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Effects of Antimuscarinic Antiparkinsonian Drugs on Brightness Discrimination Performance in Rats

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LIU, W. F. *Effects of antimuscarinic antiparkinsonian drugs on brightness discrimination performance in rats.* PHARMACOL BIOCHEM BEHAV **54**(2) 425–430, 1996. – Biperiden (BPR) and trihexyphenidyl (THP), the current antimuscarinic drugs of choice in the management of parkinsonism, have been shown to exert anticonvulsant effects induced by poisoning by the organophosphorus compound soman. The present study was undertaken to evaluate the effects of these drugs on performance of a simple light-intensity discrimination task in rats under a tandem schedule of fixed-ratio (FR) reward/differential-reinforcement-of-low-rate (DRL) nonreward contingencies, for water reinforcement in 2-h experimental sessions. Both BPR (0.125–2.0 mg/kg, SC) and THP (0.25–8.0 mg/kg, SC) in general decreased overall reinforcement rates in a similar dose dependent and parallel manner, concurrent with increased overall nonreinforced responses in an inverted U-shaped dose-response relationship. Lower doses of BPR (0.125–0.5 mg/kg) and and THP (0.25–2.0 mg/kg) produced a moderate reduction in reinforcement (≥ 50% of baseline controls), which was correlated well with increases in nonreinforced responses emitted, whereas, higher doses of BPR (>0.5 mg/kg) and TPH (≥2.0 mg/kg) markedly decreased reinforcements, which mainly resulted from the pausing of responding in the presence of stereotyped behavior. The behavioral disruption induced by BPR was much more rapid than that induced by THP. The ED_{50} values (0.6 mg/kg vs. 1.3 mg/kg, respectively) and parallel dose-effect curves suggest that these drugs have similar efficacy, and that BPR is about twice as potent as THP, a ranking that corresponds with their binding affinity at M-1 muscarinic acetylcholine receptors in rat cerebral cortex. Based on the similarity between the anticonvulsant doses of these drugs and the maximal doses that in this study did not disrupt operant responses (0.125 mg/kg vs. 0.25 mg/kg, respectively), it is suggested that both drugs may be useful in protection against seizures produced by the cholinesterase inhibitor soman. Overall, these results suggest that this multiple schedule operant contingency may have promise as a behavioral model to identify the therapeutic or toxic potentials of centrally acting antimuscarinic antiparkinsonian drugs based on their congnitive side effects.

Antimuscarinics Biperiden Trihexyphenidyl FR/DRL schedule Brightness discrimination
Operant behavior U-Shaped dose-response curve

THE antimuscarinic agents,such as biperiden (BPR), trihexyphenidyl (THP), and others are widely used in psychiatric practice for the management of Parkinsonism, and the treatment and prevention of the extrapyramidal side effects of neuroleptic medications (5,16). In addition, it also has been found that both BPR and THP are potent anticonvulsants in soman poisoning (4,17,20). However, the use of these agents has been reported to have stimulant-euphoric and deliriant or psychotoxic effects and abuse liability, which are dose and individual susceptibility dependent, in both psychiatric and normal populations (5,7,16,19,21). Relatively few animal studies examining the effects of BPR and THP on schedule-controlled behavior have been conducted, although they have been shown to increase motor activity in mice (10) and cats (2).

It has recently been shown that THP, like scopolamine, produced a dose-dependent decrease in the rate of responding under a variable-interval schedule of food reinforcement (9) and disrupted memory performance in an operant task of spatial alternation (3) in rats. To the author's knowledge, no operant behavior data for BPR has been reported previously. Thus, a comprehensive comparison of the effects of BPR and THP on schedule-controlled behavior in one single experiment has yet to be carried out.

The present experiment was designed to assess the effects of BPR and THP on performance by rats of a simple bright-

ness discrimination task under a multiple (alternative) FR 10-response/DRL 10-s schedule for water reinforcement. Both dose-response and time course data were collected for both drugs. This multiple schedule has been used in the investigation of cholinergic drug effects in rat (13,14).

METHOD

Subjects

Ten male Sprague-Dawley rats weighing between 300–400 g were used in this study. They were housed individually in polycarbonate cages in a room of constant temperature (20–24°C) under a 12 L : 12 D cycle (light onset 0600 h). The rats were maintained on a 22-h water deprivation schedule. Purina rat chow was freely available in the home cage. The rats had no prior experimental or pharmacological experience.

Apparatus

Four identical standard rat operant chambers with grid floors were used to train and test all subjects. Each chamber was fitted with a response lever and dipper mechanism that delivered 0.01 ml of tap water. The discriminative stimuli were provided by a 10 W (110 VAC) houselight bulb. Luminance of the visual stimulus in each chamber was controlled by a rheostat in series with the bulb. The intensity ratio of the stimuli (dim/bright, S−/S+) was approximately 0.6. No other illumination was present during the session. All events were controlled by an Omron C-20 programmer (Japan), and the data were collected by an Acer 1100 computer (Taiwan, R.O.C.). The computer recorded the number of lever responses (i.e., S+ and S− responses, designated as reinforced and nonreinforced responses) and the number of reinforcements per 10-min blocks, and the total number of lever presses per 120-min session made by the rat. These measures were printed out at the end of each session and constituted the raw data for analysis.

Behavioral Procedure

The multiple FR 10-response, DRL 10-s schedule used in the present experiments was as follows. The duration of discriminative stimuli was 10 s. When the houselight was bright (S+), the FR-10 component was in effect such that the animal had 10 s to make 10 responses to earn a water reward; when the houselight was dim (S−), the DRL-10 s component was in effect such that each lever press response during the 10 s S− period had no water reward, but postponed the opportunity to initiate an FR component for an additional 10 s. Schedule components alternated regularly after the 10 s limited hold elapsed.

Experimental sessions always started in the FR-10 component and lasted for 2 h. Each animal was run at the same time each day and in the same cage 5 days a week (Monday through Friday). To maintain normal water/food balance, an additional 10 min free access to drinking water was made available in the home cage following operant sessions. This procedure is described in more detail elsewhere (14).

Drugs

Biperiden lactate (BPR; Akineton, from Abbott, UK) was obtained commercially in a solution of 5 mg/ml. Trihexyphenidyl hydrochloride (THP) was purchased from Sigma Chemical Company (St. Louis, MO). Both drugs were dissolved in sterile saline solution and administered subscutaneously (SC) in a volume of 1.0 ml/kg of body weight. Drug solutions were prepared on the day of injection and all doses are expressed in terms of the salt.

Pharmacological Procedure

After all 10 rats reached steady performance on this multiple schedule, drug treatments were initiated. The steady performance was defined as a coefficient of variation less than 10% on both the overall reinforced and nonreinfored responses during three consecutive sessions. They were allocated into two groups of five (n = 5/group). One group received five doses of BPR (0.125, 0.25, 0.5, 1.0, and 2.0 mg/kg) or saline, and the other received six doses of THP (0.25, 0.5, 1.0, 2.0, 4.0, and 8.0 mg/kg) or saline. Injections were given once a week (usually on Fridays), and data from Thusday's sessions were treated as noninjection controls. This procedure was employed to avoid any carryover effects of the drugs on the succeeding days. Each drug dose was given in a random order. The drugs were administered SC immediately before the start of the sessions.

Data Analysis

The measures of main interest were total reinforcements earned and total nonreinforced responses emitted per 2-h session, expressed as percentages of the predrug control values, and the number of reinforcements earned in each 10-min blocks, which were used for the time course determinations. An overall analysis of the data was carried out using an analysis of variance (ANOVA) with repeated measures. Prior to the analysis of nonreinforced responses, the data were Square Root transformed ($X' = \sqrt{x + 0.5}$) to achieve normality of distribution. If the outcome of the ANOVA reached a level of $p < 0.05$, dose group comparisons were then performed using a two-tailed protected Tukey's test. In addition, regression analysis was performed on each data set to test for the presence of a linear dose trend and to estimate the ED_{50} values. Significant treatment effects were accepted at only $p < 0.05$.

Because both biperden and trihexyphenidyl produced individual subject-dependent and dose-related pausing in responding over the 10-min blocks, the TD50 values (i.e., the dose-eliciting evidence of paucing in 50% of rats), analyzed by the method of Litchfield and Wilcoxon analysis (12), and the onset and duration of pausing on the 10-min time based were also calculated.

RESULTS

Control Performence

The rats exhibited stable performance after approximately 8 to 10 weeks of training under the tandem FR/DRL schedule. The theoretical maximun number of reinforcements in a 120-min session is 360. The average baseline number of reinforcements and nonreinforced responses per session for the BPR group of (n = 5) was 254.8 ± 36.2 (range 120–320) and 25.2 ± 5.0 (range 19–44), respectively. The average baseline number of reinforcements and nonreinforced responses per session for the THP group of rats (n = 5) was 242.6 ± 31.0 (range 160–331) and 31.4 ± 7.3 (range 12–51), respectively. These baseline data as noted above are obviously comparable for both group of animals; however, both groups of animals had great variance in the efficiency of reinforcement, ranging from 33 up to 92%.

Dose-Response Effects

The overall effects of BPR (0.125-2.0 mg/kg) and THP (0.25-8.0 mg/kg) on the reinforcement rate under the multiple schedule are shown in Fig. 1. A repeated measures ANOVA revealed significant effects of both BPR, $F(5, 20) = 28.1$, $p < 0.001$, and THP, $F(6, 24) = 66.9$, $p < 0.001$, treatments. The lowest doses of BPR and THP to produce reliable ($p < 0.05$) suppression of operant performance were 0.25 and 0.5 mg/kg, respectively. Linear regression analyses on the functions of effective doses produced by these two drugs revealed a significant log dose vs. mean % response relationships for BPR, with a correlation coefficient of $r = 0.983$ ($p < 0.05$) and the slope $S = -66.9$; and for THP, with $r = 0.997$ ($p < 0.01$) and $S = -64.6$. Obviously, the dose-effect curves for these drugs are parallel in nature (see Fig. 1). The ED_{50}s with 95% confidence limits for the suppressant effects compared to the saline controls were 0.6 (0.5-0.7) mg/kg for BPR and 1.3 (1.2-1.4) mg/kg for THP, respectively.

The effects of BPR and THP on nonreinforced responses are shown in Fig. 2. A repeated measures ANOVA revealed significant treatment effects for both BPR, $F(5, 20) = 3.01$, $p < 0.05$, and THP, $F(6, 24) = 3.70$, $p < 0.01$; with significant dose effects at 0.25 and 0.5 mg/kg for BPR, and at 0.5-4.0 mg/kg for THP. As shown in this figure, both drugs produced inverted U-shaped dose-dependent increments in nonreinforced response, with maximal effects at doses of 0.5 mg/kg and 2.0 mg/kg for BPR and THP, respectively. The finding that the doses higher than the peak ones, which reduced reinforcements to $\leq 50\%$ of baseline control (see Fig. 1), yielded a nonsignificant increase in nonreinforced responses may be attributed to the finding that some rats actually did not emit any responses over a certain period of time

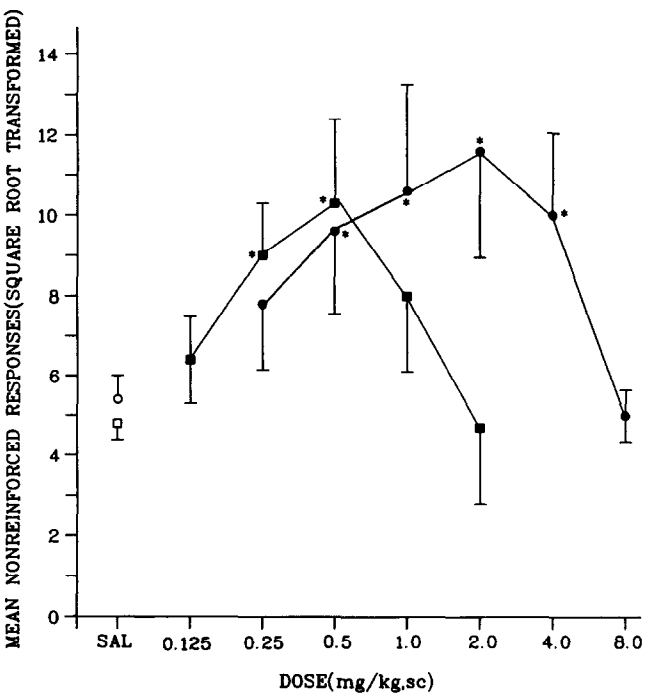

FIG. 2. Dose-effect functions of biperiden (squares) and trihexphenidyl (circles) on the overall nonreinforced responses under a multiple FR/DRL, brightness discrimination schedule of water reinforcement in rats. Each point represents the mean ± SEM of nonreinforced responses/session (square root transformed) of five rats. Asterisks indicate significant differences from respective saline controls (p's < 0.05; Tukey's test).

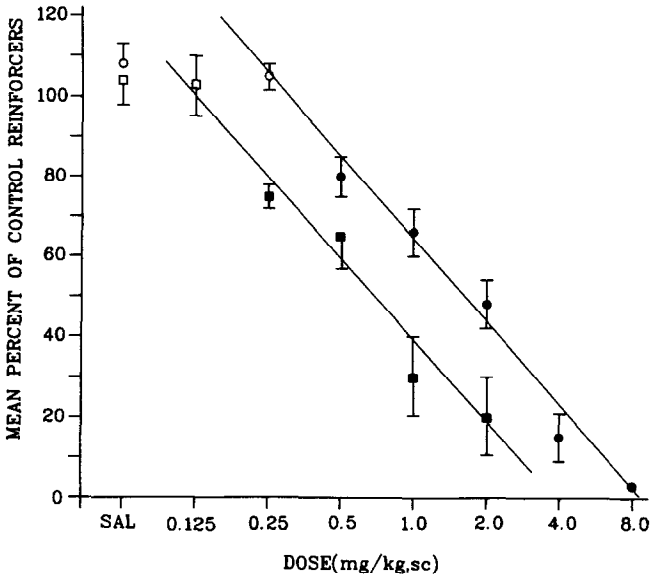

FIG. 1. Dose-effect functions of biperiden (squares) and trihexphenidyl (circles) on the overall rate of reinforcement in rats under a multiple FR/DRL, brightness discrimination schedule of water presentation. Each point represents the mean ± SEM of five rats expressed as percentage of control performence. The filled symbols indicate significant differences from respective saline control values as determined by Tukey's test (p's < 0.05). Lines were fitted by the method of least squares.

during the operant sessions. This can be observed from the raw data recorded (see Table 1). The relationships between the mean increment in nonreinforced responses and the mean % of decrement in reinforcements over the doses that reduced reinforcements to approximately $\geq 50\%$ of baseline control values appeared to be well correlated, i.e., BPR at doses of 0.125-0.5 mg/kg with $r = -0.998$ ($p < 0.05$) and THP at doses of 0.25-2.0 mg/kg with $r = -0.990$ ($p = 0.01$).

Time Course Effects

The time course effects of BPR and THP on operant performance as indicated by the reduction of reinforcements, analyzed for the 12 consecutive 10-min periods, were analyzed as follows.

A two-way repeated measures ANOVA (dosages × time blocks) revealed significant BPR effects for dose, $F(5, 24) = 9.12$, $p < 0.001$, time, $F(11, 264) = 6.28$, $p < 0.001$, and the dose × time interaction, $F(55, 288) = 5.97$, $p < 0.01$. Using the Tukey's test it was found that at 0.125 and 0.25 mg/kg BPR, the mean numbers of reinforcers were not significantly (p's > 0.05) below the saline control level during any time blocks. At 0.5 mg/kg, the mean number of reinforcers was significantly ($p < 0.05$) below the saline control level during the 4th to 12th time blocks. At 1.0 mg/kg, it was significantly lower than control level from the 3rd time block to the end of the 10-min time blocks. At 2.0 mg/kg, it was significantly below control during the whole session.

A two-way repeated measures ANOVA (dosages × time

TABLE 1

TIME-COURSE EFFECTS OF BIPERIDEN AND TRIHEXYPHENIDYL INDUCED OVERALL REINFORCEMENT LOSS AND CESSATION OF RESPONDING UNDER A MULTIPLE FR/DRL, BRIGHTNESS DISCRIMINATION SCHEDULE OF WATER REINFORCEMENT IN A 120-MIN SESSION IN RATS

	Overall Reinforcement Loss		Cessation of Responding		
Drug and Dose (mg/kg, SC)	Onset	Duration	No. Rats Affected	Onset	Duration
Biperiden					
0.125	–	–	0	–	–
0.25	–	–	0	–	–
0.5	30	90	2	20 ± 0	35 ± 5
1.0	20	100	2	5 ± 5	115 ± 5
2.0	<5	120	3	3 ± 3	117 ± 3
Trihexyphenidyl					
0.25	–	–	0	–	–
0.5	50	20	1	50 ± 0	60 ± 0
1.0	20	100	3	73 ± 22	40 ± 15
2.0	10	110	3	70 ± 15	50 ± 15
4.0	<5	120	5	38 ± 14	82 ± 14
8.0	<5	120	5	10 ± 3	110 ± 3

n = 5/group.
Time in minutes, mean ± SEM.

blocks) also showed signifcant THP effects for dose, $F(6, 28) = 11.30$, $p < 0.001$, time, $F(11, 308) = 7.16$, $p < 0.001$, and the dose × time interaction, $F(66, 336) = 6.74$, $p < 0.001$. At 0.25 mg/kg of THP, the mean number of reinforcers was signifcantly ($p < 0.05$) below the saline control level during the 6th and 7th time blocks. At 1.0 mg/kg, it was significantly lower than the control from the 3rd time block to the end of time blocks. At 2.0 mg/kg, it was signifcantly below the control level from the 2nd time block to the end of the experimental session, while at both of the 4.0 and 8.0 doses they were significantly below the control level throughout the whole session.

The time course data as described above are arithmetically presented in Table 1.

Pause-Inducing Effects

Inspection on the raw data for reinforced and nonreinforced responses, and the associated reinforcement during the 12 consecutive 10-min periods recorded, showed that for both drugs doses ≥0.5 mg/kg, neither reinforced nor nonreinforced responses were emitted at various time blocks by some of the same rats. These rats showed stereotyped movements in the test chambers. In other words, both drugs induced dose-related pausing (i.e., cessation of responding) in an all-or-none fashion. For BPR dosings, the proportion of rats in the group ($n = 5$) exhibiting pause was 2 out of 5, 2 out of 5, and 3 out of 5 for 0.5, 1.0, and 2.0 mg/kg doses, respectively. For THP regimens, the proportion of this group of rats ($n = 5$) exibiting pausing was 1 out of 5 for 0.5 mg/kg, 3 out of 5 for both 1.0 and 2.0 mg/kg, and 5 out of 5 for both 4.0 and 8.0 mg/kg doses. The TD_{50} values (95% confidence limits) (i.e., the dose-eliciting evidence of pausing in 50% of rats), analyzed by the Litchfield and Wilcoxon procedure, were calculated as 1.3 (1.1–2.4) mg/kg and 1.0 (0.8–1.1) mg/kg for BPR and THP, respectively; this indicates that THP is slightly more potent than BPR in eliciting pausing of responding.

The onset and duration of pausing produced by BPR and THP in the affected rats, as estimated from the 12 consecutive 10-min time blocks during the 2-h experimental sessions, are presented in Table 1. On the basis of these results, it was found that the number of rats affected and their latencies to onset and duration of action were all dose related. At the same dose levels, such as 1.0 and 2.0 mg/kg, BPR had the average onset latencies (ca., 5 min) much faster than those of THP (ca., 70 min).

DISCUSSION

In the present study, a steady-state performance was maintained under a multiple schedule of FR 10-response and DRL 10-s components. The FR component was signalled by a 10-s period of bright stimulus (S+) correlated with the opportunity for reinforcement. The DRL component was signalled by a dim stimulus (S−), correlated with no likelihood reinforcement on a 10-s limited hold of responding. Both components alternated successively in a tandem procedure. Accordingly, this conjuctive schedule is functionally analogous to either a variant of nonrewarded DRL schedule or a visual conditional go/no go discrimination paradigm. Thus, any changes in performance indicate changes in the subject's capability of temporal or visual attention, and drug-induced changes in performance of this tandem schedule may also resemble those observed under a simple DRL schedule.

The results of the present study demonstrate that BPR (0.125–2.0 mg/kg) and THP (0.25–8.0 mg/kg) produced parallel dose–effect curves on the overall reinforcement loss, concomitant with inverted U-shaped dose–effect curves on the increased nonreinforced responses. This suggests that the mode of action of both drugs may be the same. Low doses of

PBR (0.125–0.5 mg/kg) and THP (0.25–2.0 mg/kg), which produced dose-related linear increases in nonreinforced response, are well correlated with the decreases in reinforcement frequencies. Higher doses of these drugs (≥0.5 mg/kg) also produced dose-related single and long pauses in responding. The exact dose level separating the increment in nonreinforced responding from the pausing of overall respondings was uniquely dependent on individual susceptability. The time course data on performance disruption in terms of the overall decrements in reinforcement reveal that both BPR at ≥0.5 mg/kg and THP at ≥1.0 mg/kg doses had suppressive effects within 30 min after SC injections, which lasted 90 min longer. In terms of the pausing effects produced, the onset and duration of actions were not quite comparable to those of their respective overall performance disruptions dose relatedly, with the exception of the highest doses of both BPR (2.0 mg/kg) and THP (8.0 mg/kg), which exhibited the same time course effects. However, at equivalent doses of both drugs (e.g., 1.0 and 2.0 mg/kg), the pausing effects occurred at the start of experimental session after BPR treatments, and at about halfway (ca., 70 min) after THP dosings (see Table 1); these results, in terms of cessation of responding, indicate that at higher dose levels, BPR has a nonspecific disruptive effect on operant performance much faster than that of THP. The finding that THP affected performance in the brightness discrimination task at the minimal effective dose (0.5 mg/kg) lower than that necessary to affect both the memory performance in a spatial alternation task (1.0 mg/kg) (3) and the operant performance in a variable-interval schedule (3.0 mg/kg) (9) in the same species, suggests that the present task may be more sensitive to antimuscarinic activity than some others.

On the basis of the above findings, both BPR and THP at low to moderate dose levels affected responding under the tandem FR/DRL schedule in a qualitatively manner similar to the other potent anticholinergics such as atropine (8), scopolamine (18), and quinuclidinyl benzilate (15) in rats responding under the simple DRL schedules of different limited hold periods, which all symmetrically increased response rate and decreased reinforcement rate. The generality of this effect may be indicative of a cholinergic involvement in sensory or decisional processes [cf. (24)] in low doses rather than an additional involvement of nonspecific actions when given in high doses. The higher doses of BPR and THP that greatly disrupted operant performance, mainly via cessation of responding, were observed to be in concert with the presence of elicited stereotyped behavior. This nonspecific suppression of responding probably reflects not a reduction of reinforcer efficacy, but rather, physical debilitation of the organism.

It has been evident that both BPR and THP, like pirenzepine, have relatively selective binding affinity on the muscarinic M-1 subtype of receptors in rat cerebral cortex (1,22,23), with the order of potency of BPR being greater than THP, which are in agreement with the behavioral data presented here that both drugs have parallel dose–response functions on operant performance disruption, with BPR approximately twice as potent as THP. These data indicate that the cerebral M-1 receptor site is likely to be involved in the behavioral effects of BPR and THP. Furthermore, it also has recently been claimed that the cerebral M-1 receptor is mainly involved in the initiation of seizure activity (6), which could explain why both drugs have protective efficacy against the convulsant effects of soman (4,17,20).

The effective anticonvulsant doses of both drugs (0.125 mg/kg) in the same species as reported by Shih and his colleagues (4,20) are equal to or below the behavioral deficit-free (BDF) doses of BPR (0.125 mg/kg) or THP (0.25 mg/kg), respectively, in the present study. These data suggest that both drugs showed have favorable protective actions against soman poisoning. In clinical practice, the current therapeutic doses in humans, expressed as mg/kg/day, used for the management of parkinsonism are 0.13 mg/kg for BPR and 0.25 mg/kg for THP, respectively (2,5), which are equivalent to the BDF doses of the present rat model. This dose equivalency on mg/kg basis suggests that the present rat model may have predictive potential for the quantitative risk assessment of the cognitive toxicity of antimuscarinic drugs under clinical conditions with therapeutic use of these drugs.

In conclusion, BPR and THP produced similar effects on the performance of rats whose behavior was maintained under a multiple FR/DRL schedule of brightness discrimination. Both drugs generated an inverted U-shaped dose–effect curve on the increased nonreinforced responses, and concomitently decreased the reinforcement efficiency in a dose-related and parallel manner. The present results show that a) these drugs have similar efficacy; b) their behavioral potencies parallel the pharmacological data for binding affinity at central M-1 muscarinic receptors; and c) suggest based on the similarity of the psychometric properties between the present rat model and clinical findings that this task may serve as a sensitive and reliable measure to identify, qualitatively and quantitatively, the cognitive toxicity of centrally active antimuscarinic drugs.

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