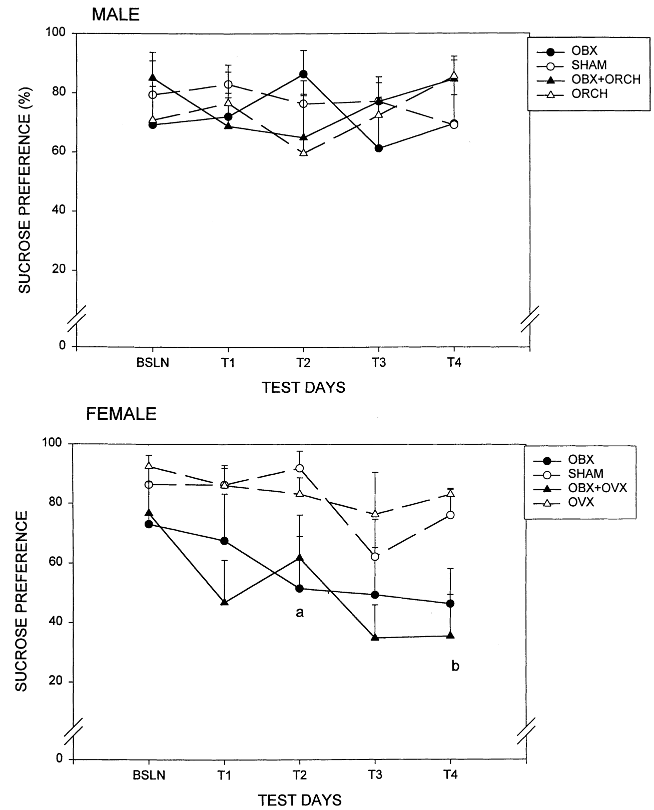

Fig. 4. Each data point represents the mean sucrose preference levels (±SEM) measured during the 5-week experimental period, across the different gonadal hormone conditions (intact male (n = 6–8), ORCH male (n = 6–7), intact female (n = 7–8), OVX female (n = 6–7)). Animals underwent either olfactory bulbectomy (OBX: dark symbols) or sham surgery (sham: open symbols). (a) Two weeks post-OBX, OBX-females (i.e., both intact and gonadectomized) had significantly lower sucrose preference levels than their sham controls (i.e., both intact and gonadectomized) ($p < 0.05$). (b) Four weeks following OBX OBX-females (i.e., both intact and gonadectomized) had significantly lower sucrose preference levels than all groups tested ($p < 0.05$). The baseline data presented is from the second week of testing (i.e., post-gonadectomy).

3. Discussion

The present study was conducted to examine the possible interaction between OBX and the rat gonadal hormone milieu, using measures of open-field activity, sucrose preference, and body weight in Long–Evans rats. The results showed that OBX-gonadectomized male and female rats exhibited greater open-field activity levels than their sham controls. Four weeks following OBX, OBX-female rats (both intact and gonadectomized) exhibited significantly lower sucrose preference levels than OBX-male rats (both intact and gonadectomized). Following OBX, no significant effect on body weight was detected.

The open-field activity data suggest that the gonadal hormone milieu of the animal alters changes in activity levels following OBX, via direct or indirect influences on either (a) general locomotor activity levels or (b) habituation rates to a novel environment. While OBX resulted in increased open-field activity in gonadectomized animals, this increase in activity was not observed in gonadally intact animals. The inability of OBX to increase open-field activity in intact males is inconsistent with what has been generally reported in the literature [25–27,48]. One explanation for our findings may be that gonadally intact and gonadectomized rats habituate differently to a novel environment; therefore, pre-exposing the rats to the open-field apparatus before OBX may have altered the increase in open-field activity levels that have previously been observed following OBX. In fact, previous research has shown that gonadally intact males that were habituated to an open-field apparatus failed to show an increase in open-field activity levels when tested following OBX surgery [52]. This explanation is also supported by the fact that in the present study, OBX-gonadectomized animals had significantly greater fecal boli counts than their sham controls, while OBX gonadally intact animals did not differ significantly from their sham controls. Fecal boli counts, measured during the open-field test, have been reported to be an indirect measure of emotionality in rats [47,55].

The fact that OBX-gonadectomized animals differed from gonadally intact animals in the open-field test, (following the removal of sex differences in baseline by the use of a percent change from baseline score), suggests a possible role for the activational effects of the gonadal hormones. Prior research has demonstrated that the activational effects of gonadal hormones play a role in mediating open-field activity levels. OVX-females show significantly lower activity levels then gonadally intact females [33], although this is not a universal finding (see Ref. [4] for references). ORCH males, however, show no locomotor changes compared to their gonadally intact controls [4,33]; this suggests estrogen may be particularly important for the greater activity levels observed in females, compared to males, when tested in the open-field test. Administration of estradiol and testosterone restored activity levels of OVX females to that of control females, whereas dihydrotesterone (DHT; a non-aromatizable form of testosterone) was ineffective [33]. ORCH males showed no changes in activity levels following treatment with either estradiol, testosterone, or DHT [33].

In the present study, OBX-females (both intact and gonadectomized) appeared to have lower sucrose preference levels than sham controls and OBX-male animals (both intact and gonadectomized), with this difference reaching significance 4 weeks post-OBX. One possible explanation for this finding is that OBX may result in differential changes in caloric intake or hydration depending upon the gonadal hormone milieu of the animal. This explanation seems unlikely for a variety of reasons. First, sucrose preference was chosen as the measure of anhedonia since this test has been used reliably with the chronic mild stress animal model of depression [14,41,57,59]. Chronic mild stress resulted in decreases in sucrose intake, saccharin intake, as well as a decrease in sucrose preference without altering total fluid intake. These findings suggest that the decrease in sucrose intake following chronic stress does not appear to be due to changes in caloric intake or hydration. Second, previous research demonstrated that gonadally intact female Long–Evans rats show no change in food or water intake following OBX [15]. Finally, in the present study, total fluid intake was unaffected by gender, OBX, or gonadectomy. It is also unlikely that the effects of OBX on sucrose preference were due to OBX-induced anosmia, since the effects of OBX on sucrose preference were gender and time specific, with female rats exhibiting a significant decrease in sucrose preference 4 weeks post-OBX. Moreover, prior research has demonstrated that OBX does not alter consumption of a bitter quinine solution compared to sham controls [11].

Previous research, has suggested that the decrement in sucrose consumption observed following exposure to chronic mild stress may be due to the decrease in body weight that is also observed following chronic mild stress [16]. In the present study, OBX-female rats (both intact and OVX) had lower sucrose preference levels as well as lower body weights then male rats. However, it is unlikely that the lower body weight in female rats, compared to male rats, affected sucrose preference. First, sham-females had sucrose preference levels that were not significantly different from males (both OBX and shams), even though female rats weighed significantly less then male rats. Secondly, female OBX rats had lower sucrose preference levels then their sham controls, but no significant differences in body weight between sham and OBX-females were observed.

While possible changes in caloric intake and/or hydration following OBX cannot be excluded, the most parsimonious explanation for the present findings is that the OBX model reveals a sexually dimorphic change in an anhedonic state. These findings further suggest that the gonadal hormones may have an organizational influence in modulating sucrose preference levels following OBX, in that both intact and gonadectomized female rats exhibited lower sucrose preference levels for a longer time period than intact and gonadectomized male rats.

While the gonadal hormone milieu of the animal also modulated body-weight changes, no effect of OBX was detected. OBX did not appear to affect body weight in females (both intact and OVX) or ORCH males, however, OBX gonadally intact males did have lower body weights than their sham controls, although this difference was not significant. This finding is similar to previous work showing that male rats exhibit a significant, but transient (i.e., 1 to 4 weeks post-OBX), decrease in body weight after OBX [27,53], while female rats demonstrate no decrease in body weight [15].

The present results also extend the findings on the effects of OBX on body weight to gonadectomized males and females. In the present study, OVX resulted in a significant increase in body weight compared to gonadally intact females. This finding supports previous research that demonstrated estrogen's ability to inhibit body weight [4,54]. While OBX has been reported to increase reactivity to estrogen in OVX females, no interaction between OBX and body weight was observed in females (i.e., both intact and gonadectomized). Further studies will be needed to assess the role of gonadal hormones in modulating body weight following OBX.

Alterations in central 5-HT and dopamine activity may be involved in the changes seen in the open field and sucrose preference following OBX. The increase in open-field activity levels following OBX may be due to decreased serotonergic activity. In fact, it has been reported that the majority of the behavioral changes observed following OBX may result from deficits in central serotonergic activity [37,53]. Specific serotonergic lesions produced by the administration of 5,6-dihydroxytryptamine, a specific 5-HT neurotoxin, into the olfactory bulb has been reported to induce the complete behavioral syndrome that is normally observed following OBX [53]. In contrast, selective noradrenergic lesions reproduce some, but not all, of the behavioral changes that are normally observed following OBX (see Ref. [53]). Furthermore, electrolytic lesions of the medial raphe nucleus has been reported to increase open-field behavior in rats (see Ref. [17]). The serotonergic system of the rat has been reported to be sensitive to the gonadal hormone milieu of the animal [46]. It is generally reported that female rats have greater central levels of 5-HT than male rats [46]. Interestingly, ORCH decreased central 5-HT levels compared to sham controls [8]. This finding supports the results of the present study, in that ORCH males had greater activity levels than sham controls following OBX, which may be due to lowered 5-HT levels in the ORCH animals following both ORCH and OBX; however, future testing will need to be conducted to determine the validity of this possibility.

Alterations in midbrain dopamine activity may play a role in the anhedonia observed following OBX. Mesolimbic dopaminergic activity has been reported to be important for mediating the rewarding effects of drugs of abuse [1,32,49]. Following OBX, a decrease in midbrain dopamine turnover has been reported [24]. Furthermore, OBX has been reported to block cocaine-induced conditioned place preference, which has been proposed to be mediated by mesolimbic dopamine activity [13]. The dopaminergic system has also been reported to be sensitive to the gonadal hormone milieu of the animal [5]. Male rats have greater levels of striatal DA release than females [5]. In addition, female rats have been shown to exhibit greater levels of cocaine self-administration than male rats [45], and this behavior is believed to be mediated by mesolimbic dopamine activity [1,32,49].

Serotonin may also play a role in mediating the anhedonia observed following OBX. While it is generally believed that the 5-HT system may have an inhibitory role in mediating the rewarding effects of drugs of abuse [3], prior research has demonstrated that specific serotonergic lesions induced by 5,7-dihydroxytryptamine into the nucleus accumbens blocked morphine-conditioned place preference [50]. Furthermore, the anhedonia following chronic mild stress is reversed by WAY800135, a specific serotonin 1A antagonist [44]. The results of these studies suggest that the increase in open-field activity and anhedonia observed following OBX may be due to a decreased central serotonergic and dopaminergic activity.

Another mechanism through which gonadal hormones may modulate behavioral responding following OBX is by alteration of the hypothalamic-pituitary-adrenal (HPA) axis. Female rats have greater stress-induced CORT levels than male rats, and this gender dimorphism is removed following adult OVX [31,51]. Previous research has reported that OBX animals have greater CORT levels than sham controls, although this is not a universal finding [10,12,27,48,53]. Previous research has demonstrated an interaction between CORT and 5-HT functioning. Chronic treatment with physiological levels of CORT that mimic stress CORT levels inhibit postsynaptic 5-HT functioning. Furthermore, following chronic restraint stress, female rats show less 5-HT post-synaptic activity compared to male rats. This sexual dimorphism is blocked when the female's CORT levels are lowered to the levels of stressed males by metyrapone administration [19].

In summary, the results of the present study suggest that the organizational and activational effects of the gonadal hormones may be involved in changes in open-field activity, sucrose preference and body weight following OBX. The activational effects of the gonadal hormones may (a) offer some protection against the activity-enhancing effects that are observed following OBX or (b) play a role in the habituation to a novel environment. In addition, following OBX the organizational effects of the gonadal hormones may result in female rats exhibiting a more pronounced anhedonic state than males, as measured by decreased sucrose preference levels. Gonadal hormones may also exert their effects by modulating changes in neurochemical systems and/or HPA-axis functioning differently in male and female rats following OBX. Future studies will need to be conducted to determine the interaction between the gonadal hormones and neurotransmitter systems as well as HPA-axis functioning in relation to the behavioral changes associated with OBX.

The anhedonic component is very important when developing an animal model of depression, because the two major characteristics for a diagnosis of MDD are depressed mood and persistent anhedonic state [2,14,58]. With this in mind, the present model may provide an appropriate method for studying putative biological mechanisms of gender differences in major depressive disorder. Future studies will need to be conducted to better understand the relationship between the gonadal hormones and the neurochemical changes following OBX in explaining the behavioral changes observed in the present study.

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