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Evaluation of age and sex differences in locomotion and catalepsy during repeated administration of haloperidol and clozapine in adolescent and adult rats

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ABSTRACT

Adolescence is associated with characteristic behavioral patterns as well as with substantial neuronal pruning and re-organization of the brain. Recent research has determined that the effects of various centrally active drugs differ in adolescents and adults. This study examined the motor effects of two prototypic antipsychotics in adult [>postnatal day 70 (PN70)] and adolescent (PN30–PN39) rats. Rats were injected daily with saline, 0.3 mg/kg haloperidol, or 10 mg/kg clozapine for 10 days and activity and catalepsy were measured. Adolescents of both sexes were less sensitive to the cataleptic effects of haloperidol than were adults. Male adolescents were also less sensitive to the cataleptic effects of clozapine, although this difference was transitory. In contrast, female adults showed decreased sensitivity to clozapine's effects, differing from all other groups. These results suggest that adolescents of both sexes may be less sensitive to the extrapyramidal motor effects of haloperidol. Translational implications of the clozapine results are less clear; however, results suggest that developmental differences in neurochemical systems affected by clozapine that are also related to motor behavior may play a role. These results also emphasize the importance of age and sex as determinants of the pharmacological effects of these antipsychotics.
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1. Introduction

Antipsychotics are prescribed for children and adolescents during the course of treatment for a wide variety of psychiatric disorders and other medical conditions, including psychosis, bipolar disorder, Tourette's syndrome, sedation during surgery, and antiemesis [1,2]; however, research to determine whether the effects of these drugs are different during development is sparse. Because this type of research cannot be done in human adolescents, rats and other animal models are typically used. In rats, adolescence occurs from approximately postnatal days 28–42 (PN28–PN42) [3]. During this time period, rats display a characteristic pattern of behaviors (e.g., increased risk taking, novelty seeking, and increased orientation towards peers) that has been observed in adolescent mammals of many species, including humans. In addition, preclinical research results to date have suggested that substantial pruning and re-organization of the dopamine system occurs over the course of development to adulthood, and particularly, during adolescence [for a review, see [3]]. Both typical and atypical antipsychotics (i.e., antipsychotics that have high vs. low liability for producing extrapyramidal motor side effects, respectively) block dopamine D2 receptors in the brain and their affinities for doing so are positively correlated with their clinical potencies [4,5]. Hence, it would not be surprising if ongoing dopamine receptor changes resulted in age differences in responses to antipsychotic administration. Further, these observed developmental differences in the dopamine system may be most likely to be expressed in behaviors for which strong dopaminergic involvement has been demonstrated (e.g., motor behavior), albeit other neurotransmitter systems also modulate motor behavior. To this end, the purpose of this study was to determine whether or not the effects of haloperidol and clozapine (prototypic typical and atypical antipsychotics, respectively) on locomotor activity and catalepsy were age-related. Although clozapine does not produce extrapyramidal motor effects in humans, we have reported previously that it produces motor suppression and catalepsy in adult rodents [6]. Nevertheless, the purpose here was not to model extrapyramidal effects *per se*, but rather to use motor activity and catalepsy as behavioral measures to examine age and sex differences that may be related to underlying developmental and/or hormonal differences in the functioning of neurotransmitter systems that are in the process of re-organization during adolescence, albeit information gained from

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these experiments may also have relevance for motor disorders such as idiopathic or antipsychotic-induced Parkinsonism.

2. Materials and methods

2.1. Animals

Male and female Long–Evans rats were ordered from a commercial breeder (Harlan, Dublin, VA) at ages of PN22–25 or >PN65. These rats would subsequently serve as adolescent or adult subjects, as described in the procedures section below. Upon arrival, rats were housed in clear plastic cages in same-sex, same-age pairs and allowed at least 5 days to habituate to the vivarium. Because of this adaptation period, adult rats did not begin testing until at least PN70. Except for daily test sessions, all rats received free access to food and water in their home cages. The studies reported in this manuscript were carried out in accordance with guidelines published in the *Guide for the Care and Use of Laboratory Animals* [7] 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) and locomotor activity was measured as total number of beam breaks for the entire session. The bar apparatus that was used to measure catalepsy-like behavior consisted of a 280-mm bolt (10 mm diameter) that was attached to a frame by eyebolts. Height of the bar was adjusted based upon the age of the rat (98 mm for adolescents and 130 mm for adults). Each bar apparatus was housed in its own box that was open in the front for experimenter access.

2.3. Procedure

Adolescent (PN30–PN39) and adult (>PN70) rats of both sexes were randomly assigned to receive daily injections of saline, 0.3 mg/kg haloperidol, or 10 mg/kg clozapine for 10 consecutive days. Antipsychotic doses were chosen based upon results of dose–effect curves with each drug that were done as part of another (unpublished) study. In this unpublished study, we found that the chosen doses of haloperidol and clozapine produced catalepsy across a 10-day dosing period whereas lower doses of each drug did not reliably alter the amount of time spent on the bar as compared to saline levels. After at least 30 min habituation time in the lab, each rat was weighed and was injected with saline or with their assigned drug. Subsequently, at 30, 45 and 60 min after the initial injection, the rat was tested in the bar test. The times were chosen within a range that is typically used for adult male rodents, as information concerning onset of action and peak effect for female and adolescent rodents was limited. At each time point, the front paws of the rat were placed on the bar apparatus for 5-min. The total amount of time (in s) that both of the rat's front paws remained in contact with the bar during the 5-min session was recorded. If both of the rat's paws dropped from the bar, they were re-positioned as before. The session timer was stopped during the brief time needed for re-positioning. If the rat voluntarily removed its paws from the bar 10 times during the session, the session was stopped and amount of time on bar was recorded as 0. Invariably, this situation occurred during the first minute of the session and was almost always associated with saline treatment. After the final 5-min bar test (i.e., 65 min after injection), rats were placed into the locomotor chamber for a 15-min session. Locomotor activity was measured as total number of beam breaks for the entire session. After the session, rats were returned to their home cages and transported back to the animal facility. This procedure was repeated daily for 10 days. In order to complete all testing during the short duration of adolescence in rats (approximately 2 weeks), habituation to the locomotor chambers prior to drug administration was not included in the study design. Timing and sequence of tests and injections and handling procedures for the adolescent and adult rats were identical.

2.4. Drugs

Haloperidol (McNeil Pharmaceutical, Spring House, PA) was prepared by adding saline to a commercially available 5 mg/ml stock solution containing 1.8 mg methyl *p*-aminobenzoic acid (paraben), 0.2 mg propylparaben, and lactic acid. Clozapine (NIMH Chemical Synthesis Program, Bethesda, MD) was mixed in purified distilled water. All injections were administered intraperitoneally (i.p.) at a volume of 1 ml/kg.

2.5. Statistical analysis

Locomotor activity was assessed as the total number of photocell beam breaks over the 15-min session. Catalepsy was defined as the amount of time both of the rat (s forepaws were in contact with the elevated bar, as measured during three separate 5-min sessions. Catalepsy score was expressed as percentage of the total 5-min session duration. Mean (±S.E.M.) values for each dependent variable were calculated separately for each sex, treatment condition, day, and age. Locomotor counts and catalepsy scores for each post-injection time point (30, 45, and 60 min) were analyzed separately for each antipsychotic with four-way age × sex × treatment condition (saline vs. drug) × day (repeated) split-plot ANOVAs. Significant two-factor interactions were further analyzed by Tukey *post hoc* tests ($\alpha = 0.05$) were used to compare individual means.

3. Results

Fig. 1 presents the effects of repeated dosing with saline and 0.3 mg/kg haloperidol on catalepsy (top three rows) and locomotor activity (bottom row) in adolescent (PN30–PN39) and adult female and male rats (left and right panels, respectively). The cataleptic effects of haloperidol were assessed at three time points (i.e., 30-, 45- and 60-min after injection). Data for each assessment time were analyzed separately. All comparisons described below for haloperidol-induced catalepsy refer to results of the separate overall 4-factor age × dose × sex × day ANOVAs performed at each assessment time, with Tukey *post hoc* tests (as necessary) used to specify the nature of significant interactions between combinations of two of the four variables. Based on these analyses, haloperidol produced significant catalepsy (compared to saline) in both sexes and at both ages on every day of the 10-day dosing period [dose × day interaction: $F(9, 288) = 9.03$, $p < 0.05$ at 30-min; $F(9, 288) = 5.38$, $p < 0.05$ at 45-min; $F(9, 288) = 3.47$, $p < 0.05$ at 60 min]. Further, at each of the three assessment times, male adolescents were less cataleptic than male adults as well as less cataleptic than females of either age [age × sex interaction: $F(1, 32) = 16.4$, $p < 0.05$ at 30-min; $F(1, 32) = 14.6$, $p < 0.05$ at 45-min; $F(1, 32) = 47.7$, $p < 0.05$ at 60-min]. In contrast, the magnitude of haloperidol-induced

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