Available online at www.sciencedirect.com

SCIENCE DIRECT

European Journal of Pharmacology 498 (2004) 125–134

www.elsevier.com/locate/ejphar

Within-session repeated acquisition behavior in rats as a potential model of executive function

Harlan E. Shannon*, Patrick L. Love

The Lilly Research Laboratories, Neuroscience Division, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, United States

Received 25 March 2004; accepted 8 April 2004
Available online 21 August 2004

Abstract

Higher levels of cognition, such as executive functions, are known to be disrupted in psychiatric disorders such as schizophrenia. As a potential model of executive function, rats were trained in a three-lever operant conditioning chamber to respond on two of the three levers in one of six possible correct sequences. When the rat completed a two-response sequence correctly for 10 consecutive trials, the correct sequence was randomly changed to another two-response sequence without signaling the rat. Rats readily acquired the behavioral baseline and completed all six response-sequences within a 60-min session. Phencyclidine, MK-801 ((5*S*,10*R*)-(+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine), apomorphine, scopolamine and triazolam all produced dose-related decreases in the total number of sequences completed. Phencyclidine and MK-801 markedly increased all errors while scopolamine produced modest increases; triazolam increased only total and intrarule errors, while apomorphine had no significant effect on errors. The present results suggest that within-session repeated acquisition of response sequences has the potential to be a useful model for studying executive function in rats.

Keywords: MK-801; Phencyclidine; Triazolam

1. Introduction

Since its earliest conception as ‘dementia praecox’ (i.e., early onset dementia), impaired cognitive function has been recognized as an important part of the symptomatology of schizophrenia (e.g., Kraepelin, 1919; Bleuler, 1950). Patients with schizophrenia exhibit deficits in a variety of cognitive domains, including sensorimotor gating, attention, memory, language, and executive function (e.g., Goldberg and Gold, 1995; Nathaniel-James et al., 1996; Weickert et al., 2000; Kuperberg and Heckers, 2000). There are well-known animal models for studying sensorimotor gating (e.g., Braff et al., 1978, 1992), attention (e.g., Muir, 1996) and memory (e.g., Spear et al., 1990). However, animal models for studying executive function are relatively unknown; and therefore, there is a need to develop animal models for studying executive function.

Executive function is a hypothetical construct which refers to a collection of loosely related higher-order cognitive processes which include planning, hypothesis generation, cognitive flexibility, decision making, judgment and feedback utilization (e.g., Lezak, 1982). In humans, one method for investigating executive function is the Wisconsin Card Sort Test (WCST; e.g., Goldberg and Gold, 1995). The WCST requires subjects to sort into groups, according to one of four possible rules, cards that vary simultaneously in a number of dimensions (color, form and number of elements). The subject is told only whether each placement is correct or incorrect, and must discover the correct sorting rule from this feedback. When a rule has been learned, the correct rule is changed without informing the subject of this change. An animal model of executive function, therefore, might then involve requiring animals to respond according to a ‘rule’ until it has exhibited mastery of the rule, and then to change the

* Corresponding author. Tel.: +1 317 276 0751; fax: +1 317 276 5546.
E-mail address: H.Shannon@Lilly.com (H.E. Shannon).

0014-2999/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.04.054

rule without signaling the change to the subject. Behavioral models similar to the Wisconsin Card Sorting Test would require animals to learn several rules within each session, thereby requiring the animal to utilize executive function.

Boren (1963) first introduced a behavioral method where subjects are required to learn one sequence of behavioral responses (e.g., lever presses or key pecks) that was varied between each experimental session. The subjects were thus required to learn a different 'rule' each session, and this method has become known as repeated acquisition of response sequences (e.g., see review by Cohn and Paule, 1995). This general procedure has permitted the investigation of steady states of 'rule' learning across experimental sessions and has been an important behavioral baseline for determining the effects of drugs on learning (e.g., Cohn and Paule, 1995; Campbell et al., 1999). A behavioral procedure which might more closely parallel the WCST might therefore be one in which the subject is required to learn more than one sequence of behavioral responses within each experimental session, that is, within-session repeated acquisition of behavioral sequences.

A major purpose of the present study was to train animals to perform under a schedule of within-session repeated acquisition of behavioral responses. Rats were trained in a three-lever operant conditioning chamber to respond on two of the three levers in one of six possible correct sequences to obtain food reinforcement. When the rat completed the two-response sequence correctly for 10 consecutive trials, the correct sequence was randomly changed to another two-response sequence without signaling the rat. A second purpose of the present study was to compare the effects on executive function-related behavior of representative drugs that previously have been shown to affect cognitive function in humans and/or animals: phencyclidine (e.g., Javitt and Zukin, 1991; Ellison, 1995), MK-801 ((5*S*,10*R*)-(+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine) (e.g., Wiley et al., 2003; Ahlander et al., 1999), apomorphine (e.g., Davis et al., 1990), triazolam (e.g., Greenblatt, 1992) and scopolamine (e.g., Robbins, 1997; Iversen, 1997). Accordingly, dose–response curves were determined for phencyclidine, MK-801, apomorphine, triazolam and scopolamine on within-session repeated acquisition of response sequences.

2. Materials and methods

2.1. Subjects

Twelve experimentally naïve male Fischer-derived F344 rats (300 to 325 g; Harlan Sprague–Dawley, Indianapolis, IN) were housed individually in a colony room with a 12-h light–dark cycle (lights off at 6:00 P.M.). All sessions were conducted during the light part of the cycle. The rats were maintained at approximately 85% of free-feeding weights by food earned during the session and supplemental food (approximately 7.5 g of rat chow per day) after sessions. The rats had constant access to water in their home cages. All experiments were conducted in accordance with the "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) and were approved by the Eli Lilly Institutional Animal Care and Use Committee.

2.2. Apparatus

The apparatus consisted of operant conditioning chambers located within sound- and light-attenuating enclosures (model E10-10, Coulbourn Instruments, Lehigh Valley, PA). The chambers were equipped with a tone generator centered near the top of the front panel. Directly below the tone generator was a white house light. A food hopper was centered below the house light. During food availability, a white light located within the food hopper was illuminated. Below the food hopper, three response levers were located 2.5 cm above the cage floor with 1.5 cm between response levers. Operation of the house light, food hopper, tone generator, delivery of food pellets (45-mg Dustless Precision Pellets, BioServ, Frenchtown, NJ), and recording of data were controlled by a computer using Med-State Notation software (Version 2; Med Associates, St. Albans, VT).

2.3. Procedure

Initial training included acclimation of the rats to the operant chamber, magazine training and training of the animals to respond on each of the three response levers. Upon completion of this training, behavior was maintained under a two-link chain schedule of food reinforcement where the rats were required to complete a two-lever response sequence in order to earn a food pellet. The rats were required to learn a new two-lever response sequence (i.e., 'rule') each session. Sequences requiring the rat to press any particular lever twice, e.g., left–left, were excluded. Thus, there were six possible two-lever sequences: LR, RL, CL, RC, LC and CR, where L is left, R is right and C is center. In order to obtain reinforcement, rats were required to press the required two-lever sequence, e.g. CL, without making an error; that is, a response on any lever that was not correct during each component of the chain. Sequences were presented across sessions in a different order for each rat using a Latin-square design. Each session began with a presession blackout lasting 5 min, followed by the illumination of the house light. A response on the correct lever in each link produced a 0.2-s tone. An incorrect response produced a 4-s blackout. During the 4-s blackout, the chamber was dark and responses had no scheduled consequences. After the 4-s blackout, the house light was again illuminated, and the rat

was required to begin the two-link sequence again. When the rat completed a correct two-link chain of responses, the hopper light was illuminated, and a food pellet was presented, followed by a 5-s blackout. The session ended after 60 min had elapsed or the rat had completed 200 correct two-lever response chains (thereby obtaining 200 reinforcements), whichever occurred first. Each rat received at least 30 training sessions where the two-lever sequence was held constant throughout each session, but was changed between each session.

In the terminal schedule, the sequence, or "rule," was changed within each session (i.e., within-session repeated acquisition of response sequences). Upon completion of 10 consecutive correct two-lever sequences under one rule, the computer program randomly selected another two-lever sequence from the remainder of the six possible two-lever sequences (i.e., random selection without replacement). There was no explicit stimulus that signaled the change in the required two-lever sequence. All other schedule contingencies remained as described above. The session ended after 60 min had elapsed or after the six possible two-lever sequences had been completed.

2.4. Drugs

Phencyclidine hydrochloride, MK-801 HCl, apomorphine hydrochloride hemihydrate, (−)scopolamine hydrobromide, (Sigma, St. Louis, MA) and triazolam (RBI, Natick, MA) were used. Phencyclidine, MK-801, apomorphine and scopolamine were dissolved in deionized water; triazolam was dissolved in 25% 2-hydroxypropyl-β-cyclodextrin. Drugs were administered in a volume of 1.0 ml/kg subcutaneously, except triazolam, which was administered intraperitoneally. A dose of drug or the appropriate vehicle was administered 30 min before the start of a session, except for apomorphine, which was administered 5 min before the start of a session.

2.5. Data analysis

Total session time was recorded to the nearest second. A rule was recorded as completed (i.e., learned) when 10 consecutively correct chains were emitted; there was a maximum of six rules per session. Total errors were the sum of all errors made within the session. Intrarule, or sequence, errors were responses that were to a lever required by the current rule in effect, but in the incorrect sequence. Interrule, or perseverative, errors were responses that would have been correct according to the immediately preceding response sequence rule but were incorrect according to the current rule. By definition, there were no interrule errors in the first rule of each session, and thus the number of interrule errors was always smaller than the number of intra-rule errors. Inter- and intrarule errors were not necessarily mutually exclusive, depending on the order in which the rules were presented; thus, in a few instances, an incorrect response could be counted as both an inter- and an intrarule error if it met the definition for both. A correct chain was defined as a two-lever sequence completed without an error of any type. The total number of chains completed, as well as the number of correct chains, incorrect chains and the percent correct chains (percentage of those chains completed which were correct) was recorded for each session. The number of total chains divided by the number of rules completed as well as the number of total errors per number of rules completed was also calculated each session.

Dose–response curves were analyzed using one-way analysis of variance (ANOVA), and comparisons of drug-treated groups to the appropriate vehicle-treated group were made using a Dunnett's *t*-test in JMP statistical software (SAS Institute, Cary, NC). Data were expressed as means ± S.E.M.

3. Results

Under the terminal schedule, all of the animals completed all six of the possible rules within the allotted session duration after vehicle administration (upper left panel of each Figure). Moreover, after administration of vehicle, the rats completed all six of the rules in an average of approximately 1800 s (upper middle panel of each Figure).

Each of the drugs produced a dose-dependent decrease in the total number of rules completed (upper left panel of Figs. 1–5). The maximum number of rules completed was reduced to two or less by each of the drugs at the highest dose tested. The number of rules completed was significantly decreased after the administration of doses of 3.0 and 5.6 mg/kg of phencyclidine, 0.056, 0.1 and 0.3 mg/kg of MK-801, 0.1 and 0.3 mg/kg of apomorphine and scopolamine and by 0.3 mg/kg of triazolam. Thus, the approximate order of potency of the drugs was MK-801≥apomorphine=scopolamine≥triazolam>phencyclidine.

After administration of each of the vehicles, the animals completed all six rules in an average of approximately 1600 to 2000 s, i.e., 25 to 35 min (upper middle panel of Figs. 1–5). Total session time was increased in a dose-dependent manner, to the maximum value of 3600 s (i.e., 60 min), by each of the drugs tested. Total session time was significantly increased after doses of 3.0 mg/kg and higher of phencyclidine, 0.1 mg/kg and higher of MK-801, 0.03 mg/kg and higher of apomorphine and scopolamine and 0.1 mg/kg and higher of triazolam. Thus, the drugs significantly increased total session time at doses similar to the doses required to significantly decrease the number of rules completed.

Rates of responding on the levers are presented in Table 1. Rates of responding were significantly decreased after doses of 5.6 mg/kg of phencyclidine, 0.3 mg/kg of MK-801, 0.03 mg/kg and higher of apomorphine, 0.3 mg/kg of triazolam and 0.03 mg/kg of scopolamine.

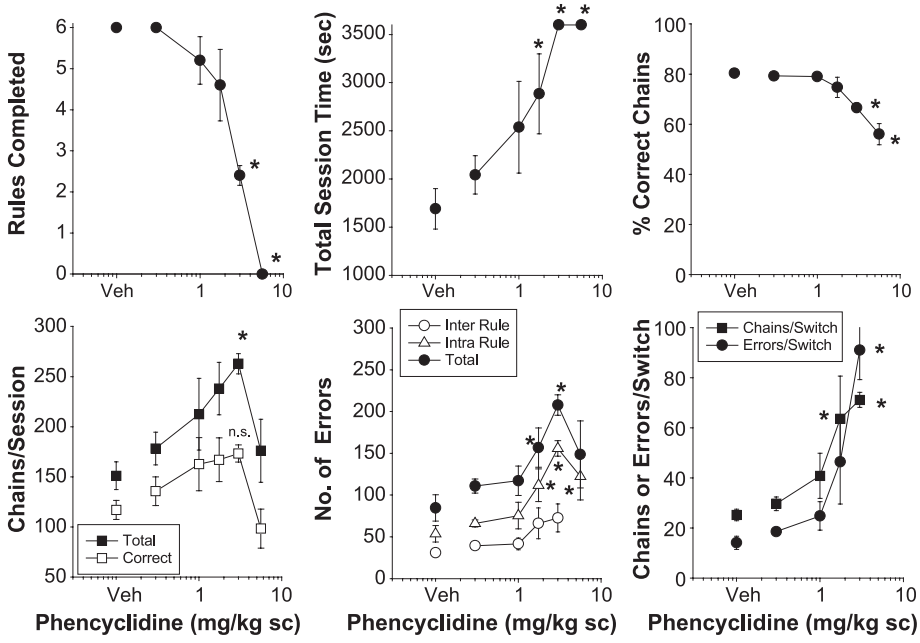

Fig. 1. Dose–response curves for phencyclidine on behavioral parameters in rats required to learn up to six two-lever response sequences (within-session repeated acquisition of response sequences) in order to earn food presentation. Each point represents the mean±S.E.M. of one observation in each of five rats. Veh, vehicle. *P<0.05 vs. vehicle, Dunnett's test.

After vehicle administration, the percentage of the total chains completed during the session that were correct averaged approximately 80% (upper right panels in Figs. 1–5). Phencyclidine, MK-801 and triazolam significantly decreased the percentage of correct chains in a dose-related manner (Figs. 1, 2 and 4, respectively). The largest decrease was produced by MK-801 to approximately 10% correct. Phencyclidine and triazolam reduced the percent correct chains to approximately 50%. In contrast, the percentage of correct chains was not affected

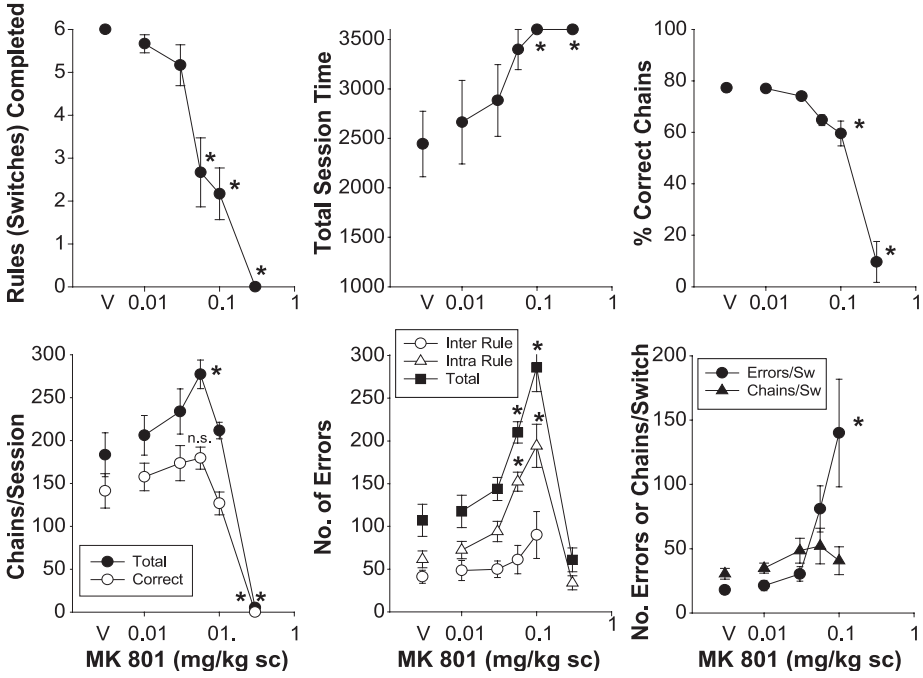

Fig. 2. Dose–response curves for MK801 on behavioral parameters in rats required to learn up to six two-lever response sequences (within-session repeated acquisition of response sequences) in order to earn food presentation. Each point represents the mean±S.E.M. of one observation in each of six rats. Veh, vehicle. *P<0.05 vs. vehicle, Dunnett's test.

Table 1
Effects of the drugs tested on rates of responding averaged across the test session

Drug	Dose (mg/kg)	*N*	Rate of responding (responses/s)
Phencyclidine	0	5	0.88±0.11
	0.3	5	0.87±0.05
	1	5	0.89±0.21
	1.75	5	0.86±0.12
	3	5	0.66±0.07
	5.6	5	0.19±0.09[a]
MK801	0	6	0.61±0.13
	0.01	6	0.74±0.17
	0.03	6	0.86±0.15
	0.056	6	0.93±0.08
	0.1	6	0.66±0.10
	0.3	6	0.03±0.01[a]
Apomorphine	0	5	0.85±0.03
	0.003	5	0.82±0.13
	0.01	5	0.84±0.09
	0.03	5	0.33±0.02[a]
	0.1	5	0.17±0.02[a]
	0.3	5	0.04±0.01[a]
Triazolam	0	6	0.75±0.08
	0.01	6	0.77±0.14
	0.03	6	0.77±0.16
	0.1	6	0.40±0.07
	0.3	2	0.12±0.03[a]
Scopolamine	0	5	0.75±0.10
	0.01	5	0.61±0.06
	0.03	5	0.36±0.07[a]
	0.1	5	0.20±0.02[a]
	0.3	5	0.10±0.02[a]

[a] $P<0.05$ vs. vehicle, Dunnett's *t*-test.

either by apomorphine or scopolamine over the dose range tested.

The animals required an average of approximately 150–175, out of a maximum of 200 total correct chains to complete all six rules after vehicle administration (lower left panel of Figs. 1–5). Increasing doses of phencyclidine and MK-801 first produced a dose-related increase in total chains, with significant increases after doses of 3.0 and 0.1 mg/kg, respectively (Figs. 1 and 2, lower left panels). After a dose of 5.6 mg/kg of phencyclidine, the total number of chains completed was not different from control. After a dose of 0.3 mg/kg of MK-801, behavior was disrupted and the animals completed less than approximately 10 trials during the 60-min session. Apomorphine and triazolam were without significant effect on the total number of chains completed except at the highest dose tested of each drug (0.3 mg/kg; Figs. 3 and 4, lower left panels). Scopolamine produced a more graded decrease in the total number of chains completed but significantly decreased the total number of chains completed only after 0.3 mg/kg (Fig. 5, lower left panel). The changes in the absolute number of correct chains completed are also presented for purposes of comparison (Figs. 1–5, lower left panels, open symbols).

After vehicle administration, the animals completed the six rules with an average of approximately 75–110 total errors/session (Figs. 1–5, lower middle panel, closed symbol). Phencyclidine (Fig. 1), MK-801 (Fig. 2) and triazolam (Fig. 4) first produced an increase and then a decrease (or had less effect on) total errors with increasing dose. Total errors were significantly increased after doses of 1.0 and 3.0 mg/kg of phencyclidine, 0.056 and 0.1 mg/kg of MK-801 and 0.1 mg/kg of triazolam. MK-801 produced the largest increase in total errors per session. On the other hand, apomorphine (Fig. 3, lower middle panel) did not affect the total number of errors except at the highest dose tested (0.3 mg/kg) where it significantly reduced the number of errors. Scopolamine produced a modest increase in total errors after 0.1 mg/kg, but this increase was not statistically significant.

The number of intrarule errors was approximately 50 to 75 per session and the number of interrule errors was approximately 30 to 50 per session after vehicle administration [Figs. 1–5, middle panel; (△) and (○) above Veh, respectively]. With increasing doses, phencyclidine first produced an increase and then had less effect or decreased intra- and interrule errors (Fig. 1, lower middle panel, open symbols). Doses of 1.75 mg/kg and higher of phencyclidine significantly increased intrarule errors, while interrule errors were significantly increased after a dose of 3.0 mg/kg; after a dose of 5.6 mg/kg of phencyclidine, the animals failed to complete even one rule, and therefore, there were no interrule errors. Similarly, doses of 0.056 and 0.1 mg/kg of MK-801 significantly increased intrarule errors; 0.3 mg/kg decreased intrarule errors (Fig. 2, lower middle panel). Interrule errors were not significantly altered by MK-801, with the exception that after a dose of 0.3 mg/kg, the rats failed to complete even one rule, and therefore, there were no interrule errors. Apomorphine was without significant effect on the number of intra- and interrule errors except at the highest dose (0.3 mg/kg) where it significantly decreased errors (Fig. 3, lower middle panel). Triazolam was without significant effect on intrarule errors, but first increased and then had less effect on interrule errors, significantly increasing interrule errors after a dose of 0.1 mg/kg (Fig. 4, lower middle panel). Scopolamine significantly increased both intra- and interrule errors after 0.1, but not 0.3, mg/kg (Fig. 5, lower middle panel).

After vehicle administration, the number of total (correct+incorrect) chains *per rule change* was approximately 25 to 30 and the number of total error responses *per rule change* was approximately 15 to 20 (Figs. 1–5, lower right panel, closed symbols). Phencyclidine produced dose-related increases in both the total number of chains and errors per rule change, with significant increases after a dose of 3.0 mg/kg (Fig. 1, lower right panel). MK-801 similarly increased the total number of chains and errors per rule change, but only the number of errors per rule change was statistically significant (Fig. 2, lower right panel). Triazolam and scopolamine also increased the total number of chains and errors per rule

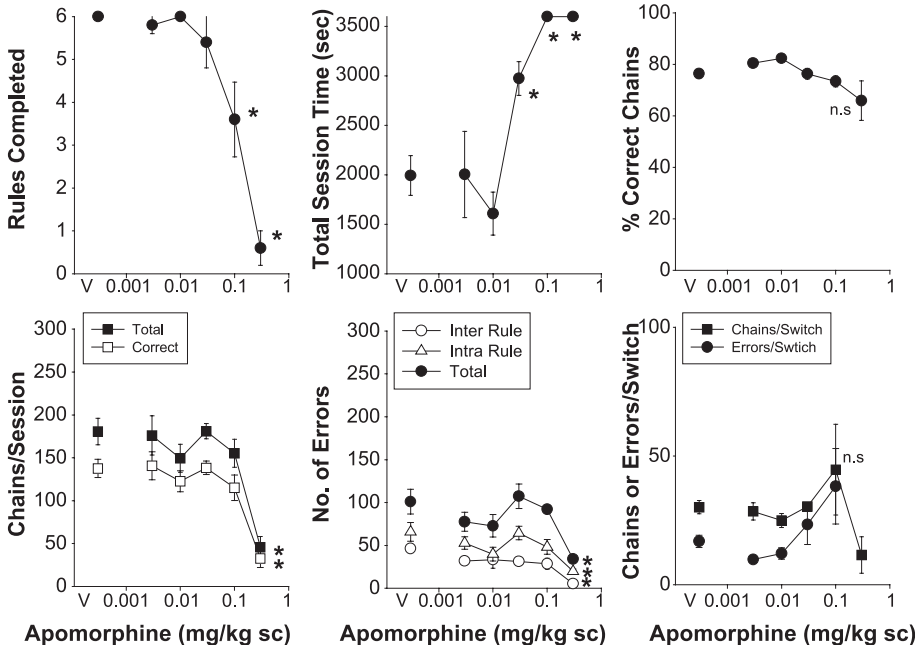

Fig. 3. Dose–response curves for apomorphine on behavioral parameters in rats required to learn up to six two-lever response sequences (within-session repeated acquisition of response sequences) in order to earn food presentation. Each point represents the mean±S.E.M. of one observation in each of five rats. Veh, vehicle. *P<0.05 vs. vehicle, Dunnett's test.

change, but with only the increase in the number of errors per rule change being statistically significant (Fig. 4, lower right panel). On the other hand, apomorphine did not significantly affect either the number of chains or errors per rule change.

4. Discussion

In the present study, rats acquired and performed with a high degree of accuracy in the within-session repeated acquisition of two-lever response sequences. During each

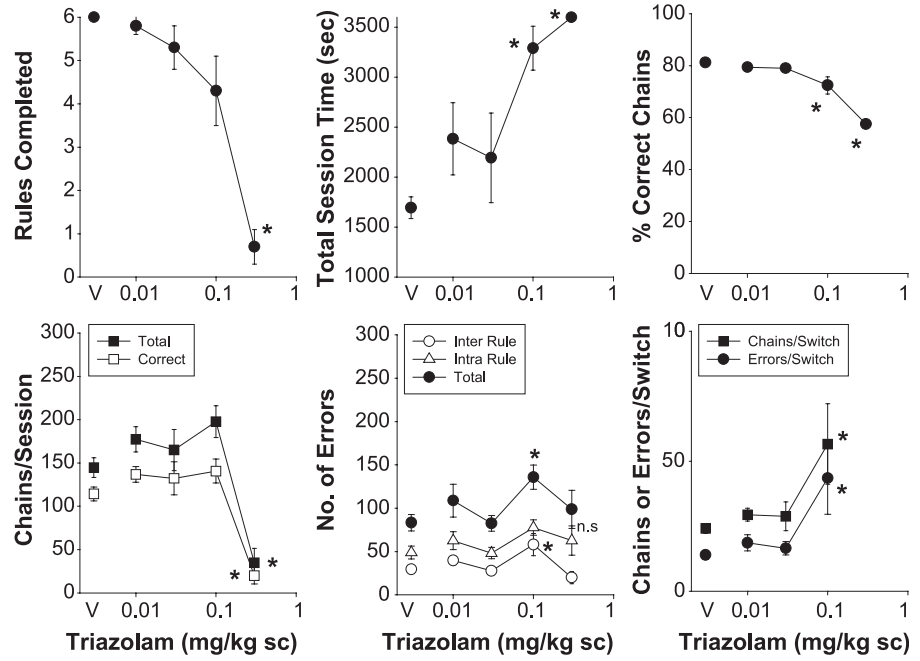

Fig. 4. Dose–response curves for triazolam on behavioral parameters in rats required to learn up to six two-lever response sequences (within-session repeated acquisition of response sequences) in order to earn food presentation. Each point represents the mean±S.E.M. of one observation in each of six rats. Veh, vehicle. *P<0.05 vs. vehicle, Dunnett's test.

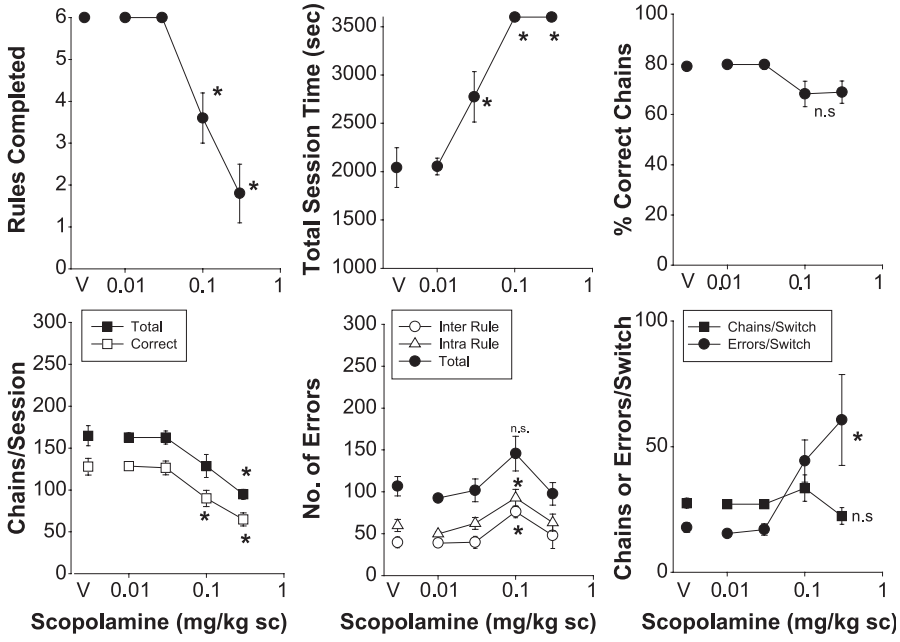

Fig. 5. Dose–response curves for scopolamine on behavioral parameters in rats required to learn up to six two-lever response sequences (within-session repeated acquisition of response sequences) in order to earn food presentation. Each point represents the mean±S.E.M. of one observation in each of five rats. Veh, vehicle. *P<0.05 vs. vehicle, Dunnett's test.

session, the rats were required to correctly acquire each of six possible response sequences in random order in the absence of any explicit stimulus to indicate which of the response sequence rules was in effect. The rats required approximately 150 to 175 response sequence chains to complete the six possible sequence rules to an accuracy level of 10 consecutively correct sequences for each rule; thus, the rats acquired each new rule in an average of approximately 15 to 20 chains, excluding the final 10 which were required to be consecutively correct. Furthermore, the rats emitted on average approximately 75 to 110 total errors during the session or approximately 13 to 18 errors per each rule before completing 10 *consecutively* correct chain sequences. The rats made slightly more intrarule, or sequential, errors than interrule, or perseverative, errors per session. Not unexpectedly, the most common type of error was the rat responding during the first part, or first link, of a sequence on the lever that produced the food pellet if emitted correctly in the second part of the sequence, i.e., on the lever most closely associated with immediate food presentation. Random errors; that is, those which could not be classified as either intra- or interrule errors, were the least frequent and there were typically less than 10 to 20 such errors per session (data not shown). Thus, the within-session acquisition of response sequences appears to be a viable procedure for investigating cognitive behavior relating to executive function.

Phencyclidine, MK-801, apomorphine, triazolam and scopolamine, which are known to disrupt cognitive function in animals as well as humans (see also below), each disrupted the within-session acquisition of response sequences. All four of these drugs produced dose-related decreases in the number of rules completed and increases in the total session time; the latter perhaps reflecting increased cognitive processing time. However, changes in locomotor activity could also have influenced the number of rules completed and session time. On the other hand, there were differences in the manner in which these drugs altered the numbers of error responses as well as error response types. Apomorphine was without appreciable effect on the percentage of correct chains, total errors, or, intra- or interrule errors, and did not significantly alter the number of chains or errors per rule change, up to the highest dose tested (0.3 mg/kg). Thus, the effect of apomorphine was primarily to decrease response output, as measured by, e.g., the total number of chains completed per session, without increasing errors. Scopolamine produced a nonsignificant decrease in the percentage of correct chains and produced modest but significant increases in intra- and interrule, but not total, errors, as well as errors per rule change. Triazolam significantly decreased the percentage of correct chains and also increased total and interrule, but not intrarule, errors and increased the number of errors/rule change. Thus, scopolamine and triazolam produced modest increases in error measures up to doses that markedly decreased response output. In contrast, phencyclidine and MK-801 produced large increases in all three types of errors as well as increases in the average number of errors and chains per rule change. The increase in error responding produced by phencyclidine and MK-801 was accompanied by large increases in behavioral output up to the highest doses of phencyclidine (5.6 mg/kg) or MK-801 (0.3 mg/kg) tested, which decreased behavioral output. Thus, phencyclidine and

MK-801 uniquely produced large increases in all error measures.

Dopamine and acetylcholine have long been demonstrated to have an integral involvement in cognition (e.g., see reviews by Levin et al., 1990; Robbins, 1997; 2000). Apomorphine has been well documented to disrupt the (pre-) attentional process of sensorimotor gating in rats (e.g., Mansbach et al., 1988; Davis et al., 1990), and it has been suggested that the sensorimotor gating deficits observed in patients with schizophrenia may be due to hyperdopaminergic function (Braff et al., 1992). The dopamine system has also been implicated in attentional processes, and suboptimal dopaminergic functioning has been suggested to underlie attention deficit disorders (e.g., Solanto, 2000). The prefrontal cortex dopaminergic system, in particular dopamine D1-like receptors, has also been implicated in executive functions in monkeys, including working memory (e.g., Goldman-Rakic, 1999; Robbins, 2000). The present findings that the mixed dopamine D1/D2 receptor agonist apomorphine disrupted the within-session acquisition of response sequences, without increasing error measures, suggests that hyperdopaminergic function may not only disrupt sensorimotor gating, but may also disrupt executive function. However, in the present study, doses of apomorphine as low as 0.1 to 0.3 mg/kg disrupted repeated acquisition behavior, whereas doses approximately 10-fold higher are required to disrupt sensorimotor gating in rats (Mansbach et al., 1988; Davis et al., 1990). The lower doses of apomorphine which were disruptive in the present study may have been acting primarily presynaptically to inhibit dopamine release, whereas the higher doses of apomorphine required to disrupt prepulse inhibition would be expected to act primarily by stimulating postsynaptic receptors. It will be of interest to determine in future studies if apomorphine administered into the prefrontal cortex disrupts performance in the present task and if typical and/or atypical antipsychotic drugs reverse the effects of apomorphine in this model of executive function.

The muscarinic acetylcholine receptor antagonist scopolamine has long been known to disrupt cognitive function. For example, scopolamine has been demonstrated to disrupt sensorimotor gating in rats (Wu et al., 1993; Jones and Shannon, 2000) as well as working memory as measured by delayed spatial alternation behavior in rats (e.g., Heise et al., 1976; Shannon et al., 1990a,b). Moreover, scopolamine has been demonstrated in numerous clinical studies to disrupt cognitive processes in humans (e.g., Drachman, 1978; Rusted and Warburton, 1988; Little et al., 1998). As with apomorphine, lower doses of scopolamine (0.03 to 0.3 mg/kg) were required to disrupt repeated acquisition behavior than were required to disrupt prepulse inhibition (1 to 2 mg/kg) in previous studies (Jones and Shannon, 2000). However, even lower doses of scopolamine (0.003 to 0.1 mg/kg) produced disruption of delayed alternation behavior (Shannon et al., 1990a,b), a potential model of working memory. The present results extend previous findings that scopolamine disrupts between-session repeated acquisition behavior (Cohn et al., 1992; Savage et al., 1996). Taken together, the present findings provide further evidence that both dopamine and acetylcholine have important roles in cognitive processes, including attention, working memory and executive function, but that different domains of cognitive processes differ in their sensitivity to alterations in these neurotransmitter systems.

The major excitatory and inhibitory neurotransmitters in the central nervous system (CNS), glutamate and γ-aminobutyric acid (GABA), are also well known to play important roles in cognitive processes. For example, glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine and ketamine have been demonstrated to disrupt cognition in both monkeys and humans (e.g., Ellison, 1995; Jentsch et al., 1999). The present findings that the noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonists phencyclidine and MK-801 disrupted within-session repeated acquisition behavior is consistent with previous findings that phencyclidine and MK-801 disrupted between-session repeated acquisition behavior (e.g., Thompson et al., 1986; Cohn et al., 1992; Campbell et al., 1999) as well as working memory as evaluated by delayed alternation behaviors (e.g., Baron et al., 1998; Pontecorvo et al., 1991). Although further studies are needed, it appears that phencyclidine disrupts all cognitive domains at approximately the same doses (ca. 3.0 mg/kg), suggesting either that NMDA receptors are involved to similar extents in several, if not all, cognitive domains, or, that antagonism of NMDA receptors nonspecifically disrupts performance of cognitive behaviors. In contrast to the disruptive effects of reducing glutamate neurotransmission, enhancing GABAergic neurotransmission can disrupt cognition. The present findings that triazolam, which acts at benzodiazepine receptors to enhance GABAergic neurotransmission, disrupted within-session repeated acquisition behavior extends previous findings that triazolam disrupted between-session repeated acquisition behavior in squirrel monkeys (Pakarinen et al., 1996; Winsauer et al., 2002) and humans (Rush et al., 1999). In humans, triazolam, as well as other benzodiazepines, have been reported to impair a broad range of cognitive processes (Nikaido and Ellinwood, 1987; Weingartner et al., 1992), including attentional processes such as prepulse inhibition and working memory, and also produces anterograde amnesia. Additional studies are needed to further delineate if there are cognitive domains in animals that exhibit greater sensitivity to enhanced GABAergic neurotransmission relative to other neurotransmitter systems.

The present studies have demonstrated that rats can be trained to perform a within-session repeated acquisition of response sequences and that this behavior may be a viable model for investigating executive function in rodents. Like executive function behaviors in humans, within-session repeated acquisition was disrupted by a dopaminergic agonist, a muscarinic acetylcholine receptor antagonist,

NMDA receptor antagonists and a positive allosteric modulator of GABAergic neurotransmission. Further studies are needed to fully evaluate the functional similarities between the present methods in rodents and methods such as the WCST in humans and to determine if drugs used in the treatment of schizophrenia can impact baseline behavior and/or reverse the effects of apomorphine or phencyclidine in this model. Moreover, the present model may serve as a behavioral baseline to more fully evaluate the relative role of different neurotransmitter systems in executive function.

References

Ahlander, M., Misane, I., Schott, P.A., Ogren, S.O., 1999. A behavioral analysis of the spatial learning deficit induced by the NMDA receptor antagonist MK-801 (dizocilpine) in the rat. Neuropsychopharmacology 21, 414–426.

Baron, S.P., Wright, D., Wenger, G.R., 1998. Effects of drugs of abuse and scopolamine on memory in rats: delayed spatial alternation and matching to position. Psychopharmacology 137, 7–14.

Bleuler, E., 1950. Dementia Praecox or the Group of Schizophrenia. International Universities Press, New York.

Boren, J.J., 1963. Repeated acquisition of new behavioral chains. Am. Psychol. 17, 421.

Braff, D., Stone, C., Callaway, E., Geyer, M., Glick, I., Bali, L., 1978. Prestimulus effects of human startle reflex in normals and schizophrenics. Psychophysiology 15, 339–343.

Braff, D.L., Grillion, C., Geyer, M.A., 1992. Gating and habituation of the startle reflex in schizophrenic patients. Arch. Gen. Psychiatry 49, 206–215.

Campbell, C.M., Butelman, E.R., Woods, J.H., 1999. Effects of (+)-HA-966, CGS-19755, phencyclidine, and dizocilpine on repeated acquisition of response chains in pigeons: systemic manipulation of central glycine sites. J. Pharmacol. Exp. Ther. 289, 521–527.

Cohn, J., Paule, M.G., 1995. Repeated acquisition of response sequences: the analysis of behavior in transition. Neurosci. Biobehav. Rev. 19, 397–406.

Cohn, J., Ziriax, J.M., Cox, C., Cory-Slechta, D.A., 1992. Comparison of error patterns produced by scopolamine and MK-801 on repeated acquisition and transition baselines. Psychopharmacology 107, 243–254.

Davis, M., Mansbach, R.S., Swerdlow, N.R., Campeau, S., Braff, D.L., 1990. Apomorphine disrupts the inhibition of acoustic startle induced by weak prepulses in rats. Psychopharmacology 102, 1–4.

Drachman, D.A., 1978. Central cholinergic system and memory. In: Lipton, M.A., DiMaschio, A.A., Killam, K.F. (Eds.), Psychopharmacology: a Generation of Progress. Raven Press, New York, pp. 651–662.

Ellison, G., 1995. The *N*-methyl-D-aspartate antagonists phencyclidine, ketamine and dizocilpine as both behavioral and anatomical models of the dementias. Brain Res.-Brain Res. Rev. 20, 250–267.

Goldberg, T.E., Gold, J.M., 1995. Neurocognitive deficits in schizophrenia. In: Hirsch, S.R., Weinberger, D.R. (Eds.), Schizophrenia. Blackwell Science, Oxford, pp. 146–162.

Goldman-Rakic, P.S., 1999. The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. Biol. Psychiatry 46, 650–661.

Greenblatt, D.J., 1992. Pharmacology of benzodiazepine hypnotics. J. Clin. Psychiatry 53, 7–13 (Suppl.).

Heise, G.A., Conner, R., Martin, R.A., 1976. Effects of scopolamine on variable intertrial interval spatial alternation and memory in the rat. Psychopharmacology 49, 993–1002.

Iversen, S.D., 1997. Behavioural evaluation of cholinergic drugs. Life Sci. 60, 1145–1152.

Javitt, D.C., Zukin, S.R., 1991. Recent advances in the phencyclidine model of schizophrenia. Am. J. Psychiatry 148, 1301–1308.

Jentsch, J.D., Taylor, J.R., Elsworth, J.D., Redmond Jr., D.E., Roth, R.H., 1999. Altered frontal cortical dopaminergic transmission in monkeys after subchronic phencyclidine exposure: involvement in frontostriatal cognitive deficits. Neuroscience 90, 823–832.

Jones, C.K., Shannon, H.E., 2000. A comparison of the effects of scopolamine, apomorphine and phencyclidine on prepulse inhibition of the acoustic startle reflex in rats. Eur. J. Pharmacol. 391, 105–112.

Kraepelin, E., 1919. Dementia Praecox and Paraphrenia. In: Robertson, G.M. (Ed.), Translated by Barclay, R.M., Krieger, R.E., 1971. Huntington, NY.

Kuperberg, G., Heckers, S., 2000. Schizophrenia and cognitive function. Curr. Opin. Neurobiol. 10, 205–210.

Levin, E.D., McGurk, S.R., Rose, J.E., Butcher, L.L., 1990. Cholinergic–dopaminergic interactions in cognitive performance. Behav. Neural Biol. 54, 271–299.

Lezak, M.D., 1982. The problems of assessing executive functions. Int. J. Psychol. 17, 281–297.

Little, J.T., Johnson, D.N., Minichiello, M., Weingartner, H., Sunderland, T., 1998. Combined nicotinic and muscarinic receptor blockade in elderly normal volunteers: cognitive, behavioral, and physiologic responses. Neuropsychopharmacology 19, 60–69.

Mansbach, R.S., Geyer, M.A., Braff, D.L., 1988. Dopaminergic stimulation disrupts sensorimotor gating in the rat. Psychopharmacology 94, 507–514.

Muir, J.L., 1996. Attention and stimulus processing in the rat. Cogn. Brain Res. 3, 215–225.

Nathaniel-James, D.A., Brown, R., Ron, M.A., 1996. Memory impairment in schizophrenia: its relationship to executive function. Schizophr. Res. 21, 85–96.

Nikaido, A.M., Ellinwood Jr., E.H., 1987. Comparison of the effects of quazepam and triazolam on cognitive–neuromotor performance. Psychopharmacology 92, 459–464.

Pakarinen, E.D., Faust, W.B., Moerschbaecher, J.M., 1996. Effects of convulsant and anticonvulsant agents on memory in squirrel monkeys. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 20, 883–898.

Pontecorvo, M.J., Clissold, D.B., White, M.F., Ferkany, J.W., 1991. *N*-methyl-D-aspartate antagonists and working memory performance: comparison with the effects of scopolamine, propranolol, diazepam, and phenylisopropyladenosine. Behav. Neurosci. 105, 521–535.

Robbins, T.W., 1997. Arousal systems and attentional processes. Biol. Psychol. 45, 57–71.

Robbins, T.W., 2000. Chemical neuromodulation of frontal-executive functions in humans and other animals. Exp. Brain Res. 133, 130–138.

Rush, C.R., Frey, J.M., Griffiths, R.R., 1999. Zaleplon and triazolam in humans: acute behavioral effects and abuse potential. Psychopharmacology 145, 39–51.

Rusted, J.M., Warburton, D.M., 1988. The effects of scopolamine on working memory in healthy young volunteers. Psychopharmacology 96, 145–152.

Savage, U.C., Faust, W.B., Lambert, P., Moerschbaecher, J.M., 1996. Effects of scopolamine on learning and memory in monkeys. Psychopharmacology 123, 9–14.

Shannon, H.E., Bemis, K.G., Hart, J.C., 1990a. Assessment of working memory in rats using spatial alternation behavior with variable retention intervals: effects of fixed-ratio size and scopolamine. Psychopharmacology 100, 491–497.

Shannon, H.E., Bemis, K.G., Hendrix, J.C., Ward, J.S., 1990b. Interactions between scopolamine and muscarinic cholinergic agonists or cholinesterase inhibitors on spatial alternation performance in rats. J. Pharmacol. Exp. Ther. 255, 1071–1077.

Solanto, M.V., 2000. Clinical psychopharmacology of AD/HD: implications for animal models. Neurosci. Biobehav. Rev. 224, 27–30.

Spear, N.E., Miller, J.S., Jagielo, J.A., 1990. Animal memory and learning. Annu. Rev. Psychol. 41, 169–211.

Thompson, D.M., Mastropaolo, J., Winsauer, P.J., Moerschbaecher, J.M., 1986. Repeated acquisition and delayed performance as a baseline to assess drug effects on retention in monkeys. Pharmacol. Biochem. Behav. 25, 201–207.

Weickert, T.W., Goldberg, T.E., Gold, J.M., Bigelow, L.B., Egan, M.F., Weinberger, D.R., 2000. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch. Gen. Psychiatry 57, 907–913.

Weingartner, H.J., Hommer, D., Lister, R.G., Thompson, K., Wolkowitz, O., 1992. Selective effects of triazolam on memory. Psychopharmacology 106, 341–345.

Wiley, J.L., Harvey, S.A., Balster, R.L., Nicholson, K.L., 2003. Affinity and specificity of *N*-methyl-D-aspartate channel blockers affect their ability to disrupt prepulse inhibition of acoustic startle in rats. Psychopharmacology 165, 378–385.

Winsauer, P.J., Delatte, M.S., Stevenson, M.W., Moerschbaecher, J.M., 2002. Effects of triazolam, 8-OH-DPAT, and buspirone on repeated acquisition in squirrel monkeys. Exp. Clin. Psychopharmacol. 10, 392–399.

Wu, M., Jenden, D.J., Fairchild, M.D., Siegel, J.M., 1993. Cholinergic mechanisms in startle and prepulse inhibition: effects of the false cholinergic precursor *N*-aminodeanol. Behav. Neurosci. 107, 306–316.