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Evaluation of the potential of antipsychotic agents to induce catalepsy in rats: Assessment of a new, commercially available, semi-automated instrument

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ABSTRACT

Haloperidol induced catalepsy was determined using the classic bar test and a new MED Associates Catalepsy Test Chamber instrument. The dose that produced an adverse effect in 50% of rats (AED_{50}) for haloperidol was calculated using the instrument data as 0.29 mg/kg. Hand scoring of the video recordings gave AED_{50} values of 0.30 and 0.31 mg/kg, both well within the 95% CL of the instrument data. Clozapine was also evaluated and catalepsy was not detected up to 40 mg/kg. No significant difference was found between the instrument and hand scoring data. The instrument was useful for testing haloperidol and clozapine, relieving much of the tedium and variability experienced without its use. It was especially valuable at measuring shorter time periods, where the researcher cannot react as quickly. Finally, olanzapine was also evaluated. However, clenched forepaws and hind paws prevented the use of the instrument alone at higher doses. A backup stopwatch was used for the bar test in these cases. Some of the advantages and limitations are discussed.

Results are also compared to the crossed-legs position (CLP) test for all three antipsychotics. While haloperidol gave similar results at all concentrations tested, clozapine deviated significantly at the highest dose (40 mg/kg) displaying catalepsy in the CLP test but not in the bar test. Olanzapine displayed catalepsy in rats significantly different from vehicle at 40 mg/kg in both the bar and CLP tests. However, the CLP test may be more suited to compounds with gripping problems which prevent the consistent grasping of the bar.

Overall, the instrument was found to be a useful aid in conducting the bar test for catalepsy. The CLP test was found to complement the bar test under certain conditions and could provide additional data that might be missed by the bar test for compounds producing grasping problems.

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1. Introduction

Results from Phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study indicated that 74% of schizophrenic patients discontinued the use of antipsychotic drugs within 18 months due to medication efficacy problems, intolerable side effects, or the patient's decision (Lieberman et al., 2005). Extrapyramidal side effects (EPS) accounted for 8% and patient decision (patient independently chose to stop treatment) accounted for 30% of the discontinuation of low doses of the representative typical antipsychotic drug perphenazine in this study. Consequently, the development of new antipsychotics with reduced or no EPS has been a major driving force in drug development to improve patient compliance in taking of antipsychotic medications (Åberg et al., 2010; Meltzer et al., 2003; Wadenberg, 1996).

To affect that end, the rodent catalepsy test has been developed to predict EPS in patients using antipsychotic medications and is an important component of the drug discovery process (Hoffman and Donovan, 1995). Neuroleptics producing severe EPS in patients have been found to also produce potent catalepsy in rats (Seeger et al., 1995). Most definitions of catalepsy in rodents refer to placing the animal in an unusual position and observing the time the animal remains in this position (Castagne et al., 2009; Sanberg et al., 1988; Wadenberg, 1996). For a given set of experimental and apparatus variables, the longer the rat stays in the position, the more cataleptic the response and hence the prediction of more pronounced EPS in patients taking the antipsychotic.

One of the most widely used catalepsy tests is the bar test (Ellenbroek, 1993; Sanberg et al., 1988). Typically, in this test, the forepaws of the rat are placed on a bar elevated to 10 cm for example, with the hind paws remaining on the floor. The time until descent to the floor or some other change in posture is then recorded. Unfortunately, as pointed out by Sanberg et al., 1988 and others (Ferre et al., 1990; Sanberg et al., 1996), this simple sounding test is anything but simple, with numerous variations having been used throughout the literature, making comparison of data from different laboratories difficult, especially if all the details are not defined in the article. Some of the variables include number of forepaws on the ground to define catalepsy time, height of bar, diameter of bar, shape of bar (round, rectangular, twisted wire), material used for bar (smooth steel, wood, wire), weight of animal, species of animal, cut-off times for recording catalepsy, reporting seconds in cataleptic position or converting seconds to a score, repeated

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testing versus one time testing, researcher interpretation of postural change, and researcher reaction time, fatigue or inattention. Automation would help simplify and standardize some of these variables.

Various prototypes for automating the measurement of catalepsy using the bar test have been described in the literature, including a timer activated by the rat with no computer storage of data (Moss et al., 1981), using an animal infrared beam activity monitoring system to record vertical motion to detect when one paw was removed from the bar (Sanberg et al., 1988) and a homemade electronic system consisting of a wooden chamber with metal floor and metal bar, Reduced Instruction Set Computer (RISC) microcontroller, Electrically Erasable Programmable Read Only Memory (EEPROM), and other electronic components interfaced to a personal computer (Alvarez-Cervera et al., 2005). Our lab has routinely utilized the bar test and the crossed legs position (CLP) test in evaluating the potential of synthetic antipsychotic agents to induce catalepsy (Bricker et al., 2012; Ablordeppey et al., 2008; Lyles-Eggleston et al., 2004; Sikazwe et al., 2003). In an attempt to overcome some of the challenges related to the use of the bar test in evaluating the potential of synthetic agents to induce catalepsy in rats, we selected a commercially available instrument to use in our work. The purpose of this study is two-fold: first, to evaluate the relatively new, commercially available, electronic, complete system for catalepsy in rodents using the bar test, and secondly, to compare the bar test to the CLP test so as to ascertain their effectiveness in identifying the potential of standard drugs (haloperidol, clozapine, and olanzapine) to induce catalepsy in rats.

2. Materials and methods

2.1. Animals

All experiments were carried out on male Sprague–Dawley rats (120–200 g), (5.5–7 weeks old) from Harlan Laboratories, Inc., with no prior drug experience. Animals were housed in the Florida A&M University Animal Care Facility which is fully AAALAC accredited, and operates with a 12 h light/dark cycle and controlled temperature (24 ± 2 °C). The rats were given free access to food and water and at least 5 days to adjust before the start of each experiment. Rats were then fasted the night before each experiment. All experimental procedures were performed in accordance with protocols approved by the Florida A&M University Institutional Animal Care and Use Committee.

2.2. Drugs and chemicals

Haloperidol and clozapine were purchased from Sigma and Olanzapine was purchased from AK Scientific in free base form and were dissolved in filtered (0.22 μ) 1% lactic acid vehicle for all the animal studies. The lactic acid was from Fisher Scientific (ACROS) and was ACS grade. Water used to make solutions was HPLC grade. Doses are reported as the free base and were given in a volume of 10 mL/kg by intraperitoneal (ip) injection.

2.3. Instrument description

As first partially reported by us in Bricker et al., 2012, a new instrument, the Catalepsy Test Chamber (Med Associates, Inc., St. Albans, VT) shown in Fig. 1, was used to assist in performing the classic catalepsy bar test with rats and is further evaluated in this work. The forelimbs were placed on a 1.3 cm diameter (4 diameters available) horizontal cylindrical metal bar at a comfortable standing height of 10 cm (8 heights available) and the hind limbs were placed on the stainless steel floor. The instrument measures the time that contact is maintained between the floor and the bar and collects the data using computer software. Contact time in seconds was recorded up to a maximum of 30 s. The instrument automatically began collecting data as soon as a complete electrical circuit was made. A video-recorder was available to record each session. Two researchers per compound independently analyzed the video recordings at a later date for comparison to the instrument data. Four chambers were used although up to 8 chambers may be connected per input card.

2.4. Behavioral procedures

2.4.1. Bar test for catalepsy

Sixty minutes after injection with haloperidol, clozapine, olanzapine, or vehicle, the rats were evaluated in the bar test for 30 s followed by the CLP test (see Section 2.4.2) for 30 s, followed by the righting test (see Section 2.4.3) then returned to their home cage. The 60 minute time

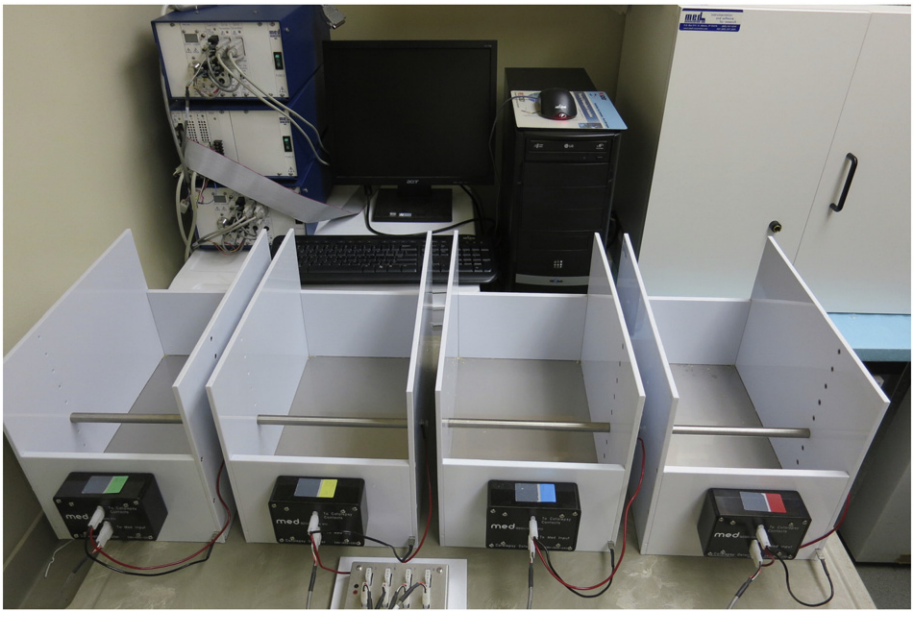

Fig. 1. Med Associates Catalepsy Test Chamber system. Four white test chambers with bars are shown in the foreground. Computer used for data collection and associated hardware (center blue module on left only) are shown in the background. Other units are for other test systems.