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Interactions between estradiol and haloperidol on perseveration and reversal learning in amphetamine-sensitized female rats

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ABSTRACT

There are sex differences associated with schizophrenia, as women exhibit later onset of the disorder, less severe symptomatology, and better response to antipsychotic medications. Estrogens are thought to play a role in these sex differences; estrogens facilitate the effects of antipsychotic medications to reduce the positive symptoms of schizophrenia, but it remains unclear whether estrogens protect against the cognitive symptoms of this disorder. Amphetamine sensitization is used to model some symptoms of schizophrenia in rats, including cognitive deficits like excessive perseveration and slower reversal learning. In this experiment female rats were administered a sensitizing regimen of amphetamine to mimic these cognitive symptoms. They were ovariectomized and administered either low or high estradiol replacement as well as chronic administration of the antipsychotic haloperidol, and were assessed in tests of perseveration and reversal learning. Results of these experiments demonstrated that, in amphetamine-sensitized rats, estradiol alone does not affect perseveration or reversal learning. However, low estradiol facilitates a 0.25 mg/day dose of haloperidol to reduce perseveration and improve reversal learning. Combined high estradiol and 0.25 mg/day haloperidol has no effect on perseveration or reversal learning, but high estradiol facilitates the effects of 0.13 mg/day haloperidol to reduce perseveration and improve reversal learning. Thus, in amphetamine-sensitized female rats, 0.25 mg/day haloperidol only improved perseveration and reversal learning when estradiol was low, while 0.13 mg/day haloperidol only improved these cognitive processes when estradiol was high. These findings suggest that estradiol facilitates the effects of haloperidol to improve perseveration and reversal learning in a dose-dependent manner.

1. Introduction

There are sex differences in the progression of schizophrenia and the response to antipsychotic drugs, with women exhibiting later onset of the disorder, and reduced symptom severity (Häfner, 2003; Seeman, 1982). Additionally, natural declines in plasma estrogen levels that occur pre-menstruation (Endo et al., 1978; Glick and Stewart, 1980), post-partum (Kendell et al., 1987; McNeil, 1987), and following menopause (McNeil, 1987), are associated with increased vulnerability to psychosis. In addition to protecting against psychosis, estrogens are also linked to better treatment outcomes (Chua et al., 2005; Kulkarni et al., 2012; Seeman, 1982); women require lower doses of antipsychotics to treat both acute (Chouinard and Annable, 1982; Chouinard and Turnier, 1986) and chronic schizophrenia (Seeman and Lang, 1990; Seeman, 1982), compared to men. When women were administered estradiol (E2) in conjunction with antipsychotic medication they exhibited fewer positive, negative and general psychopathology symptoms compared to controls that received antipsychotic treatment alone (Akhondzadeh et al., 2003; Khan, 2016; Kulkarni et al., 2015). However, the combined effect of E2 and antipsychotic medication on the cognitive symptoms of schizophrenia is relatively unknown. Recent clinical evidence suggests that estrogens may protect against some of the cognitive symptoms of schizophrenia, but further research is needed to confirm this (Weickert and Weickert, 2016; Weickert et al., 2016).

The experiments presented here focused on two related cognitive symptoms of schizophrenia: excessive perseveration and deficits in reversal learning. Perseveration is a cognitive process defined by the repetition of a previously reinforced behavior, despite the fact that reinforcement is no longer provided (Crider, 1997; Holahan et al., 2011). Reversal learning is defined as the cognitive capacity to discontinue a behavior that is no longer relevant in a particular context, and adopt a novel behavior that reflects the contextual change (Pantelis et al., 1999). Patients with schizophrenia are capable of acquiring an initial rule but perseverate once the rule changes; they persist using the

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previously effective behavior with longer latencies to modify their behavior to reflect a new rule (Pantelis et al., 1999; Reed et al., 2002; Waford and Lewine, 2010; Waltz and Gold, 2007). Typical antipsychotic medications, including haloperidol (HAL), effectively treat the positive symptoms of schizophrenia, but are frequently ineffective in alleviating the cognitive symptoms associated with this disorder (Bowie and Harvey, 2006). Since the cognitive symptoms of schizophrenia are the best predictor of functional outcome (Bowie and Harvey, 2006), there is an impetus to discover treatments that improve these symptoms.

Amphetamine (AMPH) sensitization is an animal model that induces some neurobiological and behavioral changes associated with schizophrenia (Featherstone et al., 2007). The dopamine hypothesis of schizophrenia states that this disorder is caused, in part, by elevated dopamine in the striatum (STR) and nucleus accumbens (NAc), and reduced dopamine transmission in prefrontal regions (Abi-Dargham et al., 1998; Howes and Kapur, 2009). The commonality between antipsychotic medications used to treat schizophrenia is that these drugs act as antagonists at the dopamine D2 receptor (Gründer et al., 2003), and D2-receptor occupancy predicts the efficacy of the antipsychotic HAL (Farde et al., 1988). The fact that the drugs used to treat schizophrenia do so by reducing transmission at the D2 receptor also suggests that schizophrenia results from excessive dopamine transmission. In humans, AMPH administration increases dopamine availability in the dorsal and ventral striatum (Boileau et al., 2006) and repeated AMPH use can cause psychosis (Bell, 1965). In rats, repeated AMPH administration also results in an increase in evoked dopamine transmission in the NAc and STR, even after extended periods of abstinence from AMPH, a phenomenon known as neurobiological sensitization (Fiorino and Phillips, 1999; Paulson and Robinson, 1995). Together these findings suggest that repeated AMPH administration induces a neurobiological state and similar to that observed in schizophrenia. Repeated AMPH administration to rodents and humans leads to increased locomotor activity in response to the same dose of drug, which is referred to as locomotor sensitization (Boileau et al., 2006; Featherstone et al., 2007; Paulson and Robinson, 1995; Sax and Strakowski, 2001). Research in rats has demonstrated that locomotor sensitization develops in parallel with neurobiological sensitization (Pierce and Kalivas, 1995; Robinson and Berridge, 2008), so it can be used as a behavioral marker for neurobiological sensitization. This research on AMPH sensitization as a model for schizophrenia is primarily in males. However, an acute dose of AMPH results in increases in dopamine transmission in females, and female rats develop neurobiological and locomotor sensitization more rapidly than males (Camp and Robinson, 1988).

There is behavioral evidence that repeated AMPH administration models some of the cognitive symptoms of schizophrenia. AMPH sensitization to the locomotor activating effects of the drug induces deficits in latent inhibition in male rats (Murphy et al., 2001; Russig et al., 2002; Tenn et al., 2005), which are ameliorated by the antipsychotic drugs HAL and clozapine (Russig et al., 2002). More pertinent to this study, an acute dose of AMPH increases perseveration in a Y-maze task in male rats, which is ameliorated by HAL treatment (Oades et al., 1985). Similarly, acute AMPH administration induces deficits in reversal learning in female rats which are reversed by acute HAL treatment (Idris et al., 2005). Repeated AMPH treatments also induce deficits in reversal learning in male rats (Featherstone et al., 2008; Fletcher et al., 2005) and marmosets, which are ameliorated by an acute administration of HAL (Ridley et al., 1981). These findings demonstrate that AMPH induces cognitive deficits similar to those observed in schizophrenia, which are alleviated by administration of antipsychotic drugs. This suggests that AMPH sensitization can model some of the cognitive symptoms associated with schizophrenia.

Despite clinical research indicating that estrogens improve the efficacy of antipsychotic medication, little preclinical research has examined the possible interaction between estrogens and antipsychotic drugs. Previous research in this lab along with others suggests that administration of combined E2-HAL treatment in ovariectomized (OVX) rats improves selective attention significantly more than HAL alone (Almey et al., 2013; Arad and Weiner, 2009), paralleling clinical research findings (Akhondzadeh et al., 2003; Kulkarni et al., 2015). The experiments in this study attempt to clarify the effects of E2, administered alone and in conjunction with HAL, on perseveration and reversal learning in AMPH-sensitized female rats. It was hypothesized that HAL would reduce perseveration and improve reversal learning in these animals. It was predicted that E2 would facilitate the effects of HAL to decrease perseveration and improve reversal learning.

2. Methods

2.1. Subjects

The subjects consisted of 121 female Sprague-Dawley rats (for group sample sizes see Figs. 2–4), weighing 220–240 g upon arrival (Charles River Laboratories, St. Constant, QC). Rats were pair housed in clear shoebox cages in a colony room maintained on 12 h reverse light cycle at constant temperature (21 °C) and humidity (60%). One week before behavioral training, rats were housed individually and food restricted to 90% of their free feeding weight. All procedures were in accordance with the guidelines of the Canadian Council on Animal Care, and approved by Animal Research Ethics Committee of Concordia University.

2.2. Surgery and estradiol replacement

2.2.1. Ovariectomy and capsule implantation

All rats were ovariectomized to control for naturally cycling estrogens. Ovaries were removed via lumbar incision under isoflurane gas anesthesia (4% induction, 2% maintenance). Rats were administered 0.1 mL of the analgesic Anafen (10 mg/mL) by subcutaneous (SC) injection, and 0.1 mL of the antibiotic penicillin (30,000 IU/mL) by intramuscular injection. Rats were assigned to one of three groups: no E2 replacement, low E2 replacement, or high E2 replacement. During the ovariectomy rats in the low and high E2 replacement groups were implanted with a silastic capsule containing E2, described below. Rats in the no E2 group had a sham capsule implantation surgery, but no actual capsule was implanted.

2.2.2. Hormone treatment

Low E2 replacement was administered via silastic capsule containing 5% 17-β E2 in cholesterol (Sigma-Aldrich, St. Louis, MO). These capsules produce a plasma concentration of ~20–25 pg/mL E2 (Almey et al., 2013), which corresponds to plasma levels of E2 observed during the diestrus phase of the estrous cycle (Butcher et al., 1974). In addition to capsules, rats in the high E2 replacement group received injections of E2 in sesame oil once every four days (10 μg/kg, SC), starting at the beginning of the final training phase (see Procedures). The combination of the E2 capsule and this SC injection of E2 achieved an average plasma level of 90 pg/mL across 12 h (Almey et al., 2013), similar to average plasma levels of E2 during the proestrus phase of the cycle (Butcher et al., 1974). Rats in the no E2 and low E2 groups received sesame oil injections at this time.

2.3. Drug treatments

2.3.1. Amphetamine

D-amphetamine sulphate (AMPH; Sigma-Aldrich, St. Louis, MO) was repeatedly administered via intraperitoneal injection (IP) to induce locomotor sensitization. For the induction phase of sensitization all rats were administered 1 mg/kg AMPH daily for four consecutive days; locomotor activity was assessed for 1 h following AMPH administration. After induction all rats underwent a 7 day period when they received no AMPH, and then they were given an AMPH challenge (0.5 mg/kg,