



Abnormally rapid reversal learning and reduced response to antipsychotic drugs following ovariectomy in female rats

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Summary Epidemiological and clinical life cycle studies indicate that favorable illness course and better response to antipsychotic drugs (APDs) in women with schizophrenia are positively correlated with estrogen levels. Accordingly, the estrogen hypothesis of schizophrenia proposes a neuroprotective role of estrogen in women vulnerable to schizophrenia. Previously we demonstrated in the rat that low levels of estrogen induced by ovariectomy led to disruption of latent inhibition (LI) reflecting impairment of selective attention, a core deficit of schizophrenia. LI disruption was reversed by 17 β -estradiol and the atypical APD clozapine, whereas the typical APD haloperidol was ineffective unless co-administered with 17 β -estradiol. Here we aimed to extend these findings by testing ovariectomized rats in another selective attention task, discrimination reversal. Ovariectomy led to a loss of selective attention as manifested in abnormally rapid reversal. The latter was normalized by high dose of 17 β -estradiol (150 μ g/kg) and clozapine (2.5 mg/kg), but not by haloperidol (0.1 mg/kg) or lower doses of 17 β -estradiol (10 and 50 μ g/kg). However, co-administration of haloperidol with 17 β -estradiol (50 μ g/kg) was effective. In sham rats low 17 β -estradiol (10 μ g/kg) produced rapid reversal, while high 17 β -estradiol (150 μ g/kg), haloperidol alone, or haloperidol-17 β -estradiol combination reduced reversal speed. Clozapine did not affect reversal speed in sham rats. These results strengthen our previous results in suggesting that schizophrenia-like attentional abnormalities as well as reduced response to APDs in female rats are associated with low level of gonadal hormones. In addition, they support the possibility that estrogen may have an antipsychotic-like action in animal models.
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1. Background

Women with schizophrenia have a more favorable course of illness than men during the reproductive years, characterized by later onset of symptoms, lower symptom severity and better response to antipsychotic treatment (Hafner, 2003; Hafner et al., 1989; Kulkarni, 2009; Kulkarni et al., 1996,

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2008b; Riecher-Rossler and Hafner, 1993; Seeman and Lang, 1990). However, elevated symptom severity and reduced response to treatment are seen postmenopausally, and there is a second onset peak unique to postmenopausal women (Horacek et al., 2006; Kulkarni et al., 1996, 2008b; Lane et al., 1999; Riecher-Rossler et al., 1994; Salokangas, 1995; Saugstad, 1989; Seeman and Lang, 1990). These observations have led to the suggestion that estrogen may be protective in women vulnerable to schizophrenia, and by extension, that exogenous estrogen may have therapeutic potential in schizophrenia given on its own or as an adjuvant to antipsychotic drugs (APDs), but clinical data have been inconsistent (Akhondzadeh et al., 2003; Cyr et al., 2002; Korhonen et al., 1995; Kulkarni et al., 1996, 2008a, 2008b, 2001; Mortimer, 2007; Riecher-Rossler, 2002). Lately the estrogen hypothesis of schizophrenia received further support from genetic studies suggesting a mutation in estrogen receptor alpha is correlated with increased risk for schizophrenia (Mellios et al., 2010; Perlman et al., 2004, 2005; Weickert et al., 2008; Wong and Weickert, 2009; Wong et al., 2011). Another support comes from a study showing a therapeutic effect of estradiol in schizophrenic men (Kulkarni et al., 2011).

While there is a large body of preclinical research on the neuroprotective and pro-cognitive effects of estrogen relevant to depression, anxiety, Parkinson's and Alzheimer's diseases (Daniel, 2006; Frick, 2009; Gibbs, 2010; Henderson, 2007; Liu and Dluzen, 2007; Osterlund, 2010; Sherwin and Henry, 2008; Walf and Frye, 2006), the study of the estrogen hypothesis in 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 tested the estrogen hypothesis in the latent inhibition (LI) model of schizophrenia (Arad and Weiner, 2008, 2009, 2010a,b). LI is a cross-species selective attention phenomenon whereby the behavioral control of stimuli is downgraded following their inconsequential (nonreinforced) pre-exposure (Weiner, 2003; Weiner and Arad, 2009). Since selective attention deficit, typically described as an inability to ignore irrelevant stimuli, is a hallmark cognitive deficit of schizophrenia and a central target for treatment (Hajos, 2006; Itagaki et al., 2011; Kapur, 2003; Lubow, 2005; Luck and Gold, 2008; Nuechterlein et al., 2006), disrupted LI has been extensively used to model deficient attention in schizophrenia (Gosselin et al., 1996; Joseph et al., 2000; Killcross et al., 1994; Killcross and Robbins, 1993; Moran et al., 1996; Moser et al., 2000; Powell and Miyakawa, 2006; Ruob et al., 1997; Russig et al., 2003; Weiner, 1990, 2003; Weiner and Arad, 2009; Weiner et al., 1996, 1997a, 1997b). Disrupted LI is found in rats and humans treated with the psychosis inducing dopamine releaser amphetamine as well as in acute schizophrenia patients, and APDs restore LI in amphetamine-treated rodents and schizophrenia patients (Baruch et al., 1988; Gosselin et al., 1996; Gray et al., 1991; Moser et al., 2000; Powell and Miyakawa, 2006; Rasclé et al., 2001; Solomon et al., 1981; Warburton et al., 1994; Weiner, 1990, 2003; Weiner et al., 1994, 1996).

We reported that following ovariectomy, female rats did not show LI (Arad and Weiner, 2009) but this was reversed by 17β -estradiol. Interestingly, unlike amphetamine-induced disrupted LI, ovariectomy-induced disrupted LI was restored by the atypical APD clozapine but was resistant to the typical

APD haloperidol. Haloperidol regained efficacy when was co-administered with 17β -estradiol (Arad and Weiner, 2009). These results provided the first demonstration in animals that low levels of hormones induce a psychotic-like attentional deficit that has reduced sensitivity to at least typical APD treatment. Since ovariectomy is considered to model hormonal cessation occurring in menopause (Bosse and Di Paolo, 1995; Le Saux and Di Paolo, 2006; Vaillancourt et al., 2002), we suggested that resistance to haloperidol may mimic reduced response to treatment seen in schizophrenic women during menopause.

Here we sought to test the effects of ovariectomy on another selective attention phenomenon, namely, discrimination reversal (DR). In DR tasks animals are first reinforced for responding to one of two stimuli or places and then reinforced for responding to the previously non-reinforced alternative. As in LI, previously acquired information slows down the acquisition of behavioral control by the new contingencies. Since in the LI task, ovariectomy caused rats to rapidly switch to respond according to the new stimulus-reinforcement contingency prevailing in conditioning, we anticipated the same effect in DR task, which would be manifested as rapid reversal. We further expected that rapid reversal would be counteracted by 17β -estradiol and clozapine but not by haloperidol, and that haloperidol would regain efficacy if administered with 17β -estradiol, as we have found previously using the LI task (Arad and Weiner, 2009).

2. Materials and methods

2.1. Animals

Female Wistar rats bred in our laboratory were housed 3–4 per cage under reversed light cycle (lights on: 19:00–07:00 h) with ad lib access to food and water. They were about seven weeks old and weighing 150–275 g when submitted to ovariectomy and approximately twelve weeks old and weighing 250–480 g when behavioral testing begun. 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 September 30, 2011). All efforts were made to minimize the number of animals used and their suffering.

2.2. Ovariectomy

Rats were bilaterally ovariectomized under isoflourane (Nichols Piramal, UK) anaesthesia. 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 ten days later. Sham-operated controls underwent an identical surgical procedure without the removal of the ovaries. Rats were allowed additional 3 weeks of recovery after removal of the sutures, before behavioral testing. 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 ovariectomized rats, to confirm presence or discontinuation

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