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Antipsychotic-induced suppression of locomotion in juvenile, adolescent and adult rats

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Abstract

Schizophrenia is a serious psychiatric disorder that is most frequently treated with the administration of antipsychotics. Although onset of schizophrenia typically occurs in late adolescence, the majority of preclinical research on the behavioral effects of antipsychotics and their mechanism(s) of action has been conducted on adult male animals. In this study, the acute effects of haloperidol (0.03–0.3 mg/kg, i.p.) and clozapine (1–10 mg/kg, i.p.) on locomotor activity were examined in juvenile [postnatal day 22 (PN22)], adolescent (PN40), and adult (>PN70) rats of both sexes. Subsequently, in order to determine whether tolerance to the activity suppressive effects of these drugs would occur in adolescents, PN40 rats were dosed and assessed for an additional nine days. While all groups exhibited some degree of suppression following acute administration of both drugs, juvenile rats were considerably more sensitive to this effect. With sub-chronic administration during late adolescent development (PN40–PN49), tolerance failed to develop. These results emphasize the importance of age in pharmacological characterization of antipsychotics and suggest that pre-adolescents may have enhanced sensitivity to the motor effects of these drugs. Further, they suggest that, similar to adults, older adolescents may not develop tolerance to the activity suppression induced by these two antipsychotics.

Keywords: Adolescence; Clozapine; Haloperidol; Locomotion; Sex differences; Tolerance

1. Introduction

Chronic administration of antipsychotics represents the most common pharmacotherapy for treatment of schizophrenia and other psychotic disorders. The primary mechanism of action of antipsychotic drugs is presumed to be dopamine antagonism, as all known antipsychotics block dopamine receptors with affinities that are positively correlated with their clinical potencies (McQuade et al., 1992; Schotte et al., 1996). Many antipsychotics also affect non-dopamine neurotransmission, which may contribute to their overall pharmacological profile and perhaps to their therapeutic effects. Since onset of schizophrenia (i.e., "first break" psychotic episode) typically occurs during late adolescence or young adulthood, adolescence is a frequent time of initial exposure to antipsychotics. Despite this fact, little research has been done to evaluate the effects of antipsychotics during adolescence. Given that mechanistic research in humans is restricted, most studies that have been done on the behavioral and neurochemical effects of antipsychotics have used animal models.

The majority of this preclinical research has focused on the effects of antipsychotics in adult male animals. Less is known about their effects in females and in adolescent animals. In rats, adolescence is characterized by observation of patterns of behavior that have been observed in young mammals across species (e.g., increased risk taking, novelty seeking, and increased orientation towards peers) and occurs from approximately postnatal day 28 to 42 (PN28–PN42) (Spear, 2000). While dopamine D_1 and D_2 receptors are functional prenatally (Moody et al., 1993) and during the pre-weanling period (Weihmuller and Bruno, 1989), substantial postnatal development of these receptors also occurs between weaning and adulthood. During the periadolescent period, significant pruning of D_1 and D_2 dopamine receptors has been observed in the nucleus accumbens and caudate putamen which is accompanied by increases in the densities of these receptors in rat cortical and hippocampal areas (Tarazi and Baldessarini,

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2000). These differential developmental patterns of dopamine receptors across brain region result in a major shift of predominance of dopamine D_1 and D_2 receptor functioning from subcortical to cortical areas during early adolescence (for a review, see (Spear, 2000)).

Surprisingly, the effects of these pronounced developmental alterations in dopaminergic systems on the behavioral effects of antipsychotics have not been well-studied. Rather, most (but not all) developmental research with these drugs has focused primarily on delineation of their effects after pre- and perinatal administration (Coyle et al., 1985; Cuomo et al., 1985; Napier et al., 1985; Spear et al., 1980), as opposed to dosing during adolescence. Hence, the objective of this study was to investigate the behavioral effects of two prototypic antipsychotics, haloperidol and clozapine, during late adolescence. Older, traditional antipsychotics, such as haloperidol and chlorpromazine, are known to produce extrapyramidal motor effects that are associated with their blockade of dopamine D_2 receptors in the basal ganglia. In contrast, second generation, atypical antipsychotics, such as clozapine and olanzapine, do not produce these motor effects. Preclinically, however, one of the most consistent effects observed with the acute administration of both typical and newer atypical antipsychotics is suppression of voluntary behavior, including motor activity (Simon et al., 2000; Wiley and Martin, 2003) and operant responding for food and water (Gramling and Fowler, 1985; Varvel et al., 2002). Because the ability of immature animals to acquire operant behavior quickly has not been demonstrated, motor activity was selected as the behavioral endpoint for this study.

2. Materials and methods

2.1. Subjects

Adult female Long-Evans rats (Harlan, Dublin, VA) were impregnated by adult male Long-Evans rats (Harlan) in our animal room facility. After breeding, dams were individually housed in clear plastic cages in a temperature-controlled (20–22 °C) environment with a 12-hour light–dark cycle (lights on at 7 a.m.). Plenty of sawdust bedding was available in each cage for nesting. The dams were left undisturbed except for providing food, water, and fresh bedding until they gave birth (postnatal day 0, PN0). Pups were sexed and culled to no more than 10 pups per litter. Pups that were not used in this study were used in other independent studies. They remained with their dams until weaning at PN21. On PN21, pups were separated from the dam and were pair-housed with a same-sex rat from another litter that was assigned to receive the same treatment. Rats in the different dose groups for each drug were randomly chosen from different litters, with the exception that one male and one female from each litter may have been assigned to the same treatment condition. Adult male and female rats (Harlan, Dublin, VA) were aged PN70 or greater when tested. The studies reported in this manuscript were carried out in accordance with guidelines published in guide for the care and use of laboratory animals (National Research Council, 1996) and were approved by our Institutional Animal Care and Use Committee.

2.2. Apparatus

Clear plastic rat cages (22.5 cm width × 44 cm length × 20 cm height) were housed in sound-attenuating cabinets and were used as locomotor chambers. Each cabinet contained up to 12 chambers, with a maximum of 2 per shelf. Chambers did not contain bedding and were wiped with alcohol solution between sessions. Sessions occurred in darkness (i.e., with the cabinet doors closed). A cage rack system with 4 × 8 equally spaced photocell beams on the *X*- and *Y*-axes (Lafayette Instrument, Lafayette, IN) was placed around each chamber (4.5 cm from bottom of cage). Locomotor activity was assessed as total number of beam breaks during the entire 20-minute session.

2.3. Drugs

Haloperidol (McNeil Pharmaceutical, Spring House, PA) was diluted with saline from a commercially purchased 5 mg/ml stock solution. Clozapine (NIMH Chemical Synthesis and Drug Supply Program, Bethesda, MD) was mixed in purified distilled water. Physiological saline was used as a control treatment. All drugs were administered intraperitoneally in a volume of 1 ml/kg. Drugs and saline were administered one hour prior to testing.

2.4. Procedure

Male and female Long-Evans rat pups were randomly assigned to receive one of dose of haloperidol (0.03, 0.1, or 0.3 mg/kg), clozapine (1, 3, or 10 mg/kg), or saline. On test days, rats were transported to the laboratory and were injected intraperitoneally with assigned doses of antipsychotic or saline. One hour later they were placed in locomotor chambers and activity was measured as total number of beam breaks during a 20-min session. After the session, each rat was returned to its home cage. Acute dosing tests for each pup occurred on either PN22 or PN40, dependent upon group assignment (i.e., between subjects design). Test conditions for adult rats were identical to those for the pups. In order to assess tolerance development during late adolescence/young adulthood, some of the rats that were aged PN40 on the day of the acute dosing experiment continued to receive daily injections of saline or their assigned dose of antipsychotic for an additional nine days. Throughout this repeated dosing regimen, an individual rat was always tested in the same locomotor chamber. Because the same rats were used in the acute and repeated dosing experiments, habituation to the locomotor chambers prior to drug administration was not included in the study design.

2.5. Data analysis

For the acute antipsychotic tests, mean (±S.E.M.) numbers of total locomotor counts during the entire 20-min session were calculated for each sex, dose, and age separately. Data for each drug were analyzed separately by sex with two-way factorial (age × dose) ANOVAs. Due to the sex differences in baseline (vehicle) activity (particularly in adults), direct comparisons