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Sex-Dependent Antipsychotic Capacity of 17β-Estradiol in the Latent Inhibition Model: A Typical Antipsychotic Drug in Both Sexes, Atypical Antipsychotic Drug in Males

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The estrogen hypothesis of schizophrenia suggests that estrogen is a natural neuroprotector in women and that exogenous estrogen may have antipsychotic potential, but results of clinical studies have been inconsistent. We have recently shown using the latent inhibition (LI) model of schizophrenia that 17β-estradiol exerts antipsychotic activity in ovariectomized (OVX) rats. The present study sought to extend the characterization of the antipsychotic action of 17β-estradiol (10, 50 and 150 μg/kg) by testing its capacity to reverse amphetamine- and MK-801-induced LI aberrations in gonadally intact female and male rats. No-drug controls of both sexes showed LI, ie, reduced efficacy of a previously non-reinforced stimulus to gain behavioral control when paired with reinforcement, if conditioned with two but not five tone-shock pairings. In both sexes, amphetamine (1 mg/kg) and MK-801 (50 μg/kg) produced disruption (under weak conditioning) and persistence (under strong conditioning) of LI, modeling positive and negative/cognitive symptoms, respectively. 17β-estradiol at 50 and 150 μg/kg potentiated LI under strong conditioning and reversed amphetamine-induced LI disruption in both males and females, mimicking the action of typical and atypical antipsychotic drugs (APDs) in the LI model. 17β-estradiol also reversed MK-induced persistent LI, an effect mimicking atypical APDs and NMDA receptor enhancers, but this effect was observed in males and OVX females but not in intact females. These findings indicate that in the LI model, 17β-estradiol exerts a clear-cut antipsychotic activity in both sexes and, remarkably, is more efficacious in males and OVX females where it also exerts activity considered predictive of anti-negative/cognitive symptoms.

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INTRODUCTION

Epidemiological and life cycle studies have indicated that women with schizophrenia have a more favorable illness course than men during reproductive years, characterized by later onset of symptoms, lower symptom severity and better response to antipsychotic drugs (APDs); however, the menopausal period is associated with increased symptom severity and reduced sensitivity to treatment (Hafner, 2003; Hafner *et al*, 1989; Kulkarni, 2009; Kulkarni *et al*, 1996, 2008b; Riecher-Rossler and de Geyter, 2007; Seeman and Lang, 1990). This has led to the suggestion that exogenous estrogen may have therapeutic potential in women with schizophrenia, but results of clinical studies have been inconclusive (Akhondzadeh *et al*, 2003; Korhonen *et al*, 1995; Kulkarni *et al*, 2008a; Kulkarni *et al*, 1996; Kulkarni *et al*, 2008b; Kulkarni *et al*, 2001; Mortimer, 2007; Riecher-Rossler, 2002; Riecher-Rossler and de Geyter, 2007; Riecher-Rossler and Hafner, 1993; Riecher-Rossler *et al*, 1994). Interestingly, estradiol improved psychotic symptoms also in schizophrenic men (Kulkarni, 2009).

Support for the antipsychotic action of estrogen can be derived from animal studies showing that 17β-estradiol blocks/reduces the behavioral response to the pro-psychotic dopaminergic drugs, amphetamine and cocaine, (Becker and Beer, 1986; Becker and Rudick, 1999; Bedard *et al*, 1983; Bedard *et al*, 1978; Gordon and Diamond, 1981; Hafner *et al*, 1991; Naik *et al*, 1978; Segarra *et al*, 2009) and potentiates APD-induced catalepsy (Bedard *et al*, 1982; Chiodo *et al*, 1979; De Ryck *et al*, 1982; Di Paolo *et al*, 1979; Nicoletti *et al*, 1983; Palermo-Neto and Dorce, 1990). 17β-estradiol has been also shown to improve cognitive performance in humans and rodents of both sexes (Barnes *et al*, 2006; Daniel and Bohacek, 2010; Frick, 2009; Gogos *et al*, 2006; Kitamura *et al*, 2009; Packard *et al*, 1996; Sherwin *et al*, 2009; Soderstrom *et al*, 2009). Such action would be beneficial in schizophrenia which is characterized by profound cognitive deficits (Barch and Carter, 2008).

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To date, the study of the antipsychotic capacity of estrogen in formal animal models of schizophrenia has been limited (Chavez *et al*, 2009; Gogos *et al*, 2010; Hafner *et al*, 1991; Sutcliffe *et al*, 2008; Van den Buuse and Eikelis, 2001).

We have recently provided evidence for antipsychotic properties of estrogen using the latent inhibition (LI) model of schizophrenia (Arad and Weiner 2008, 2009, 2010). LI is one of the best-documented cross-species manifestations of attentional selectivity in associative learning (Lubow, 1989; Mackintosh, 1975), whereby repeated non-reinforced pre-exposure to the to-be-conditioned stimulus interferes with its subsequent efficacy to generate conditioned response. Amphetamine-induced disruption of LI is considered to model the inability to ignore irrelevant stimuli associated with positive symptoms of schizophrenia (Weiner, 2003). Conversely, rodents treated with NMDA receptor antagonists such as MK-801 or PCP that produce and exacerbate negative symptoms and cognitive deficits (Javitt and Zukin, 1991; Krystal *et al*, 2003), persist in expressing LI under conditions that prevent/reduce LI expression in untreated rats (Gaisler-Salomon *et al*, 2008; Gaisler-Salomon and Weiner, 2003; Lipina *et al*, 2005; Palsson *et al*, 2005). Thus, persistent LI induced by MK-801 has been suggested to model attentional perseveration associated with negative/cognitive symptoms of schizophrenia (Gaisler-Salomon *et al*, 2008; Weiner and Arad 2009). Both typical and atypical APDs restore LI in amphetamine-treated rats, and this is paralleled by their capacity to restore LI in naive animals under conditions that do not yield robust LI in no-drug controls (Weiner and Arad 2009). MK-801-induced persistent LI is reversed by atypical but not typical APDs, as well as by glycinergic NMDA enhancers, consistent with the differential efficacy of these treatments in improving negative/cognitive symptoms (Harvey *et al*, 2005; Heresco-Levy *et al*, 2005).

In support of the antipsychotic action of 17β-estradiol, we (Arad and Weiner 2008, 2009, 2010) showed that (a) disruption and restoration of LI are associated with low and high levels of endogenous estrogen; (b) behaviorally inactive dose of 17β-estradiol restores the capacity of ineffective APD doses to block amphetamine-induced LI disruption; and (c) 17β-estradiol given on its own reverses amphetamine-induced LI disruption in ovariectomized (OVX) as well as in sham-operated female rats. Our aim here was to extend the characterization of the antipsychotic action of 17β-estradiol by testing its capacity to reverse amphetamine-induced LI disruption and MK-801-induced LI persistence in gonadally intact female and male rats. In addition, we tested whether 17β-estradiol on its own potentiates LI.

MATERIALS AND METHODS

Animals

Female and male Wistar rats, 3-month old, bred in our laboratory were housed by sex, four per cage under reversed cycle lighting (lights on: 07 : 00–19 : 00 h) with ad lib access to food and water except for the duration of the LI experiments. All experimental protocols conformed to the guidelines of the Institutional Animal Care and Use Committee of Tel-Aviv University, Israel, and to the guidelines of the NIH (animal welfare assurance number A5010–01, expires on 30 September 2011). All efforts were made to minimize the number of animals used and their suffering.

Ovariectomy (OVX)

Female rats were bilaterally ovariectomized under isoflurane (Nichols Piramal, UK) anesthesia. After shaving the abdominal area, a midline incision was made through the skin and muscle layer. Fallopian tubes were ligated by a nylon thread, after which the ovaries were carefully removed. Sutures of muscle layer and skin were removed 10 days later. Rats were allowed additional 3 weeks of recovery after removal of the sutures before the beginning of water restriction (see below). Within the 3-week recovery period, about a week after removal of sutures, vaginal smears were collected daily in the morning for 8 days in sham and OVX rats, to confirm presence or discontinuation estrous cycle, respectively. Phases of the estrous cycle were determined by the morphology of cells in the vaginal smear under a light microscope (Marcondes *et al*, 2002). Sham-operated female and male controls (in experiment 4) underwent an identical surgical procedure without ovaries' removal. Sham females with two regular 4-day cycles in succession and OVX rats without estrous cycle were used for behavioral testing.

Apparatus and Procedure

LI was measured in a thirst-motivated conditioned emotional response procedure in Campden Instruments rodent test chambers with a retractable bottle, each enclosed in a ventilated sound-attenuating chest. When the bottle was not present, the hole was covered with a metal lid. The pre-exposed (PE) to-be-conditioned stimulus was a 10 s, 80 dB, 2.8 kHz tone produced by a Sonalert module. Shock was supplied through the floor by a Campden Instruments shock generator and shock scrambler set at 0.5 mA intensity and 1 s duration. Licks were detected by a Campden Instruments drinkometer. Equipment programming and data recording were controlled by the computer.

At 10 days before the beginning of the LI procedure, rats were put on a 23 h water restriction schedule and handled for about 2 min daily for 5 days. On the next 5 days, rats were trained to drink in the experimental chamber for 15–20 min/day. Water in the test apparatus was given in addition to the daily ration of 1 h given in the home cages. The LI procedure was conducted on days 11–14 and consisted of four stages given 24 h apart:

Pre-exposure. With the bottle removed, the PE rats received 40 tone presentations with an inter-stimulus interval of 40 s. The non-pre-exposed (NPE) rats were confined to the chamber for an identical period of time without receiving the tone.

Conditioning. With the bottle removed, rats received two (weak conditioning) or five (strong conditioning) tone-shock pairings given 5 min apart. Shock immediately followed tone termination. Weak conditioning produces LI in non-treated controls and thus allows the demonstration of treatment-induced LI disruption. This level of conditioning was therefore used with amphetamine (experiments 5 and 6).

Conversely, strong conditioning prevents LI in non-treated controls and thus allows the demonstration of treatment-induced abnormally persistent LI. This level of conditioning was used with MK-801 (experiments 7, 8, and 9). Both levels were used with 17β-estradiol administration on its own (experiments 1, 2, 3, and 4) to determine if 17β-estradiol disrupts and/or potentiates LI.

Rebaseline. Rats were given a 15 min drinking session as in initial training.

Test. Each rat was placed in the chamber and allowed to drink from the bottle. When the rat completed 75 licks the tone was presented for 5 min. The following times were recorded: Time to first lick, time to complete 1–50 licks, time to complete 51–75 licks (before the tone onset), and time to complete 76–100 licks (after the tone onset). Times to complete 76–100 licks were submitted to logarithmic transformation to allow parametric ANOVA. Longer log times indicate stronger suppression of drinking. LI is defined as significantly shorter log times to complete 76–100 licks of the PE compared with NPE rats.

Drug and Hormone Administration

Amphetamine, MK-801, and 17β-estradiol were administered in a volume of 1 ml/kg. Amphetamine (Sigma, Switzerland) was dissolved in saline and administered i.p. at a dose of 1 mg/kg. MK-801 (dizocilpine; Merck Research Laboratories, USA) was dissolved in saline and administered i.p. at a dose of 50 μg/kg. These doses are routinely used in our LI studies (Arad and Weiner 2010; Barak *et al*, 2009; Black *et al*, 2008). 17β-estradiol (Sigma, Israel) was dissolved in corn oil and administered s.c. at doses of 10, 50, and 150 μg/kg. These doses were used in our previous studies; they mimic low hormonal levels in female rats as seen during metestrus–diestrus, high levels as seen during proestrus–estrus, and very high levels as seen during the last trimester of pregnancy (Arad and Weiner, 2009, 2010; Galea *et al*, 2001; Gibbs *et al*, 1998; Nofrey *et al*, 2008; Van den Buuse and Eikelis, 2001; Walf and Frye, 2009). All compounds were administered before pre-exposure and conditioning sessions at 30 min interval for amphetamine and MK-801, and 120 min for 17β-estradiol. No-drug controls received the corresponding vehicles. In all experiments, rebaseline and test sessions were conducted in a drug-free state.

Experimental Design

Experiments 1 and 2. Tested the effects of 17β-estradiol on LI under weak conditioning (forty pre-exposures and two conditioning trials) in gonadally intact female and male rats. The experiments included 40 females (exp 1; n/group = 5) and 40 males (exp 2; n/group = 5) divided into eight experimental groups in a 2×4 design with main factors of pre-exposure (0, 40) and hormonal treatment (0, 10, 50, and 150 μg/kg 17β-estradiol).

Experiments 3 and 4. Tested the effects of 17β-estradiol on LI under strong conditioning (forty pre-exposures and five conditioning trials) in gonadally intact female and male rats. The experiments included 49 females (exp 3; n/group = 6–7) and 62 males (exp 4; n/group = 7–8) divided into eight experimental groups in a 2×4 design with main factors of pre-exposure (0, 40) and hormonal treatment (0, 10, 50, and 150 μg/kg 17β-estradiol).

Experiments 5 and 6. Tested the capacity of 17β-estradiol to reverse amphetamine-induced LI disruption (under weak conditioning) in gonadally intact female and male rats. The experiments included 92 females (exp 5; n/group = 7–8) and 94 males (exp 6; n/group = 7–8) divided into twelve experimental groups in a $2 \times 2 \times 3$ design with main factors of pre-exposure (0, 40), pro-psychotic treatment (0 and 1 mg/kg amphetamine), and hormonal treatment (0, 50, and 150 μg/kg 17β-estradiol).

Experiments 7, 8, and 9. Tested the capacity of 17β-estradiol to reverse MK-801-induced LI persistence (under strong conditioning) in gonadally intact female and male rats as well as in OVX female rats. The experiments included 73 intact females (exp 7; n/group = 6–7), 85 intact males (exp 8; n/group = 7–8), and 73 OVX females (exp 9; n/group = 6–7) divided into twelve experimental groups in a $2 \times 2 \times 3$ design with main factors of pre-exposure (0, 40), pro-schizophrenia treatment (0 and 50 μg/kg MK-801), and hormonal treatment (0, 50, and 150 μg/kg 17β-estradiol).

Statistical Analysis

Time to complete 51–75 licks (before tone onset) and mean log times to complete 76–100 licks (after tone onset) were analyzed using two-way ANOVAs with main factors of pre-exposure and hormonal treatment (experiments 1, 2, 3, and 4) and three-way ANOVAs with main factors of pre-exposure, treatment, and hormonal treatment (experiments 5, 6, 7, 8, and 9). In cases of significant interactions involving the factor of pre-exposure, LSD *post-hoc* comparisons were used to assess the difference between the PE and NPE groups within each treatment condition.

It is important to mention that in all experiments, females and males were run in different systems to avoid potential interference. Thus, we could not analyze their data in the same ANOVA. However, given that we had four main aims in this study, we introduced the results as well as the figures under each aim as different parts of the same experiment to allow a visual comparison between the females' and males' data.

RESULTS

There were no differences between the experimental groups in the time required to complete 51–75 licks (A period; all p's > 0.05) in any of the experiments (overall mean A periods were 6.65, 7.54, 10.25, 9.57, 7.13, 6.92, 7.02, 6.31, and 9.44 for experiments 1, 2, 3, 4, 5, 6, 7, 8, and 9, respectively).

Experiments 1 and 2: Effects of 17β-Estradiol on LI Under Weak Conditioning (40 Pre-Exposures and Two Conditioning Trials) in Female and Male Rats

The two parts of Figure 1, a (exp 1) and b (exp 2), present the mean log times to complete 76–100 licks (after tone

onset) of the PE and NPE female (Figure 1a) and male (Figure 1b) rats treated with oil, 10, 50, or 150 μg/kg 17β-estradiol. As can be seen in both parts of Figure 1, oil-treated female and male rats showed LI, whereas rats treated with 10 μg/kg of 17β-estradiol did not show LI. The higher doses of 17β-estradiol (50 and 150 μg/kg) spared LI. ANOVAs yielded significant main effects of pre-exposure (females: $F_{(1,32)}=55.9$, $p<0.0001$; males: $F_{(1,32)}=45.4$, $p<0.0001$) and hormonal treatment (females: $F_{(3,32)}=3.0$, $p<0.05$; males: $F_{(3,32)}=3.5$, $p<0.05$), as well as a significant pre-exposure × hormonal treatment interaction (females: $F_{(3,32)}=8.5$, $p<0.0005$; males: $F_{(3,32)}=8.6$, $p<0.0005$). *Post-hoc* comparisons for each of the analyses confirmed the presence of LI in female and male rats given oil, 50, or 150 μg/kg 17β-estradiol (p's <0.01), but not after 10 μg/kg 17β-estradiol.

Experiments 3 and 4: Effects of 17β-Estradiol on LI under strong Conditioning (40 Pre-Exposures and five Conditioning Trials) in Female and Male Rats

The two parts of Figure 2, a (exp 3) and b (exp 4), present the mean log times to complete 76–100 licks (after tone onset) of the PE and NPE female (Figure 2a) and male (Figure 2b) rats treated with oil, 10, 50, and 150 μg/kg 17β-estradiol. As can be seen, oil-treated female and male rats did not show LI as expected under strong conditioning. 10 μg/kg of 17β-estradiol had no effect on LI, whereas female and male rats treated with 50 and 150 μg/kg of 17β-estradiol persisted in showing LI. ANOVAs yielded a significant main effect of pre-exposure (females: $F_{(1,41)}=8.1$, $p<0.01$; males: $F_{(1,54)}=18.7$, $p<0.0001$), as well as a significant pre-exposure × hormonal treatment interaction (females: $F_{(3,41)}=5.7$, $p<0.005$; males: $F_{(3,54)}=4.2$, $p<0.01$). *Post-hoc* comparisons for each of the analyses confirmed the presence of LI in female and male rats given 50 or 150 μg/kg 17β-estradiol (p's <0.01), but not in other conditions.

Experiments 5 and 6: Effects of 17β-Estradiol on Amphetamine-Induced LI Disruption Under Weak Conditioning (40 Pre-Exposures and two Conditioning Trials) in Female and Male Rats

The two parts of Figure 3, a (exp 5) and b (exp 6), present the mean log times to complete 76–100 licks (after tone onset) of the PE and NPE female (Figure 3a) and male (Figure 3b) rats treated with saline or amphetamine (1 mg/kg), and pre-treated with oil, 50, or 150 μg/kg 17β-estradiol. As can be seen, under weak conditioning, vehicle-injected female and male rats exhibited LI, whereas amphetamine-injected female and male rats did not exhibit LI. Both doses of 17β-estradiol reversed amphetamine-induced LI disruption in females and males. On their own, both doses of 17β-estradiol spared LI in females and males. ANOVA for females yielded significant main effects of pre-exposure ($F_{(1,80)}=98.9$, $p<0.0001$) and treatment ($F_{(1,80)}=7.2$, $p<0.01$), as well as a significant pre-exposure × treatment × hormonal treatment interaction ($F_{(2,80)}=3.2$, $p<0.05$). ANOVA for males yielded a significant main effect of pre-exposure ($F_{(1,82)}=55.9$, $p<0.0001$), as well as a significant pre-exposure × treatment × hormonal treatment interaction ($F_{(2,82)}=7.4$, $p<0.005$). *Post-hoc* comparisons for each of the analyses confirmed the presence of LI in saline-injected female and male rats pre-treated with 0, 50, or 150 μg/kg 17β-estradiol and in amphetamine-injected female and male rats pre-treated with 50 or 150 μg/kg 17β-estradiol (p's <0.01), but not in the other conditions.

Experiments 7, 8, and 9: Effects of 17β-Estradiol on MK-801-induced LI Persistence Under Strong Conditioning (40 Pre-Exposures and five Conditioning Trials) in Female, Male, and OVX Female Rats

The three parts of Figure 4, a (exp 7), b (exp 8), and c (exp 9), present the mean log times to complete 76–100 licks

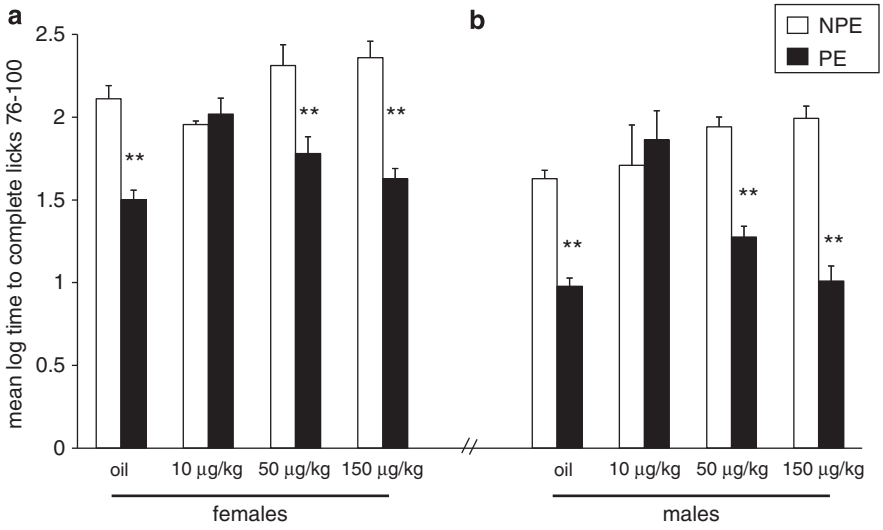

Figure 1 Effects of 17β-estradiol on LI under weak conditioning (forty pre-exposures and two conditioning trials) in female and male rats. Mean (±SEM) log time to complete 76–100 licks (after the tone onset) of the PE and the NPE female (a) and male (b) rats administered with 0, 10, 50, or 150 μg/kg of 17β-estradiol (oil, 10, 50, or 150 μg/kg, respectively). Asterisks indicate a significant difference between the PE and NPE groups, namely, presence of LI (**$p<0.01$).

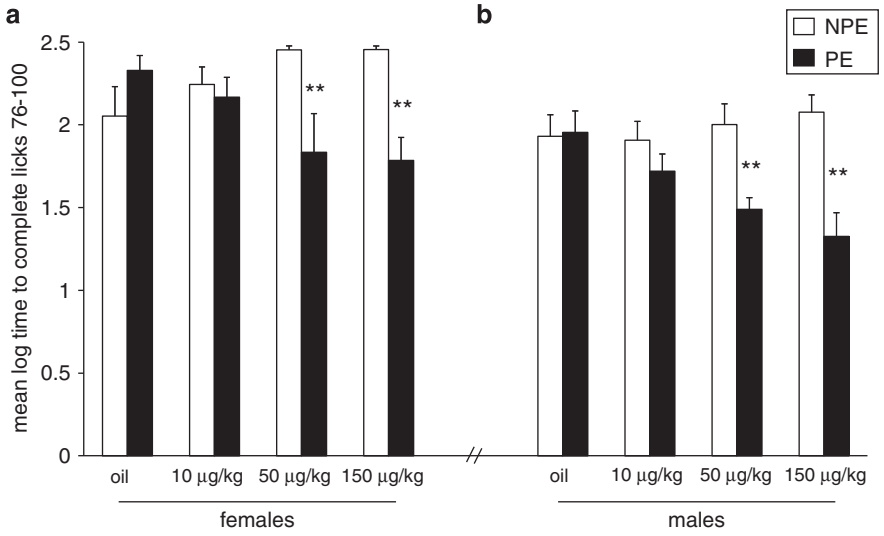

Figure 2 Effects of 17β-estradiol on LI under strong conditioning (forty pre-exposures and five conditioning trials) in female and male rats. Mean ($\pm$SEM) log times to complete 76–100 licks (after the tone onset) of the PE and the NPE female (a) and male (b) rats administered with 0, 10, 50, or 150 μg/kg of 17β-estradiol (oil, 10, 50, or 150 μg/kg, respectively). Asterisks indicate a significant difference between the PE and NPE groups, namely, presence of LI (**$p<0.01$).

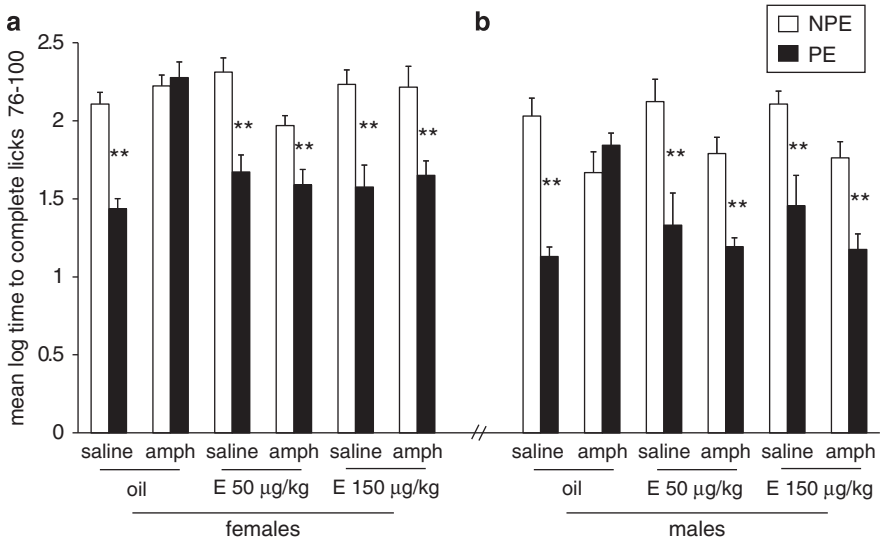

Figure 3 Effects of 17β-estradiol on amphetamine (amph)-induced LI disruption under weak conditioning (forty pre-exposures and two conditioning trials) in female and male rats. Mean ($\pm$SEM) log times to complete 76–100 licks (after the tone onset) of the PE and the NPE saline- or amph-injected female (a) and male (b) rats, administered with 0, 50, or 150 μg/kg of 17β-estradiol (oil, E 50 μg/kg, or E 150 μg/kg, respectively). Asterisks indicate a significant difference between the PE and NPE groups, namely, presence of LI (**$p<0.01$).

(after tone onset) of the PE and NPE female (Figure 4a), male (Figure 4b), and OVX female (Figure 4c) rats treated with saline or MK-801 (50 μg/kg), and pre-treated with oil, 50, or 150 μg/kg 17β-estradiol. As expected with strong conditioning, LI was absent in vehicle-injected rats, whereas MK-801-injected rats persisted in showing LI. In MK-801-treated female rats, both doses of 17β-estradiol were without any effect, whereas in males and OVX females, both doses reversed MK-801-induced LI persistence. On its own, 17β-estradiol led to LI in gonadally intact female and male rats, but not in OVX female rats. ANOVA for female rats yielded significant main effects of pre-exposure ($F_{(1,61)}=58.0$, $p<0.0001$), treatment ($F_{(1,61)}=17.7$, $p<0.0001$), and hormonal treatment ($F_{(2,61)}=5.6$, $p<0.01$), as well as a significant pre-exposure $\times$ treatment $\times$ hormonal treatment interaction ($F_{(2,61)}=3.4$, $p<0.05$). ANOVA for male rats yielded a significant main effect of pre-exposure ($F_{(1,73)}=33.2$, $p<0.0001$), as well as a significant pre-exposure $\times$ treatment $\times$ hormonal treatment interaction ($F_{(2,73)}=11.6$, $p<0.0001$). ANOVA for OVX female rats yielded significant main effects of pre-exposure ($F_{(1,61)}=6.0$, $p<0.05$) and treatment ($F_{(1,61)}=27.7$, $p<0.0001$), as well as a near significant pre-exposure $\times$ treatment $\times$ hormonal treatment interaction ($F_{(2,61)}=2.97$, $p=0.059$). *Post-hoc* comparisons for each of the analyses confirmed the presence of LI in saline-injected female and male rats given 50 or 150 μg/kg 17β-estradiol, in MK-801-injected female rats given 0, 50, or 150 μg/kg 17β-estradiol, and in MK-801-injected rats

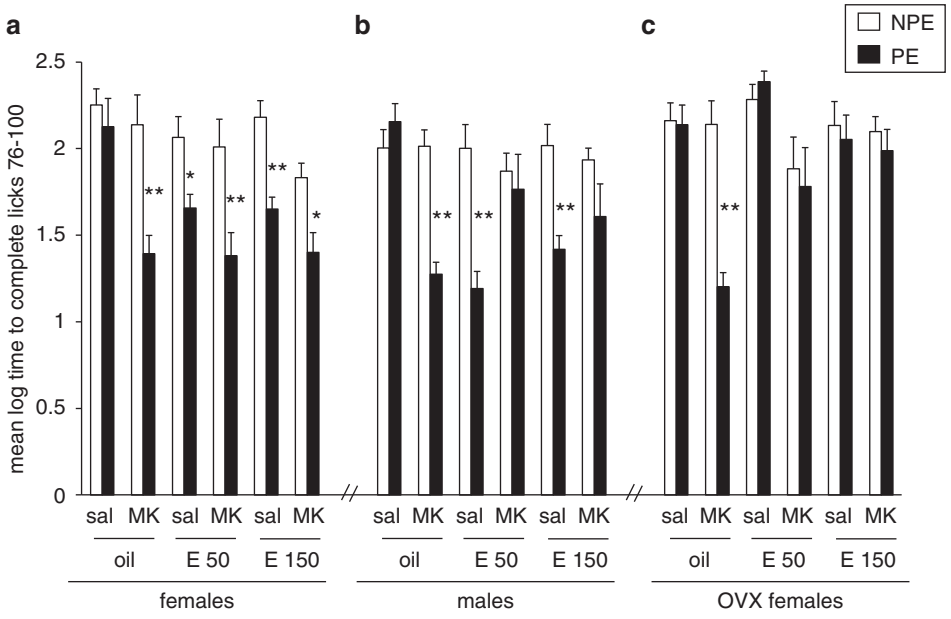

Figure 4 Effects of 17β-estradiol on MK-801 (MK)-induced LI persistence under strong conditioning (forty pre-exposures and five conditioning trials) in female, male, and OVX female rats. Mean (±SEM) log times to complete 76–100 licks (after the tone onset) of the PE and the NPE saline (sal)- or MK-injected female (a), male (b), and OVX female (c) rats, administered with 0, 50, or 150 μg/kg of 17β-estradiol (oil, E 50, or E 150, respectively). Asterisks indicate a significant difference between the PE and NPE groups, namely, presence of LI (*$p<0.05$; **$p<0.01$).

given 0 μg/kg 17β-estradiol (p's<0.05), but not in the other conditions.

DISCUSSION

The present study sought to assess whether estrogen exerts an antipsychotic action, as indexed by the LI model, in gonadally intact female and male rats. Using a non-pharmacological and two acute pharmacological LI models, we showed that: (1) under conditions yielding LI in non-treated controls, 10 μg/kg 17β-estradiol disrupted LI, whereas higher doses (50 and 150 μg/kg) were without any effect in both sexes; (2) 17β-estradiol at higher doses restored LI under conditions preventing LI in non-treated controls, an effect considered predictive for activity against positive symptoms, in both sexes; (3) 17β-estradiol at higher doses reversed amphetamine-induced disruption of LI, an effect considered predictive for activity against positive symptoms, in both sexes; and (4) 17β-estradiol at higher doses reversed MK-801-induced persistent LI, an effect considered predictive for activity against negative/cognitive symptoms, in gonadally intact male and OVX rats, but not in gonadally intact female rats (see Table 1). These findings indicate that in the LI model, 17β-estradiol exerts a clear-cut antipsychotic activity in both sexes and, remarkably, is more efficacious in males and OVX females, in which it also exerts activity considered predictive of anti-negative symptoms/pro-cognitive action.

Bimodal Effect of 17β-Estradiol on LI

17β-estradiol, administered on its own, produced a dose-dependent bimodal effect on LI in both female and male rats, with the low dose disrupting LI and the two higher doses restoring LI under conditions (strong conditioning) that disrupted LI in controls.

Potentiation or facilitation of LI under conditions of weak or absent LI in controls by APDs is a widely used index of antipsychotic activity. It is produced by a wide range of typical and atypical APDs and is also seen in normal humans (Barrett *et al*, 2004; Dunn *et al*, 1993; McCartan *et al*, 2001; Shadach *et al*, 1999; Weiner, 2003; Weiner and Arad 2009; Weiner and Feldon 1987; Williams *et al*, 1996; Williams *et al*, 1997). The fact that higher doses of 17β-estradiol produced a pattern typically found for APDs suggests that at these doses, 17β-estradiol may have antipsychotic properties.

The LI-facilitating effect of 17β-estradiol was restricted to high doses as the low dose of 10 μg/kg disrupted LI in both sexes. We have previously obtained this same bimodal effect of 17β-estradiol on LI in OVX rats (Arad and Weiner, 2010) and Nofrey *et al* (2008) have also reported LI-disrupting effect of 10 μg/kg 17β-estradiol in OVX rats. The fact that 17β-estradiol produces contrasting effects on LI at low and high doses implies that estradiol acts dose-dependently on different neural substrates. One likely substrate is the dopaminergic system. APD-induced LI potentiation is mediated by blockade of DA transmission within the nucleus accumbens (NAC) at the time of conditioning (Gray *et al*, 1995a; Gray *et al*, 1997; Joseph *et al*, 2000; Warburton *et al*, 1996; Weiner 2003). Consequently, our results imply that the higher doses of 17β-estradiol, which potentiated LI, reduced mesolimbic DA function. Conversely, low dose, which disrupted LI, may have acted by increasing DA release within the NAC as does the amphetamine (Warburton *et al*, 1996). Both reduction and increase of striatal dopaminergic function by 17β-estradiol have been reported for all indices of dopaminergic activity, including receptor levels/binding, membrane

Table 1 Summary of Experimental Design and Results

	Tone-shock pairings	Sex	Pro-psychotic treatment	Doss of 17β-estradiol			
				Vehicle	10 μg/kg	50 μg/kg	150 μg/kg
Experiments 1 and 2	2	F	—	LI	No LI	LI	LI
		M	—	LI	No LI	LI	LI
Experiments 3 and 4	5	F	—	No LI	No LI	LI	LI
		M	—	No LI	No LI	LI	LI
Experiments 5 and 6	2	F	Sal	LI	—	LI	LI
			Amph	No LI	—	LI	LI
		M	Sal	LI	—	LI	LI
			Amph	No LI	—	LI	LI
Experiments 7–9	5	F	Sal	No LI	—	LI	LI
			MK	LI	—	LI	LI
		M	Sal	No LI	—	LI	LI
			MK	LI	—	No LI	No LI
		OVX (F)	Sal	No LI	—	No LI	No LI
			MK	LI	—	No LI	No LI

Abbreviations: Amph, amphetamine; F, female; LI, latent inhibition; M, male; MK, MK-801; OVX, ovariectomy; Sal, saline; —, has not been administered.

dopamine transporter levels, and release, depending on dose and treatment paradigm (Arvin *et al*, 2000; Becker, 1999; Chavez *et al*, 2010; Di Paolo, 1994; Disshon *et al*, 1998; Dluzen and Horstink, 2003; McDermott, 1993; Morissette *et al*, 2008; Morissette and Di Paolo, 1993; Peris *et al*, 1991; Shieh and Yang, 2008; Thompson and Moss, 1994; Yu *et al*, 2009; Zhou *et al*, 2002). It has been suggested that anti-dopaminergic effects are primarily exerted by high doses of estrogen or chronic administration, whereas pro-dopaminergic actions are more associated with lower levels of estrogen (Barber *et al*, 1976; Becker, 1999; Bedard *et al*, 1977; Chavez *et al*, 2010; Cyr *et al*, 2002; Di Paolo, 1994; Di Paolo *et al*, 1981; Hruska and Silbergeld, 1980; McEwen and Alves, 1999; Riddoch *et al*, 1971; Yu *et al*, 2009). Although the specific mechanisms by which 17β-estradiol exerts its dose-dependent effects on LI observed here remain to be elucidated, if both effects are indeed DA-mediated, this would imply that low 17β-estradiol doses exert a pro-psychotic action.

An alternative mechanism for the dose-dependent effect of 17β-estradiol can be derived from our finding that a similar dose-dependent bimodal effect is produced by atypical APDs, such as risperidone, which disrupts LI at low doses and potentiates LI at higher doses (Weiner *et al*, 2003). The LI disruptive effect of atypical APDs is distinct from that of amphetamine because it occurs in the pre-exposure stage and is mediated by $5HT_{2A}$ antagonism, whereas the disruptive effect of amphetamine occurs in the conditioning stage and is mediated by enhanced DA transmission. As estrogen modulates brain serotonergic activity and specifically the $5HT_{2A}$ receptors (Fink *et al*, 1998; Sumner and Fink, 1997), this could be the mechanism underlying the LI disruptive action of low 17β-estradiol, and thus reflect an atypical antipsychotic action of this hormone. Clearly it is of interest to determine whether low estrogen is pro-psychotic or antipsychotic. Testing the effects of APDs on 17β-estradiol-induced LI disruption would be one straightforward way to answer this question; In addition, these alternatives can be teased out by assessing at which stage 17β-estradiol acts to disrupt LI.

Reversal of Disrupted LI: Putative Efficacy for Positive Symptoms

Amphetamine-induced LI disruption and its reversal by both typical and atypical APDs in the male rodent is a long standing model of positive symptoms (Weiner, 2003; Weiner and Arad, 2009). Although gender differences in response to amphetamine and other psychostimulants have been widely reported (for review see Fattore *et al*, 2008), such differences are not evident in the pro-psychotic action of amphetamine in the LI model (Arad and Weiner, 2010). Disruption of LI reflects a selective attention deficit, whereby animals lose the capacity to ignore the irrelevant stimulus, and is also observed in amphetamine-treated humans and high-schizotypal humans, (Braunstein-Bercovitz *et al*, 2002; Gray *et al*, 1992b; Salgado *et al*, 2000; Swerdlow *et al*, 2003; Thornton *et al*, 1996) as well as in acutely psychotic schizophrenia patients (Baruch *et al*, 1988; Gray *et al*, 1992a; Gray *et al*, 1995b; Rascle *et al*, 2001; Swerdlow *et al*, 2005). A failure to inhibit attention to irrelevant stimuli is likely to give rise to aberrantly increased salience perception and distractibility that are associated with psychotic symptoms (Kapur *et al*, 2005; Weiner and Arad, 2009). 17β-estradiol at 50 and 150 μg/kg doses, which potentiated LI under conditions that disrupted LI in untreated gonadally intact rats (strong conditioning), also reversed amphetamine-induced LI disruption, as typically found with APDs. The present results replicate our recent finding (Arad and Weiner, 2010) that 17β-estradiol prevents amphetamine from disrupting LI in gonadally intact female rats and extends this action of 17β-estradiol to gonadally intact male rats.

Reversal of amphetamine-induced LI disruption by APDs, like APD-induced potentiation of LI, is mediated by blockade of DA transmission within the NAC at the time of conditioning (Gray *et al*, 1995a; Gray *et al*, 1997; Joseph *et al*, 2000; Warburton *et al*, 1996; Weiner, 2003). Consequently, our findings that acute high doses of 17β-estradiol blocked the effects of amphetamine as well as potentiated LI on its own support the notion that 17β-estradiol reduces mesolimbic DA function. Taken together, the efficacy of 17β-estradiol to alleviate non-pharmacologically and pharmacologically induced LI disruption is indicative of its therapeutic capacity for positive symptoms in schizophrenia.

Previous studies showed that in OVX rats, 17β-estradiol can reverse psychosis-mimicking abnormalities induced by dopamine agonists, including hyperactivity, stereotypy and circling (Becker and Beer, 1986; Becker and Rudick, 1999; Bedard *et al*, 1983; Bedard *et al*, 1978; Earley and Leonard, 1978; Euvrard *et al*, 1979; Euvrard *et al*, 1980; Gordon, 1980; Gordon and Diamond, 1981; Naik *et al*, 1978), disrupted PPI (Gogos *et al*, 2010), and disrupted LI (Arad and Weiner, 2009, 2010). To the best of our knowledge, this is the first demonstration that 17β-estradiol exerts an antipsychotic action in gonadally intact rats of both sexes. These outcomes indicate that 17β-estradiol possesses antipsychotic properties in both sexes and, by extension, that such action is independent of endogenous estrogen levels.

Reversal of Abnormally Persistent LI: Putative Efficacy for Negative and Cognitive Symptoms

As NMDA antagonists induce in addition to positive symptoms, also negative symptoms and cognitive impairments characteristic of endogenous schizophrenia (Javitt and Zukin, 1991; Krystal *et al*, 2003; Lahti *et al*, 1995; Malhotra *et al*, 1997; Tamminga, 1998), their behavioral effects in animals, with the exception of locomotor hyperactivity, are usually used as pharmacological models of negative and/or cognitive symptoms (Bakshi *et al*, 1994; Javitt and Zukin, 1991; Moghaddam and Jackson, 2003; Nilsson *et al*, 2001; Sams-Dodd, 1996; Swerdlow *et al*, 1996). Cognitive and behavioral inflexibility that is often observed following NMDA blockade in rats and humans has been argued to be particularly relevant to the modeling of negative/cognitive symptoms (Carlsson *et al*, 1999; Carlsson and Carlsson, 1990b; Krystal *et al*, 2000; Moghaddam *et al*, 1997).

As shown previously (Gaisler-Salomon *et al*, 2008; Gaisler-Salomon and Weiner, 2003; Lipina *et al*, 2005), under strong conditioning, MK-801 induced persistent LI in male rats. In other words, whereas vehicle-injected PE male rats switched in the conditioning stage to respond according to the stimulus-reinforcement contingency, MK-801-injected PE rats persisted in responding according to the stimulus-no-event contingency acquired in pre-exposure, in line with many findings showing that NMDA receptor blockade induces behavioral and cognitive inflexibility (Carlsson and Carlsson, 1990a; Jentsch and Taylor, 2001; Moghaddam *et al*, 1997; Svensson, 2000; van der Meulen *et al*, 2003). The same effect of MK-801 on LI was shown here, for the first time, in gonadally intact and OVX females. Thus, like amphetamine, MK-801 produced its schizophrenia-relevant effect in a sex-independent manner. However, unlike amphetamine-induced disrupted LI, in gonadally intact rats, MK-801-induced persistent LI was ameliorated by 17β-estradiol in male but not female rats. The latter is rather remarkable as it suggests that 17β-estradiol is more efficient in ameliorating MK-801 effects on LI in the absence of estrogen. This suggestion was supported by our finding that 17β-estradiol was also effective in reversing MK-801-induced persistent LI in OVX rats. The basis for the sex-dependent sensitivity of MK-801-induced persistent LI to 17β-estradiol in gonadally intact rats is unclear. Greater sensitivity of gonadally intact females than males to NMDA antagonists, such as MK-801, requiring higher 17β-estradiol doses to block its effects, has been reported but for much higher, neurodegeneration-producing MK-801 doses (Andine *et al*, 1999; Auer, 1996; de Olmos *et al*, 2008; Dribben *et al*, 2003; Fix *et al*, 1995; Honack and Loscher, 1993; Wozniak *et al*, 1998). The sex-dependent effects might also be dependent on the behavioral phenomenon tested, as 17β-estradiol was found to reverse the disruptive effects of the NMDA antagonist PCP in the novel object-recognition test in gonadally intact female rats (Sutcliffe *et al*, 2007).

The mechanism/s by which 17β-estradiol reverses MK-801-induced persistence of LI remain to be investigated, but two options can be suggested based on known pharmacological reversals of this abnormality. Reversal of MK-801-induced persistent LI by atypical APDs is mediated by $5HT_{2A}$ receptor antagonism (Gaisler-Salomon and Weiner, 2003; Weiner and Arad, 2009). In addition, MK-801-induced persistent LI is reversed by a wide variety of compounds enhancing NMDA receptor function (Black *et al*, 2009; Gaisler-Salomon *et al*, 2008).

The relationship between estrogen and serotonin is well documented. Studies in intact rats of both sexes have shown that estrogen modulates brain serotonergic activity (Fink *et al*, 1998) and that during high estrogen levels, $5HT_{2A}$ density is increased (Sumner and Fink 1997). 17β-estradiol treatment in gonadectomized female and male rats increased $5HT_{2A}$ mRNA levels and receptors' density in the frontal cortex and NAC (Cyr *et al*, 1998; Fink *et al*, 1998; Summer and Fink, 1995; Sumner and Fink, 1998). Importantly, the same effect is produced in intact male rats by clozapine (Buckland *et al*, 1997). Clinical studies reported that raloxifene, a second generation selective estrogen receptor modulator, mimics 17β-estradiol effect on $5HT_{2A}$ receptor binding by increasing $5HT_{2A}$ receptor binding levels and its mRNA levels in the frontal cortex, amygdala, NAC, and striatum (Cyr *et al*, 2002).

There is also a well-established relationship between estrogen and NMDA receptor function. In OVX rats, 17β-estradiol increases hippocampal NMDA receptors and glutamate transmission, whereas in the striatum, frontal cortex, and NAC, 17β-estradiol decreases NMDA receptor binding. Furthermore, 17β-estradiol increases agonist binding but decreases antagonist binding of NMDA receptors in the hippocampus (Cyr *et al*, 2000; Cyr *et al*, 2001; Daniel and Dohanich, 2001; El-Bakri *et al*, 2004; Gazzaley *et al*, 1996; Weiland, 1992; Woolley and Schwartzkroin, 1998; Woolley *et al*, 1997). Although these effects could explain the reversal of MK-801-induced persistent LI in OVX rats seen here, it is not clear whether similar effects are exerted in intact male brains. However,

17β-estradiol does enhance glutamatergic transmission in hippocampal slices taken from male rats (Teyler *et al*, 1980).

17β-Estradiol in LI—An Antipsychotic with a Sex-Dependent Action

Although the mechanisms underlying the effects of 17β-estradiol seen here remain to be investigated, our results show that at certain doses this agent possesses an antipsychotic profile in the LI model. Moreover, this profile is sex dependent. Specifically, 17β-estradiol possesses a profile of a typical APD (consisting of LI potentiation on its own and reversal of amphetamine-induced LI disruption) in both sexes and a profile of an atypical APD (consisting of LI potentiation on its own, reversal of amphetamine-induced disrupted LI and reversal of MK801-induced persistent LI), in male rats.

In psychological terms, in all of the models, 17β-estradiol targeted selectively the processes responsible for attentional selectivity (in the PE groups) without affecting associative capacity (in the NPE groups). Furthermore, reversal of disrupted and persistent LI can be seen as normalization of two poles of dysfunctional attentional control. On the one hand, 17β-estradiol strengthens/restores the capacity to ignore irrelevant stimuli in amphetamine-treated rats and on the other hand, 17β-estradiol strengthens/restores the capacity to dis-ignore irrelevant stimuli when they become relevant, enabling flexible re-deployment of attentional resources according to current situational demands, in MK-801-treated rats. The former would be beneficial in normalizing aberrantly increased salience perception and distractibility that are associated with psychotic symptoms (Gray *et al*, 1991; Kapur, 2003; Smith *et al*, 2006; Swerdlow and Koob, 1987; Weiner and Joel, 2002), whereas the latter would be beneficial in reducing cognitive inflexibility and inattention that are associated with negative/cognitive symptoms (Carlsson and Carlsson, 1990b; Krystal *et al*, 2003; Moghaddam *et al*, 1997; Weiner, 2003). Given that 17β-estradiol reverses amphetamine-induced LI disruption in both sexes, but MK-801-induced LI persistence only in male and OVX rats, the implications of our results for the clinic are that 17β-estradiol would be beneficial against positive symptoms in both sexes but against negative/cognitive symptoms in male patients and in women with very low estrogen levels, eg, during menopause.

This conclusion seems in line with positive reports from the clinic. Efficacy of 17β-estradiol against positive symptoms in schizophrenic women has been shown in several studies (Kulkarni *et al*, 2008a; Kulkarni *et al*, 1996; Kulkarni *et al*, 2008b; Kulkarni *et al*, 2001; Riecher-Rossler and de Geyter, 2007), as it was reported to be less effective or ineffective against negative symptoms (Akhondzadeh *et al*, 2003; Kulkarni *et al*, 2008a). In an attempt to reconcile inconsistent reports in the literature regarding efficacy of estradiol treatment in schizophrenic women, Mortimer (2007) suggested that such treatment would be effective in schizophrenic women who suffer from severe estrogen deficiency. Interestingly, reduced levels of plasma estrogen were found in both male (Huber *et al*, 2005) and female (Bergemann *et al*, 2005; Huber *et al*, 2004; Huber *et al*, 2001; Riecher-Rossler *et al*, 1994) schizophrenia patients, and recently a small study of men with schizophrenia who received oral estradiol valerate also showed an abatement in psychotic symptoms (Kulkarni, 2009). The role of estrogen in schizophrenia has been supported by the finding that variation in the estrogen receptor alpha gene and cortical estrogen receptor alpha mRNA is associated with schizophrenia (Perlman *et al*, 2005; Perlman *et al*, 2004; Weickert *et al*, 2008; Wong and Weickert, 2009) and it has been suggested that the brain response to circulating estrogen may be altered in schizophrenia (Weickert *et al*, 2008). Taken together with our animal data, estrogen seems to have the potential to be useful in the treatment of schizophrenia.

In summary, our previous (Arad and Weiner, 2010) and present data are clear in showing that estrogen can exert antipsychotic activity, reversing hyperdopaminergia-induced behavioral abnormality in gonadally intact rats of both sexes and in OVX rats, and reversing hypoglutamatergia-induced abnormality in male and OVX rats. By extension, these results suggest that estrogen can be viewed as an effective treatment not only for positive symptoms in women with schizophrenia, but also for a wide spectrum of symptoms in women and men with schizophrenia, including negative/cognitive symptoms. Unfortunately, the risk of inducing cancers has limited the applicability of estrogen in humans for use in modulating the central nervous system neurotransmission (Rossouw *et al*, 2002), although recent studies found no increased risk (Anderson *et al*, 2006; Stefanick *et al*, 2006; Stevenson, 2009). Importantly in this context, our previous data showed that co-administration of a physiological dose of 17β-estradiol and APD augments APD efficacy, and in fact may be more effective than raising the dose of APD. Further research is required to determine the correct dose and duration of the use of 17β-estradiol as monotherapy, as well as an adjunctive therapy. Our present results raise the possibility that variable outcomes in the clinic may be because of the differences in the dosage of estrogen and, in general, alert to the importance of dose-response studies. Finally, new estrogenic compounds acting selectively in the brain may provide a safer, non-feminizing approach for the treatment of schizophrenia (Cyr *et al*, 2002; Kulkarni, 2009).

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DISCLOSURE

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