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Research report

Time-dependent sensitization of antipsychotic effect in adolescent male and female rats

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ABSTRACT

Many behavioral and biological effects of a psychoactive drug often undergo time-dependent change following even one single drug exposure. The present study examined whether one or two exposures of haloperidol, olanzapine or clozapine would also induce a time-dependent change in their behavioral effects in adolescent rats, and whether such a change vary between sexes. Adolescent Sprague-Dawley rats (< 40 days old) were first treated with one single injection of haloperidol (0.05 and 0.1 mg/kg, sc), clozapine (10.0 and 20.0 mg/kg, sc), 2 injections of olanzapine (1.0 and 2.0 mg/kg, sc) or vehicle, and tested in a conditioned avoidance response (CAR) model or a PCP (3.20 mg/kg, sc)-induced hyperlocomotion model to assess the drug's antipsychotic-like behavioral effects. One or three weeks later, rats were challenged with the drug and their avoidance responses and the PCP-induced hyperlocomotion were re-assessed. One-trial haloperidol and 2-trial olanzapine induced a sensitization, while 1-trial clozapine induced a tolerance effect. The 1-trial haloperidol sensitization was significantly higher at the 3-week time point than at 1-week point, especially in the females. Clozapine tolerance in the conditioned avoidance response model also exhibited the time-dependent increase in both sex groups. Olanzapine sensitization in the PCP model showed a time-dependent change in a sex-dependent fashion. Overall, the time-dependent antipsychotic sensitization and tolerance can be demonstrated in adolescent animals. Many pharmacological (e.g. specific drugs, drug doses), individual (e.g. male versus female) and environmental (e.g. specific behavioral models) factors play a role in the modulation of the strength of antipsychotic sensitization and tolerance.

1. Introduction

When a drug is given repeatedly, many behavioral and biological effects of a psychoactive drug do not remain constant. Two patterns are often reported, sensitization and tolerance, referring to the enhanced and diminished drug effects due to past drug treatment history, respectively [1–6]. Repeated treatment of antipsychotic drugs also cause a sensitization or tolerance effect in a variety of behavioral tests, such as the conditioned avoidance response and phencyclidine (PCP)-induced hyperlocomotion [7–9]. It has been shown that repeated administration of many antipsychotic drugs, including haloperidol (HAL), olanzapine (OLZ), aripiprazole, asenapine, and risperidone causes a progressively enhanced suppression of avoidance response and PCP-induced increase in motor active throughout the treatment days. In a later challenge test, when all the animals are challenged with the same drug, the previously drug-treated animals exhibit a stronger response (i.e., fewer avoidance responses or lower PCP-induced hyperlocomotion) than those previously treated with vehicle [8,10–14]. One exception is clozapine (CLZ), which tends to cause a tolerance in both tests [7,9,31]. More importantly, antipsychotic sensitization and tolerance have even been demonstrated in adolescent rats and these effects persist into adulthood [16–19], against the background of brain maturation [20].

When a drug is only given once or twice, it could still cause a sensitization or tolerance effect, and both effects (tolerance and sensitization) can then progress entirely as a function of the passage

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of time. The observation that a brief exposure to a psychotherapeutic drug such as an antipsychotic or antidepressant drug induces a clinical effect that changes with the passage of time is termed Time-Dependent Sensitization (TDS) [21]. Antelman et al. argued that TDS is a general and nonspecific process reflecting a basic principle of biological functioning in response to the foreignness of an agent (any drug is an exogenous agent to an organism). They also articulated that it is a useful principle for the explanation of clinical improvement which grows with the passage of time. For example, if a certain percentage of observed symptom improvement is due to TDS, then it is possible to manage mental disorders through administering drug treatment every few days, instead of multiple times daily [22]. It should be noted that although it is conventionally termed Time-Dependent Sensitization, it can manifest as either time-dependent enhancement (sensitization) or inhibition (tolerance) [21].

TDS is often demonstrated with agents showing an antidepressant property. Evidence supporting TDS in antipsychotic drugs is limited. In Antelman's earlier work, they found that a single exposure to a clinically low dose of HAL and fluphenazine hydrochloride in rats produced changes in catalepsy that grows over time such that 8 weeks later, when the rats were re-exposed to the drugs, they showed a marked sensitization in cataleptic response [23]. In one of our studies on the time course of antipsychotic sensitization [10], we assessed the magnitude of HAL and OLZ sensitization in the conditioned avoidance response test at 4, 10, or 17 days after the last drug treatment. We did not find that the sensitization induced by 3 daily drug injections (3-trial) changed its magnitude over time, but rather maintained at a high level throughout the post-injection period. In a follow-up study, we also did not observe the time-dependent change in risperidone and asenapine sensitization induced by 5 daily drug injections up to 50 days after the last drug exposure. One possible reason is the ceiling effect; as 3–5 days of drug treatment might have caused too strong of an effect to show any further improvement.

The present study investigated whether one or two exposures of HAL, OLZ or CLZ would induce a time-dependent change in their sensitization and tolerance effects in adolescent rats and whether such a change vary between sexes. We chose to study adolescent rats because there has been a significant increase in the number of children and adolescents who are being treated with antipsychotic drugs in recent years [24–26]. Clinically, younger patients respond to antipsychotic treatment differently (e.g., more vulnerability to the adverse effects) from adults because of their immature brain, smaller size, developing physiology, and negative impact on peer perceptions [20,27]. We were also interested in the possible sex differences because clinical evidence suggests that women react more favorably to antipsychotic therapy than men [28], and preclinical evidence also suggests that sex of animals is an important factor in the modulation of antipsychotic response, with females tending to have increased sensitivity to antipsychotic treatment [29].

2. Materials and methods

2.1. Animals

Adolescent male and female Sprague-Dawley rats (~PND 26) purchased from Charles River Inc. (Portage, MI) or raised in our colony were used. They were housed two per cage, in 39.5 cm × 34.6 cm × 21.3 cm transparent polycarbonate cages under 12-h light/dark conditions (light on between 6:30 am and 6:30 pm). Room temperature was maintained at 22 ± 1 °C with a relative humidity of 45–60%. Food and water was available ad libitum. All behavioral tests took place between 9 am and 5 pm in the light cycle. All procedures were approved by the Institutional Animal Care and Use Committee at the University of Nebraska-Lincoln.

2.2. Drugs and choices of dosage

Haloperidol (HAL) (5.0 mg/ml ampoules, Shanghai Xudong Haipu Pharmaceutical Co., Ltd, Shanghai, China) was dissolved in sterile water. Both OLZ and CLZ (gifts from the NIMH drug supply program) were dissolved in distilled sterile water with 1.0–1.5% glacial acetic acid. Two doses of HAL (0.05 and 0.1 mg/kg), OLZ (1.0 and 2.0 mg/kg) and CLZ (10.0 and 20.0 mg/kg) were tested, respectively. These doses of HAL, OLZ and CLZ acutely inhibit the conditioned avoidance responding and PCP-induced hyperlocomotion [7,9–11,13,16,30,31]. The challenge dose of 0.03 mg/kg HAL, 0.5 mg/kg OLZ and 5 mg/kg CLZ have been successfully used in our previous studies [7,9–11,13,16,30,31] and prevents the floor effect (i.e. a high dose may cause maximal avoidance disruption and obscures the sensitization effect). The injection solution of PCP (3.2 mg/kg, a gift from National Institute on Drug Abuse Chemical Synthesis and Drug Supply Program) was obtained by mixing the drug with 0.9% saline. This dose of PCP was chosen based on previous work showing robust hyperlocomotion [9,11,13,18,32] without severe stereotypy [33,34]. All drugs were administrated subcutaneously (sc) at 1.0 ml/kg body weight. Because normal estrous cycles in female rats are typically observed after 54 days of age [35]. Thus, only our 3-week female groups were expected to exhibit the regular estrous cycle at the time of the drug challenge test. In order to avoid stress associated with vaginal sampling, and ensure both male and female groups, as well as the 1-week and 3-week groups were treated identically at the drug challenge test, we decided not to monitor the estrous cycle of female rats. In addition, we expected this factor being cancelled out within a group and between groups due to the non-synchronization of the estrous cycles among female rats on the day of the drug challenge. In the literature, Prendergast et al. conducted a meta-analysis on sex differences in mice and found that "variability was not significantly greater in females than males for any endpoint." With that outcome came the recommendation that using "female mice in neuroscience research does not require monitoring of the estrous cycle" [36].

2.3. Locomotor activity monitoring apparatus

This apparatus has been described before [8,18]. Sixteen activity boxes were housed in a quiet room. The boxes were 48.3 cm × 26.7 cm × 20.3 cm transparent polycarbonate cages, which were similar to the home cages but were each equipped with a row of 6 photocell beams (7.8 cm between two adjacent photo beams) placed 3.2 cm above the floor of the cage. A computer with recording software (Aero Apparatus Sixbeam Locomotor System v1.4, Toronto, Canada) was used to detect the disruption of the photocell beams and recorded the number of beam breaks. All experiments were run during the light cycle.

2.4. Two-way avoidance conditioning apparatus

Ten 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 a partition with an arch style doorway (15 cm high × 9 cm wide at base). A barrier (4 cm high) was placed between the two compartments, so the rats had to jump from one compartment to the other. The grid floor consisted of 40 stainless-steel rods with a diameter of 0.48 cm, spaced 1.6 cm apart center to center, through which a scrambled foot shock (US, 0.8 mA, maximum duration: 5 s) was delivered by a constant current shock generator (Model ENV-410B) and scrambler (Model ENV-412). The rat location and crossings between compartments were monitored by a set of 16 photo beams (ENV-256-8P) affixed at the bottom of the box (3.5 cm above the grid floor).