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Sex differences in aripiprazole sensitization from adolescence to adulthood

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ABSTRACT

The present study investigated the potential sex differences in repeated aripiprazole (ARI) treatment-induced behavioral sensitization from adolescence to adulthood, and to determine whether ARI sensitization can be transferred to olanzapine (OLZ) and/or clozapine (CLZ) using the conditioned avoidance response (CAR) and phencyclidine-induced (PCP) hyperlocomotion tests of antipsychotic activity. Male and female Sprague-Dawley adolescence rats (P46) were first treated with ARI (10 mg/kg) for 5 consecutive days (P46–50) and tested for avoidance response and ARI-induced inhibition of PCP-induced hyperlocomotion. After they became adults (> P68), rats were challenged with ARI (1.5 mg/kg, sc) (P70), OLZ (0.5 mg/kg, sc; P73), CLZ (5 mg/kg, sc; P76) and again with ARI (1.5 mg/kg, sc; P84) and tested for avoidance response and ARI-induced inhibition of PCP-induced hyperlocomotion again. During the drug treatment period in adolescence, repeated ARI treatment suppressed avoidance response, inhibited the PCP-induced hyperlocomotion, and these effects were progressively increased across the 5-day period in both males and females, confirming the induction of ARI sensitization. On the challenge days, rats previously treated with ARI in adolescence also had significantly lower avoidance and lower PCP-induced hyperlocomotion than the previous vehicle rats, confirming the expression of ARI sensitization and its persistence into adulthood. More importantly, female rats made significantly more avoidances than males in both ARI and vehicle groups, indicating higher sensitivity to the acute and long-term effects of ARI. Further, on the OLZ and CLZ challenge days, prior ARI treatment seemed to increase sensitivity to OLZ exposure, however, this increase was not significant. Similarly, rats also showed an ARI sensitization to OLZ and CLZ on challenge days. Collectively, results from this experiment demonstrated a sex difference in response to ARI and enhanced inhibition of PCP-induced hyperlocomotion in animals that were pretreated with ARI as compared to controls.

1. Introduction

In recent years, there has been a significant increase in prescription rates for antipsychotics in adult males and females. Yet, most clinical studies have precluded females, thus much of the information available on the side effects and effectiveness of antipsychotics has been inferred from the effects found in males (Smith, 2010). Regardless, there have been some studies that have shown that sex differences in response to antipsychotic treatment exist, although not well understood. For example, it has been shown that females show increased sensitivity to the effects of antipsychotics (e.g. weight gain, type 2 diabetes, dyslipidemia, digestive, neurological/sensory symptoms and increased rates of side effects) as compared to men (Covell et al., 2007; Bigos et al., 2008). These differences are thought to be influenced by the bioavailability, distribution, metabolism, and/or excretion in the pharmacokinetics of drug response (Waxman and Holloway, 2009). In fact, studies have demonstrated that sex differences in metabolism are thought to be the primary influence in response to antipsychotic treatment (Bigos et al., 2008; Seeman, 2004). For example, the main metabolizing enzyme (CYP1A2) of olanzapine is less active in females than males and it is thought to contribute to higher olanzapine and clozapine blood concentrations shown in females. This could help explain the incidence of increased severity of side effects as seen in females.

Another important factor when considering differences in antipsychotic response is the developmental period in which treatment begins. There has been a dramatic increase of antipsychotic prescription rates in children and adolescents in recent years to treat various mental disorders (e.g. schizophrenia, disruptive behavior disorder, autism, mood disorder) (Correll, 2008; Vitiello et al., 2009; Rani et al., 2008). Most (90%) of these children and adolescents are treated with atypical antipsychotic medication (e.g. risperidone, olanzapine and aripiprazole) for the management of these disorders (Olfson et al., 2006). Surprisingly, clinical research generally only focuses on the

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efficacy, tolerability, and side effect profiles of these drugs. However, there have been some preclinical studies that have strongly suggested that antipsychotic exposure during adolescence could alter brain and behavioral functions. For example, animal receptor binding studies show that antipsychotic exposure during adolescence increases or decreases various neuroreceptors, including various dopamine receptors (Qiao et al., 2014; Vinish et al., 2013), serotonin 5-HT1A/ 5-HT2A receptors (Choi et al., 2010), and ionotropic NMDA and AMPA glutamatergic receptors (Choi et al., 2009). Further, behavioral studies have demonstrated that early adolescent antipsychotic exposure enhances animals' sensitivity to reward stimuli (Vinish et al., 2013), impairs working memory, and delays the extinction process of fear memory in adulthood (Milstein et al., 2013). Consequently, due to the lack of research in this area, it is not well understood the long-term consequences that antipsychotic treatment will have on an immature developing brain.

Importantly, the long-term consequences should be of concern as most individuals regardless of sex or developmental age typically continue antipsychotic treatment throughout their lifetime (Harrow et al., 2012). Studies have shown that neurotransmitter release, changes in neuroreceptor levels, receptor-mediated second messenger activities, cell electrophysiology, and behaviors can be affected by antipsychotic treatment (Gao et al., 2015). These changes can result in either an augmentation (sensitization) or decrease (tolerance) of the effects of the drug. For example, low doses of risperidone and olanzapine have been shown to be effective in the treatment of acute psychotic symptoms (Arango et al., 2004; Sikich et al., 2004), while haloperidol-induced sensitization has been associated with the development of extrapyramidal motor effects (Turrone et al., 2005), and increased dopamine sensitivity (Samaha et al., 2007). A critical issue associated with chronic long-term administration of antipsychotic drugs is the potential for changes in the acute effects over time. Moreover, it is likely that these changes are biological and developmentally mediated and thus will impact behavioral and neurochemical response to antipsychotics. For example, previous work in our laboratory has shown that repeated aripiprazole treatment disrupted avoidance responding and inhibition of PCP-induced hyperlocomotion, demonstrating induced sensitization behavioral effects (Gao et al., 2015). Undoubtedly, these results emphasize the need for more research designed to examine the impact of chronic administration of antipsychotic drugs and likely sex and developmental differences that would impact overall efficacy of treatment. In addition, efficacy of treatment is directly affected by compliance of treatment that is most often mediated by severity of side effects reported. Consequently, the noted increases in prescription rate in adolescents and adults have been attributed to the availability of new antipsychotics with fewer extrapyramidal side effects (Cooper et al., 2006) and greater efficacy for broader target symptoms (Buckley et al., 2001), ultimately improving the potential for compliance (Dolder et al., 2002; Menzin et al., 2003).

One such new antipsychotic drug available is aripiprazole (ARI), a third-generation antipsychotic drug, with demonstrated improved extrapyramidal side-effects compared with first generation drugs such as haloperidol and lessened metabolic effects compared with second generation drugs such as olanzapine (Khanna et al., 2014). The reduction in harmful side effects may be due in part to the mechanisms of aripiprazole, although the exact mechanisms remain unclear (Pan et al., 2015). For example, aripiprazole is a partial dopamine D2 receptor agonist, which in part may work to normalize dopamine activity. This may be accomplished by the drugs unique high affinity for dopamine D2 receptors but only as a partial agonist and not a full antagonist. Consequently, at D2 receptor sites where dopaminergic transmission is decreased aripiprazole acts as an agonist. However, at dopaminergic sites of normal or increased transmission, it functions as a stabilizer (Aihara et al., 2004; Shapiro et al., 2003; Burris et al., 2002). In addition, chronic administration of ARI has been shown to be brain region dependent (Pan et al., 2015). Clearly, this may help delineate ARI unique clinical profile and effects. Regardless, these findings suggest drug specificity in antipsychotic drug sensitization and tolerance and demonstrate a clear need to further examine this phenomenon.

The present study investigated this phenomenon by examining the long-term consequences of ARI sensitization in male and female adolescent rats, sex differences in ARI sensitization, and whether ARI sensitization can be transferred to OLZ and/or CLZ, using the conditioned avoidance (CAR) model and the PCP-induced hyperlocomotion model. This paradigm has been validated in previously conditioned place avoidance (CAR) and PCP-induced hyperlocomotion work. For example, repeated administration of ARI produced a sensitization effect in normal adult male rats in the CAR model (Gao et al., 2015). Additionally, it has been shown that repeated OLZ treatment causes sensitization, whereas repeated CLZ treatment causes tolerance (a decreased disruption of avoidance response) in both adolescent and adult rats (Shu et al., 2013). However, it is unclear whether long-term sensitization can be induced in adolescent rats in both sexes.

2. Methods

2.1. Animals

Adolescent male and female Sprague-Dawley rats (51–75 g upon arrival, Charles River, Portage, Michigan, USA) were housed two per cage, in transparent polycarbonate cages (48.3 × 26.7 × 20.3) with food and water available ad libitum, and all animals were maintained on a 12:12 on/off/light/dark cycle. All behavioral testing occurred during the light cycle. All procedures were approved by the University of Nebraska-Lincoln Committee on Animal Care which is consistent with the NIH Guide on Care and Use of Animals.

2.2. Drugs and choice of doses

Aripiprazole (gift from the National Institute of Mental Health drug supply program) was dissolved in a mixed double-distilled water solution containing 30% (v/v) dimethylformamide and 1% (v/v) glacial acetic acid. The dose of aripiprazole (10 mg/kg) was determined based on previous studies in our lab (Gao et al., 2015; Li et al., 2005) and reports in the literature (Carli et al., 2011; Cosi et al., 2006; Li et al., 2004). This dose of aripiprazole was chosen because it results in 85% occupancy, respectively, at one hour post-injection (Natesan et al., 2006), but does not cause catalepsy (Hirose et al., 2004). Importantly, this chosen dose provides animals receptor occupancies that are comparable to observed levels (65–70% occupancy) seen in the clinical population (Kapur and Mamo, 2003). The dose of PCP has been shown in previous studies (Gleason and Shannon, 1997; Kalinichev et al., 2008) to induce a robust hyperlocomotion effect without causing extreme stereotypical behavior. All drugs were administered subcutaneously (sc) at 1.0 ml/kg. OLZ and CLZ (gifts from the National Institute of Mental Health and drug supply program) were dissolved in distilled sterile water with 1% glacial acetic acid. One dose of OLZ (0.5 mg/kg) and one dose of CLZ (5 mg/kg) were tested. It has been demonstrated that repeated OLZ treatment causes sensitization, whereas repeated CLZ causes tolerance in both adolescent and adult rats (Gao et al., 2015). These doses were tested to determine how ARI sensitization would affect OLZ and CLZ exposure.

2.3. Two-way avoidance conditioning apparatus

Eight identical two-way shuttle boxes custom-designed and manufactured by Med Associates (St Albans, VT) were used. Each box was housed in a ventilated, sound-insulated isolation cubicle (96.52 cm W × 35.56 cm D × 63.5 cm H). Each box was 64 cm long, 30 cm high (from grid floor), and 24 cm wide, and was divided into two equal-sized compartments by partition with an arch style doorway (15 cm