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Research Report

Changes in brain volume in response to estradiol levels, amphetamine sensitization and haloperidol treatment in awake female rats

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ABSTRACT

Estrogen has been shown to further ameliorate symptoms when administered in conjunction with antipsychotics in patients with schizophrenia. We have previously shown that chronic haloperidol (HAL) treatment reduces amphetamine (AMPH)-induced locomotor activity in AMPH-sensitized rats, but only when paired with high levels of the estrogen, 17-β estradiol. In addition, we reported estradiol-dependent responses to AMPH in AMPH-sensitized rats as measured by functional magnetic resonance imaging. It is thus clear that estradiol and antipsychotics both affect the rat brain, however the mechanism by which this occurs is unknown. The aim of the current study was to assess this interaction by investigating the effects of estradiol, AMPH and HAL on brain volume changes in awake female rats. Repeated exposure to AMPH resulted in an overall reduction in brain volume, regardless of hormonal status (i.e. no, low or high estradiol). Similarly, chronic HAL treatment further reduced brain volume compared to acute treatment. Hormonal status affected hippocampal volume with rats receiving low estradiol replacement showing larger volume; this difference was no longer significant after repeated exposure to AMPH. Finally, we found changes in volume in response to AMPH throughout hippocampal components (i.e. CA1–CA3 and dentate) as well as components of the mesocortical system. In conclusion, brain volume seems to be influenced by hormonal status, as well as exposure to AMPH and haloperidol treatment. These findings implicate areas where estradiol, amphetamine and antipsychotics may be producing volumetric changes in the brain, pointing the way to where future studies should focus.

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1. Introduction

Sex differences in schizophrenia are well established, implicating gonadal hormones in schizophrenia pathophysiology (Angermeyer and Kuhn, 1988; Guillem et al., 2009; Hafner et al., 1991; Hafner, 2003; Jimenez et al., 2010; Mendrek et al., 2007; Riecher-Rossler et al., 1994). In addition, women differ in symptom severity depending on phase of menstrual cycle (Hallonquist et al., 1993). Accumulating evidence shows that adjuvant estrogen therapy increases responsiveness to antipsychotic medication in men and women with schizophrenia (Akhondzadeh et al., 2003; Kulkarni et al., 2001, 2011). What are not yet understood are the basic mechanisms by which, or even where for that matter, estrogen interacts with antipsychotics in the brain. Thus, the main goal of this study was to examine the effects of estrogen and an antipsychotic, haloperidol (HAL), on volumetric changes in multiple brain areas to further understand such a potential interaction. This was carried out here using a well-established rodent model of some of the behavioral and neurobiological aspects of schizophrenia, viz. amphetamine (AMPH) sensitization (Featherstone et al., 2007; Schmidt and Beninger, 2006; Vezina, 1996).

AMPH sensitization occurs when repeated, intermittent injections of AMPH increase behavioral and neurochemical responses to subsequent injections (Almey et al., 2013; Featherstone et al., 2007; Kalivas and Stewart, 1991; Madularu et al., 2014; Vezina and Queen, 2000). Furthermore, the acute and sensitizing effects of AMPH are sex-specific (Becker et al., 2001), with female rats showing increased behavioral activation to acute and repeated injections of AMPH compared to males (Forgie and Stewart, 1994). We have shown previously that the typical antipsychotic, HAL, is effective in reducing AMPH-induced hyperlocomotion in AMPH-sensitized female rats, but only after chronic use (i.e. 12 days) and only when paired with high 17-β estradiol (E2) replacement (Madularu et al., 2014). These findings show that estrogen and antipsychotics interact to determine locomotor behavior of AMPH-sensitized rats.

Recently we have shown that blood-oxygen-level dependent (BOLD) activity in response to AMPH is mediated by E2 levels in sensitized rats, with high E2 rats showing the largest activation (Madularu et al., 2015). Similarly, Sarvari et al. (2014) showed an increased BOLD response in the prefrontal cortex (PFC) and ventral tegmental area (VTA) in ovariectomized female rats receiving estrogen receptor agonist replacement compared to control. Finally, hippocampal volume changes throughout the estrous cycle have been reported, with proestrous (a period of high levels of estrogen) mice showing increased volume compared to estrous mice, when estrogen levels are low (Qiu et al., 2013).

The effects of psychostimulants such as AMPH and cocaine on brain volume have been extensively studied in humans. For example, AMPH and cocaine have been shown to decrease gray matter volume in humans (Barros-Loscertales et al., 2011; Berman et al., 2008; Franklin et al., 2002; Sim et al., 2007). However, in some cases it is difficult to control for confounding factors such as the length of drug exposure, mode of administration, and interactions with other substances. In addition, the interaction between AMPH, antipsychotics, and ovarian hormones has not been explored with regards to changes in brain volumes. Some of these potential confounds can be eliminated by examining brain volumetric changes in rodent models.

Given the recent findings from Qiu et al. (2013) showing an increase in hippocampal volume in relation to estrous cycle, the first aim of this study was to investigate this effect in ovariectomized (OVX) rats receiving physiologically-relevant E2 replacement, mimicking proestrous (high E2) and estrous (low E2) phases. The second aim of the study is based on earlier studies showing increased PFC and hippocampal spine density in response to AMPH sensitization and E2 replacement in rats (Crombag et al., 2005; Robinson and Kolb, 1997, 1999; Woolley and McEwen, 1994). We hypothesized that repeated exposure to AMPH would increase the volumes of select regions of interest (ROIs), such as the hippocampal formation as well as components of the DA mesocortical circuit. Furthermore, we expected the highest volumetric increase in animals receiving high E2 replacement, however based on clinical findings (Franklin et al., 2002; Sim et al., 2007), an overall decrease in brain volume after AMPH sensitization was expected. The third goal of this study was to investigate the effects of acute and chronic HAL on brain volume in AMPH-sensitized rats, and its possible interactions with E2. Based on clinical findings showing HAL to be associated with gray matter volume reduction (Lieberman et al., 2005), we expected HAL treatment to result in a decrease in brain volume. In order to address these hypotheses, OVX female rats receiving no, low or high E2 replacement were scanned using MRI before and after AMPH sensitization, as well as two and twelve days into chronic HAL treatment. All rats were scanned awake, in order to avoid any possible confounding effect of anesthetic (alone or in interaction with E2, HAL and AMPH) on brain morphology.

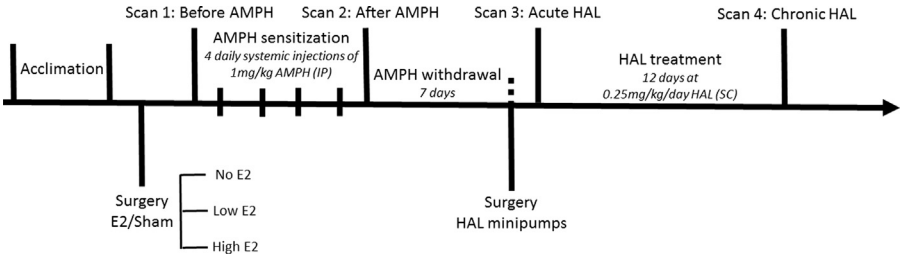

Fig. 1 – Experimental timeline delineating the succession of scanning sessions, as well as hormone replacement (17β-estradiol, E2), amphetamine (AMPH) and haloperidol (HAL) treatment.