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The Effects of Dextromethorphan on Response Acquisition with Delayed Reinforcement

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THE EFFECTS OF DEXTROMETHORPHAN ON RESPONSE ACQUISITION
WITH DELAYED REINFORCEMENT

by

Thomas B. Morgan

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
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THE EFFECTS OF DEXTROMETHORPHAN ON RESPONSE ACQUISITION WITH DELAYED REINFORCEMENT

Thomas B. Morgan, Ph. D.

Western Michigan University, 2005

The current study examined in 2-h sessions the effects of intraperitoneal injections of dextromethorphan (DM) (0.0, 40.0, 60.0, and 80.0 mg/kg) on the acquisition of lever-press responding in rats that were exposed to a two-lever procedure in which responses on the reinforcement lever (RL) were reinforced with food after a 15-s resetting delay and responses on the cancellation lever cancelled a scheduled reinforcer. Response acquisition was observed at all drug doses. A decrease in RL responses, food deliveries, and the number of subjects that acquired responding was observed at the highest dose of DM. All doses of DM increased latency to respond relative to the control group. The results of the present study suggest that DM disrupts the acquisition of a novel response at high doses. Prior studies, using other procedures, have found DM-induced disruption of learning at lower doses. Although the two-lever response acquisition procedure is a tenable assay of drug effects on learning, the sensitivity of the procedure appears to be relatively low.

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Thomas B. Morgan

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INTRODUCTION

Background on Dextromethorphan

Dextromethorphan (3-methoxy-17-methylmorphinan, DM) is the dextrorotatory isomer of levomethorphan, a codeine analog of the morphinan derivative levorphanol (Holtzman, 1994). At low doses DM is an effective antitussive that lacks most opioid-like activity and is considered to be a safe over-the-counter (OTC) cough suppressant (Jaffe & Martin, 1990). Higher doses of DM have been studied for treating pain and various acute and chronic neurodegenerative conditions but DM is rarely used for these purposes (Ikjaer, Dirks, Brennum, Wernberg, & Dahl, 1997; Nickelson, Hays & Balster., 1999). In large part, this is because high doses produce unwanted effects that are similar to those produced by phencyclidine (PCP), which is a dissociative anesthetic (Dematteus, Lallement, & Mallaret, 1998; Jasinski, Martin, & Maski., 1971; Kim et al., 1996).

DM is considered to have abuse potential. For example, episodic and sporadic abuse of DM by humans has been reported in several areas of the world and, because of its availability, its abuse is most likely to occur among adolescents and young adults (Cranston and Yoast, 1999). Also, Bem and Peck (1992) reported 64 cases of DM dependence. Furthermore, Nevin (2004) reported 100,000 annual exposures due to recreational use of DM among children less than 18 years of age in the United States and approximately 60 deaths per year that can be directly linked to the drug.

Reported effects of high doses of DM in humans include agitation, confusion, slurred speech, ataxia, increased perceptual awareness, euphoria, altered time perception, floating sensations, unusual facial movements, as well as tactile, auditory and visual hallucinations (Darobe, 1996; Darobe, Keenan, & Richards, 1996; Nairn & Diaz; 2001; Wolf & Caravati, 1995). Other reported effects include mild drunkenness, delusions, paranoia, nervousness, and dysphoria. As noted previously, the subjective effects of DM reported by humans are similar to those of PCP (Darobe, et al., 1996; Dematteis et al., 1998; Golaszewski, 2004; Holtzman, 1982; Jasinski et al., 1971; Price & Lebel, 2000; Wu, Otton, Kalow, & Sellers, 1995). Research with nonhumans using drug discrimination procedures provides further evidence that DM and PCP produce similar subjective effects (Holtzman, 1980, 1982; Nicholson, Hayes & Balster, 1999).

The PCP-like effects of DM are most likely produced by its active metabolite, dextrorphan (DR). While DM binds with low affinity to the PCP channel-site of the NMDA receptor, DR binds with high affinity to that site (Nicholson et al., 1999). PCP-like drugs have been shown to produce hyperlocomotion, stereotyped behavior, and ataxia in rodents. For example, Dematteis et al., (1998) examined the effects of 20, 30, and 40 mg/kg DM and DR on rats' locomotor activity, stereotyped behavior, and ataxia in open-field experiments. DR at 40 mg/kg significantly increased locomotor activity and stereotyped behavior while DM and lower doses of DR did not. DM at 40 mg/kg produced slight ataxia while DR at 30 and 40 mg/kg produced

moderate levels of ataxia. Therefore, DR induced PCP-like behavioral effects while DM did not.

The present study examined the acute effects of dextromethorphan on rats exposed to a learning assay that involved the acquisition of lever-press responding with delayed reinforcement. Byrne, Baker & Poling (2000) suggested that a drug-induced disruption of the initial acquisition of operant behavior “would be significant in human users, many of whom are young and in the process of acquiring new behaviors” (p. 501). Since DM is found in OTC preparations that are easily acquired by adolescents and young adults, research examining the effects of this drug on the acquisition of learning is warranted. Previous studies have examined the effects of chlorpromazine (Byrne, LeSage, & Poling, 1997; Stolerman, 1971a, 1971b), chlordiazepoxide (Stolerman, 1971a, 1971b), *d*-amphetamine (LeSage, Byrne, & Poling, 1996), pyridostigmine bromide, and permethrin (Van Haaren et al., 1999; Van Haaren et al., 2000), 3,4-methylenedioxymethamphetamine (MDMA) (Byrne et al., 2000), and gamma-hydroxybutyrate (GHB) (Laraway, Snyckerski, Baker, & Poling, 2004) on the acquisition of behavior with immediate and delayed reinforcement. The effects of DM and other opioids on the acquisition of behavior with delayed reinforcement have not been studied.

Other research methods have been used to study the influence of DM on the acquisition of learning. Sierocinska, Nikolaev, Danysz, & Kacmarek (1991) and Murata & Kawasaki (1993) examined the effects of DM on a passive avoidance task and Dematteis et al. (1998) and Bane, Rojas, Indermaur, Bennett, and Avery (1996)

studied the effects of DM on performance on several water-maze tasks. However, these assays examined negatively reinforced behavior and the effects of DM on the acquisition of positively reinforced behavior have not been examined.

Research on the Effects of Dextromethorphan on Learning

Few studies have examined the behavioral effects of DM in laboratory animals. The drug has been shown to disrupt negatively reinforced spatial learning memory in a passive avoidance task (Murata & Kawasaki 1993; Sierocinska et al., 1991), cue learning, place learning, spatial learning, place recall working memory and reference memory on water maze tasks (Bane et al., 1996; Dematteis et al., 1998), and positively reinforced schedule-controlled behavior (Taskin, 1986).

Taskin (1986) trained rats to lever press for milk under a fixed-interval 45 s schedule of reinforcement. Dose-dependent decreases in response rate were observed after intramuscular injections of DM (0, 10, 20 and 40 mg/kg). The author also showed that injections of naloxone (0.1 and 1.0 mg/kg) potentiated the rate-reducing effects of DM. This is an interesting finding, because naloxone had previously been shown to attenuate the effects of opioid agonists, but increase the effects of PCP on schedule-controlled behavior (Wagner, Masters, & Tomie, 1984).

Sierocinska et al. (1991) examined the effects of intraperitoneal (IP) injections of DR in rats performing a passive avoidance task. Subjects were placed in a two-compartment chamber after IP injections of DR (0, 3, 11, and 22 mg/kg). The safe

compartment was larger and painted white while the compartment that delivered electric shock was smaller and painted dark. Rats were placed in the white compartment and as soon as they entered the dark compartment a guillotine door was closed and the subjects were exposed to five brief footshocks. Immediately after the shocks were delivered the subjects were placed in the white compartment and latency to enter the dark compartment was recorded. Two days later, the subjects were placed in the white compartment after being injected with the same dose of DR as they had received on the first day and latency to enter the dark compartment was again measured. The authors found that, for the subjects exposed to DR, latency to enter the dark chamber was not significantly different than the control group for the trial that immediately followed exposure to shock. However, two days after the initial training session, the group of subjects exposed to DR at 22 mg/kg entered the dark chamber significantly earlier than control subjects. The results indicated that DR disrupts long-term memory without harming short-term memory.

Murata and Kawasaki (1993) used a one-trial passive avoidance task with the training and testing sessions separated by 24 h to examine the effects of injecting DM and other NMDA antagonists (D-2-amino-phosphonovaleric acid, (+/-)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid, 2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid, 7-Cl kynurenate, ifenprodil, PCP, MK-801, ketamine, (+/-)-N-allylnormetazocine, DM, ZnCl₂, and MgCl₂) into the ventricles of rats. The minimum concentration of DM that produced significant disruptions was 250 nmol/rat.

The drug also produced a reduction in muscle tone, a decrease in the number of rearings, motor incoordination, and a decrease in locomotor activity.

DM has been shown to disrupt spatial learning. Bane et al. (1996) examined the effects of IP injections of DM (10, 20, 30, and 40 mg/kg) on rats' performance in a Morris water maze. The Morris water maze is a circular container filled with water that is made opaque by adding some form of nontoxic dye. A small escape platform that rises to 1 cm beneath the surface of the water is placed in the container and the amount of time it takes for the rat to find the escape platform is measured (e.g., Compton, Dietrich, & Smith, 1997; Eichenbaum, Stewart, & Morris, 1990). Bane et al. (1996) divided the container into four equal quadrants and placed the escape platform in one of those quadrants for the initial training session. Reversal training involved changing the escape platform location to the quadrant opposite the one used in initial training. The authors found that DM produced dose-dependent disruptions during the initial training phase and during the initial retraining session when platform location was changed. The authors also found that during reversal training rats injected with the highest dose of DM (40 mg/kg) perseverated to the former location longer than the other groups. In summary, DM impaired spatial learning in the Morris water maze in a dose-dependent fashion.

Dematteis et al. (1998) examined the effects of DM (20, 30, and 40 mg/kg) and its active metabolite DR (5, 10, and 15 mg/kg) on cue learning, place learning, spatial learning, place recall working memory, and reference memory by investigating performance on water maze tasks. Cue learning was examined by placing rats in the

pool for five daily sessions and measuring the average time it took for them to reach an emerged platform placed in the middle of the tank. The rats started from the same position on each day. A final session was conducted five hours after the last injection to assess the duration of drug effects. The escape latencies for rats injected with DR at 10 and 15 mg/kg were significantly longer than control subjects. Performance was not significantly impaired when compared to control subjects for the session conducted 5 h after injection.

For the place learning procedure milk was added to make the water opaque and the platform was submerged in one quadrant of the pool. The platform location was fixed but the starting point varied across sessions. DM at 40 mg/kg and DR 10 and 15 mg/kg significantly increased escape latencies, but the lower doses of DM and DR did not. One day after the last place-learning session the rats were placed in the quadrant opposite the training quadrant without the platform present and allowed to swim for 60 s. There were no significant differences in the amount of time various group spent in the training quadrant. The place recall procedure evaluated the effects of drugs on previously acquired spatial learning so drug sessions were conducted one day after place learning without drug. No dose of either drug produced significant effects on place learning. The working memory procedure looked at performance on twice daily sessions over four days. The platform location remained the same within days but was changed across days. The authors reported a slight disruptive effect of DR at 15 mg/kg. These findings represent PCP-like effects of DR on learning and working memory.

Research on the Acquisition of Behavior with Immediate and Delayed Reinforcement

Developments in the study of response acquisition with delayed reinforcement have offered a sensitive and fruitful measure to study the effects of various drugs on the acquisition of behavior (including chlorpromazine, *d*-amphetamine, pyridostigmine bromide, permethrin, MDMA and GHB) (Byrne et al., 1997; LeSage et al., 1996; Van Haaren et al., 1999; Van Haaren et al., 2000; Byrne et al., 2000; Laraway et al., 2004). Although there have been many variations in the response acquisition procedure, experimental sessions are typically preceded by a magazine training session where subjects are placed in an experimental chamber containing no operandum and where food delivery is not dependent on the subject's behavior. For the experimental session, subjects are placed in the chamber containing one or more operandi where responses are immediately reinforced (fixed ratio 1, FR 1 schedule) or responses are reinforced after a delay (e.g., tandem fixed-ratio 1 fixed time 30 s) (e.g., Byrne et al., 1998; Lattal & Gleeson, 1990; Snyckerski, Laraway, Byrne & Poling, 1999; Stoleran, 1971a, 1971b; Sutphin, Byrne & Poling, 1998; Wilkenfield, Nickel, Blakely, & Poling, 1992).

Neuringer (1970) showed that experimentally naïve pigeons acquire a key-peck response on an FR 1 schedule of reinforcement after magazine training, without any form of shaping. Stoleran (1971a) examined the effects of injections of chlorpromazine and chlordiazepoxide on rats' acquisition of a lever press with immediate reinforcement. He found that rats injected with chlorpromazine and

chlordiazepoxide before experimental sessions experienced a delay in the acquisition of a lever pressing response and emitted fewer total responses compared to rats that received injections of saline. The aforementioned results suggest that the acquisition of behavior might be helpful in the analysis of the effects of drugs.

Lattal and Gleeson (1990) extended previous research by examining three different variations of the response-acquisition procedure. First, the authors examined the acquisition of behavior using rats and pigeons. Second, they studied acquisition of behavior with delayed consequences. Finally, because the close proximity of the response operandum to the food delivery device may enhance the acquisition of a response, the operandum was placed on the opposite side of the chamber from the food hopper (for pigeons) or the food cup (for rats).

Subjects were first exposed to a variable-time (VT) 30-s schedule of food delivery followed by sessions involving various tandem schedules of food delivery without any form of shaping. Both species were exposed to delays that were either nonresetting or resetting. In a nonresetting procedure (tandem FR1 FT t s), the responses that occur during the delay interval have no programmed consequences and actual delays between the last response and delivery of a reinforcer may vary considerably and be shorter than the programmed delay interval. In a resetting delay, a tandem FR 1 differential reinforcement of other (DRO) schedule of reinforcement is incorporated. Under this arrangement, responses during the delay period reset that interval guaranteeing that the delay remains intact.

Both rats and pigeons acquired responding when resetting and nonresetting delays were arranged and neither operandum type nor location had an effect on

acquisition. The authors noted that increasing delays to reinforcement weakened the behavior that was examined. This was of particular interest to those conducting research on the effects of drugs on the acquisition of free-operant behavior with delayed reinforcement, because drug effects are most pronounced when behavior is weak (Byrne et al., 1996).

Wilkenfield et al. (1992) extended Lattal and Gleeson's (1990) research by examining rats' acquisition of lever response using three delay procedures, resetting, nonresetting, and stacked, with delays of 4, 8, 16 and 32 s. The procedures used in the nonresetting and resetting components were similar to those used by Lattal and Gleeson (1990), except for the delay values and the fact that responses were recorded on two levers labeled "operative" and "inoperative". Responses on the operative lever were reinforced according to one of the delay procedures and values while responses on the inoperative lever were recorded but had no programmed consequences. A higher rate of responding on the operative lever is an indication that the response is specific to that operandum (stimulus control).

The stacked delay involved delayed reinforcement for each response (e.g., each response produces a reinforcer). As in a nonresetting procedure, in a stacked delay, the delay between a response and the delivery of a reinforcer may vary and may be shorter than the programmed delay. However, unlike the nonresetting and resetting delay conditions, it ensures a direct relationship between the rate of responding and rate of reinforcement.

The authors observed acquisition of lever press response in all conditions with delays of 4, 8, and 16 s for the stacked and nonresetting conditions and with delays of

4, 8, 16, and 32 s in the resetting condition relative to the control condition.

Furthermore, response rates on the operative lever exceeded rates on the inoperative lever for all subjects at all delay values, indicating that the operative lever exerted stimulus control over the rats' behavior.

Early research on response acquisition with delayed reinforcement involved rats and pigeons as subjects and appetitive reinforcers. Lattal and Metzger (1994) examined the effects of delayed visual reinforcement on the behavior of male Siamese fighting fish (*Betta Splendens*). The behavior of swimming through a hoop, which interrupted a photocell beam, initiated an unsignaled delay that was followed by access to a mirror. Exposure to the image of a male Siamese fighting fish had previously been shown to act as a reinforcer in this species (Thompson, 1963). During 90-m sessions the ring apparatus was placed in the tank once a day for 20 sessions. Lattal and Metzger (1994) found that male Siamese fighting fish exposed to a tandem FR1 DRO 10-s or 25-s schedule of reinforcement exhibited response rates higher than those exposed to response-independent reinforcers.

Byrne, et al. (1997) extended the work of Stolerman (1971a, 1971b) by examining the effects of chlorpromazine (0, 2, 6, or 10 mg/kg) on rats' acquisition of a lever-press response with delayed reinforcement (0 or 8 s nonresetting). Two levers, one operative and one inoperative, were present during the 8-h sessions. Presses on the operative lever produced 4-s access to water and presses on the inoperative lever had no programmed consequences. Both the number of responses emitted (rate) and the development of stimulus control by the operative lever was

assessed. The latter measure provided an appraisal of drug effects that was not influenced by changes in response rate produced by that drug.

Byrne et al. (1997) found that chlorpromazine produced dose-dependent decreases in responding on both the operative and inoperative lever. Response acquisition was seen at doses of 0, 2, and 6 mg/kg but was not evident at 10 mg/kg. Chlorpromazine at 2 and 6 mg/kg disrupted the development of stimulus control by the operative lever only when reinforcement was delayed.

LeSage, et al. (1996) examined the effects of *d*-amphetamine (1.0, 5.6, and 10.0 mg/kg) on rats' acquisition of a lever-press response with delayed reinforcement (0, 8, or 16 s) under both resetting and nonresetting conditions. Each rat was placed in an experimental chamber that contained two levers for a single 8-h session. Both the number of responses emitted (rate) and development of stimulus control by the operative lever was assessed. Substantial responding on the operative lever was seen at all delay values and at all doses of *d*-amphetamine. Both the acquisition of the lever-press response and stimulus control was disrupted by the higher doses of *d*-amphetamine (5.6 and 10.0 mg/kg) in all conditions while the 1.0 mg/kg dose either had no effect or enhanced rates of operative-lever responding. Consistent with findings using the repeated acquisition procedure, the authors showed that *d*-amphetamine's detrimental effects on learning occur at doses that also produce general behavioral disruption.

Sutphin, et al. (1998) extended the research of Wilkenfield et al. (1992) by controlling for the possibility that responses on the inoperative lever may be adventitiously and immediately reinforced by the consequences of responding on the

operative lever, and therefore spread, through induction, to the operative lever. Sutphin et al. (1998) examined a two-lever procedure where responses on one lever (labeled the resetting lever) produced water after a resetting delay (delays were 8, 16, 32 and 64 s) and responses on the other lever (cancellation lever) cancelled a scheduled reinforcer (this was called the resetting/cancellation condition). The performance of the aforementioned rats was compared to that of a group of rats exposed to a two-lever procedure with a resetting lever that and a lever where there were no consequences for responding (the resetting/no consequences condition). Each rat was exposed to one 8-h session 24 h after magazine training. The authors observed differential responding on the two levers in both conditions with an 8-s delay, but differential responding at delays of 16 and 32 s only occurred with the resetting/cancellation procedure.

Byrne, Sutphin, and Poling (1998) examined the acquisition, extinction, and reacquisition of responding with delayed and immediate reinforcement. During acquisition sessions subjects were exposed to a single resetting lever that delivered water after delays of 0, 10, 20, and 30 s. Extinction, where no water was delivered, began after 50 water deliveries. Reacquisition sessions began 18 h after the end of extinction. These sessions were identical to the acquisition session, except that extinction was not implemented and sessions lasted 60 m. The authors found that resistance to extinction decreased with delayed reinforcement. They also found that responding acquired with delayed reinforcement recovered from extinction slower and less efficiently than responding that was immediately reinforced.

Byrne, et al. (2000) examined the effects of acute and neurotoxic exposure of (+ -) 3, 4- methylenedioxymethamphetamine (MDMA) on rats' acquisition of a lever-press response, in two experiments. Both experiments used a two-lever procedure similar to the resetting/cancellation procedure described by Sutphin et al. (1998).

The first experiment examined the acute effects of MDMA on the acquisition of behavior. Subjects were exposed to a single 8-h session where responses on the resetting lever were reinforced after delays of 0, 10 and 20 s. Injections of MDMA (0, 1.0, 3.2, or 5.6 mg/kg) were given 15 m before the start of the response-acquisition sessions. When responses were immediately reinforced, MDMA produced a dose-dependent increase in the total number of responses and reinforcers delivered. However, MDMA increased the latency for responding to begin but neither reduced the total number of responses emitted nor disrupted differential responding between the resetting and cancellation levers in any of the delay and drug conditions. The effects of MDMA on response acquisition with delayed reinforcement were similar to those observed with *d*-amphetamine, except MDMA disrupted response acquisition at doses that did not produce behavioral disruption.

The second experiment assessed the effects of neurotoxic exposure to MDMA on the acquisition of behavior. Half of the subjects were exposed to twice-daily injections of MDMA at 20 mg/kg for four consecutive days while the remaining subjects were given twice-daily saline injections for four consecutive days. Neurochemical analysis revealed a significant decrease in serotonin (5-HT) and its metabolite (5-hydroxyindole acetic acid) in the rats given daily MDMA injections

compared to those that received saline injections (this indicated that the dose of MDMA injected produced neurotoxic effects).

Acquisition testing was the same as in the first experiment. The second experiment revealed no significant effect of neurotoxic exposure to MDMA on acquisition at all delay values. The authors cite three possible reasons for this finding:

First, 5-HT may not play an important role in mediating performance in a given learning task, or other brain systems may compensate for 5-HT deficits.

Second, the specific assay used may not be sensitive enough to detect the effects of neurotoxicity. Third, the neurotoxic effects may not be large enough to cause any detectable behavioral deficits (p. 507).

Because acquisition curves are influenced by the onset and offset of drug effects and lever-press acquisition is evident in nearly all drug-free rats within 2 h in the absence of drug, Byrne et al. (2000) recommend using sessions that are no longer than 2 h.

Rationale for the Present Study

The primary aim of the current study was to examine the effects of DM on the acquisition of a lever-press response with delayed reinforcement, extending the application of this procedure to the study of opioid drugs. Because the response acquisition procedure examines the development of novel behavior, it may be relevant

to the development of new behaviors in young people who are at risk for abusing dextromethorphan and other drugs. The most common procedures used to examine drug effects on learning and memory in nonhumans assess drug effects on responses that are already established and may or may not resemble drug effects on initial response acquisition. If the findings from response-acquisition studies differ from findings from other studies and, at the same time, those findings resemble observed adverse effects in human users, response acquisition procedures may be of considerable value in the study of drug effects on learning.

CHAPTER II

METHODS

Subjects

A total of 80 male Sprague-Dawley rats (purchased from Charles River, Portage, MI) were used in the proposed study. The subjects were approximately 50 days old at the beginning of the study. The subjects were randomly assigned to groups and housed in pairs in plastic cages (each 24 cm long x 31.5 cm wide x 21 cm high) located in a colony room maintained on a 12-h light/12-h dark schedule and kept at a relatively consistent temperature (20-22° C). The rats were restricted to 1 h of access to Purina Rat Chow (Ralston-Purina, St. Louis) 21 h before the magazine training and experimental session. Food was available immediately after magazine training and response-acquisition sessions. Animal care and experimental procedures were approved by the Institutional Animal Care and Use Committee of Western Michigan University (Appendix A).

Apparatus

All experimental sessions were conducted in commercially available operant conditioning chambers, each 31.5 cm long x 25.5 cm wide x 25 cm high (Med Associates, St. Albans, VT). Each chamber contained two retractable response levers located 6 cm above the floor on the right and left sides of the front response panel. An

aperture was located 2 cm above the floor in the middle of the response panel to allow access to a food cup, which contained an infrared beam that recorded one head-entry (HE) response each time the beam was broken. A food magazine was programmed to deliver 45-mg food pellets (BioServ, Frenchtown, NJ). An overhead 28-v house light provided ambient illumination throughout experimental sessions. Each chamber was housed in a sound and light-attenuating shell equipped with an exhaust fan that provides masking noise and ventilation. All experimental events were controlled and recorded by MED-PC software (v. IV for Windows) operating on an IBM-compatible personal computer interfaced with the operant chambers using Med Associates interface equipment.

Drug

Dextromethorphan hydrobromide (Sigma Labs, St. Louis, MO) was dissolved in distilled water. DM injections were given IP at a volume of 1 ml/kg. The doses used had previously been shown to disrupt schedule-controlled behavior and performance on a Morris water maze task (Bane et al., 1996; Taskin, 1986). Doses used were 40.0, 60.0, and 80.0 mg/kg.

Procedures

Sixteen rats were randomly assigned to a No Food Control group while the remaining 64 rats were assigned at random to one of four groups, each comprising 16 animals. After being food deprived for 21 h, all rats received two 90-m magazine training sessions separated by 24 h. In these sessions, no levers were present in the chamber, and one pellet was placed in the food receptacle. All HE responses were recorded. Following the first HE response, the schedule of pellet delivery was changed to a variable-time (VT) 15-s schedule, under which pellet deliveries occurred randomly after an average interval of 15 s, independent of the rat's behavior. Magazine-training sessions ended after the delivery of 60 food pellets or 90 m, whichever occurred first. Each subject received 1 h access to food following the magazine-training session.

Twenty-one hours after the second magazine-training session, each rat was injected with one of the doses of drug. Thirty-minutes after injection the subjects were placed in the operant chamber for a 2-h response-acquisition session (Byrne et al., 2000). This session length was used since levels of DM and DR in the brain and plasma of Sprague-Dawley rats rise rapidly after and remain consistently high 3 h after IP injections of DM at 30 mg/kg (Wu et al., 1995). During the response-acquisition procedure a two-lever resetting/cancellation procedure was arranged as described by Sutphin et al. (1998) and Byrne et al. (2000). Subjects were placed in the experimental chambers that contained two levers. One lever was designated the

reinforcement lever (RL) and the other designated the cancellation lever (CL). A tandem fixed-ratio 1 DRO schedule was arranged on the RL. Under this schedule, presses on the RL were reinforced after a delay of 15 s, while presses on this lever during a delay interval reset the interval. Therefore, obtained delays were equal to programmed delays. Longer delay values are likely to produce greater variability in the vehicle group making drug effects more difficult to detect. Responses on the CL that occurred during a delay interval canceled a scheduled reinforcer. Presses on the CL at other times were recorded but had no programmed consequences. The location of the CL and RL was counterbalanced among subjects. All subjects were visually monitored at 10-m intervals during sessions that followed drug administration in order to ensure proper functioning of the equipment.

For the 16 rats that were in the No-Food Control group, lever-presses were recorded but had no programmed consequences during a single 2-h session. If the delivery of delayed reinforcers strengthens a given rat's response, that rat should respond more than rats in the No-Food Control group (where responses were not reinforced). Therefore, comparing performance of groups that received drug to the No-Food Control group determined whether rats in the former groups acquired the lever-press response. Comparing the performance of rats in the groups that received drug (40, 60, and 80 mg/kg DM) to that of subjects that received vehicle injections (0 mg/kg DM) determined whether doses of DM affected performance relative to that of untreated animals given the opportunity to learn.

CHAPTER III

RESULTS

The cumulative number of RL and CL responses, the number of food deliveries (i.e., Pellets), the number of RL responses that reset the delay interval (i.e., Resets) and the number of CL responses that canceled a food delivery (i.e., Cancels) were recorded in 5-s bins for each rat during the acquisition session. Figures 1 through 5 show mean cumulative RL and CL responses, Pellets, Resets, and Cancellations (acquisition curves) for each group respectively. All groups exhibited accelerated rates of RL and CL responding across time. Response rates developed more slowly in the groups that received DM compared to the vehicle control group. The drug groups exhibited lower rates of RL responding and received fewer pellet deliveries relative to the vehicle control group. The DM 60 mg/kg group emitted more RL and CL responses and earned more Pellets than the other drug groups. The DM 60 mg/kg group showed increased rates of responding on both levers starting about half way through the session, passing the control group in CL responses and Cancels, while performing similarly to the control group in RL responses and resets late in the session. As shown in Figures 1 through 5, the subjects in the DM 80 mg/kg group started responding later in the session on average than the subjects injected with lower doses or vehicle. Figures 3 and 4 have been rescaled to best display the data.

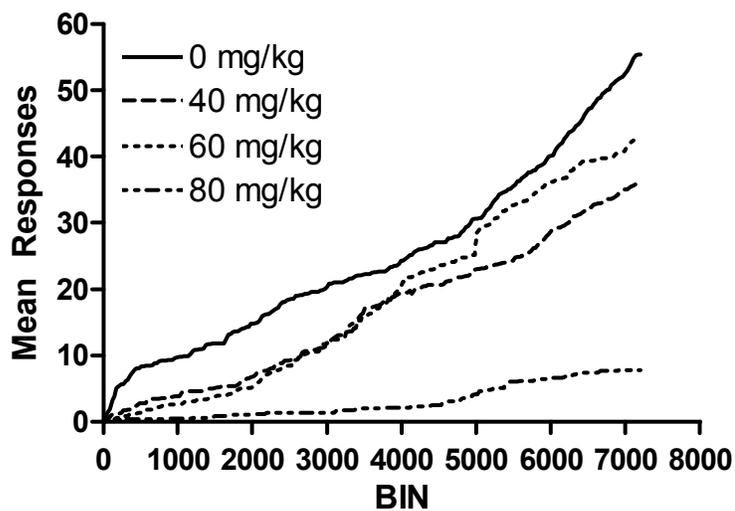


Figure 1. Cumulative records of mean RL responses.

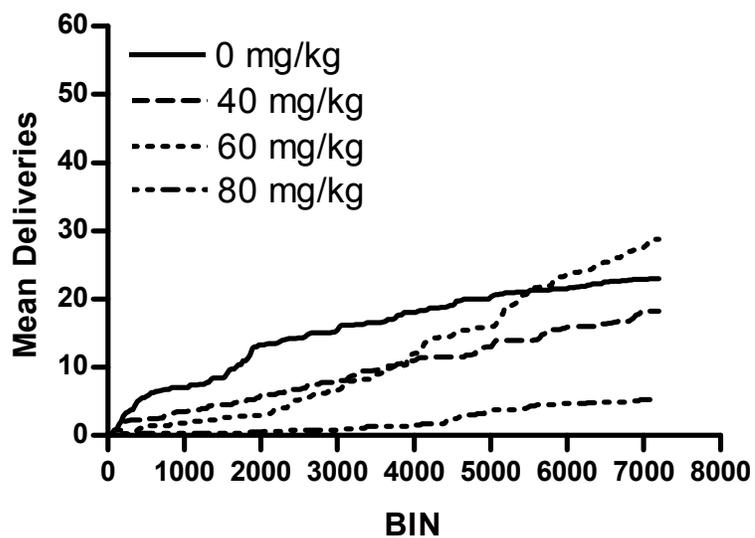


Figure 2. Cumulative records of mean CL responses.

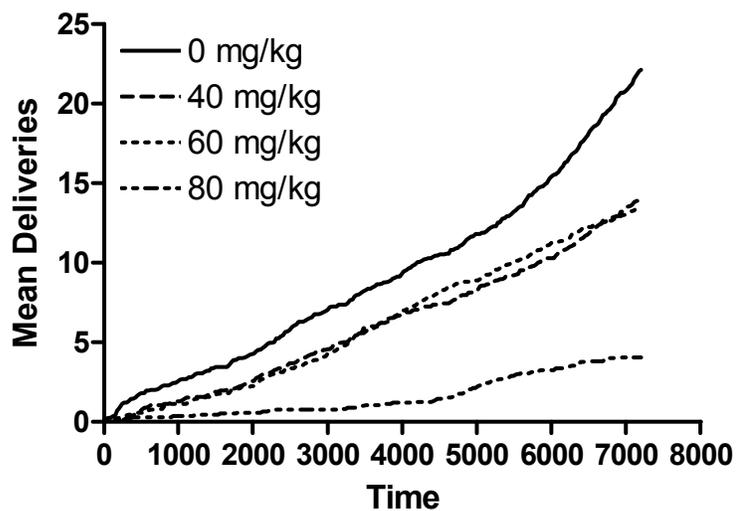


Figure 3. Cumulative records of mean Pellets.

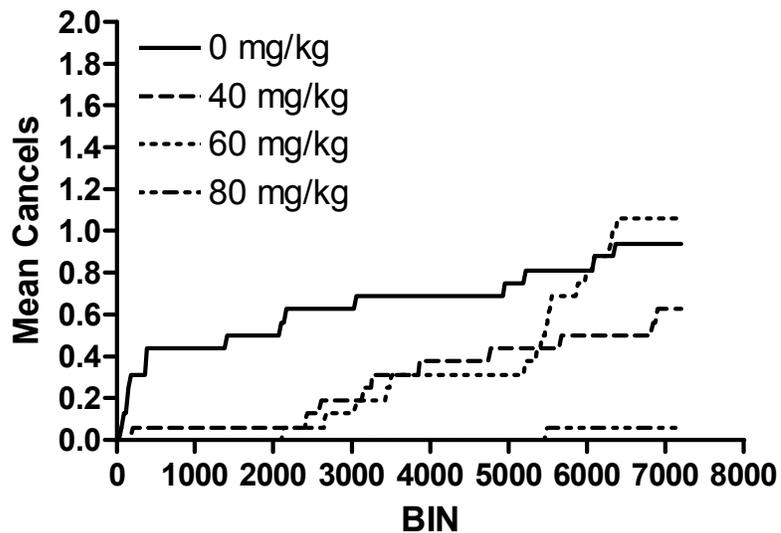


Figure 4. Cumulative records of mean Cancels.

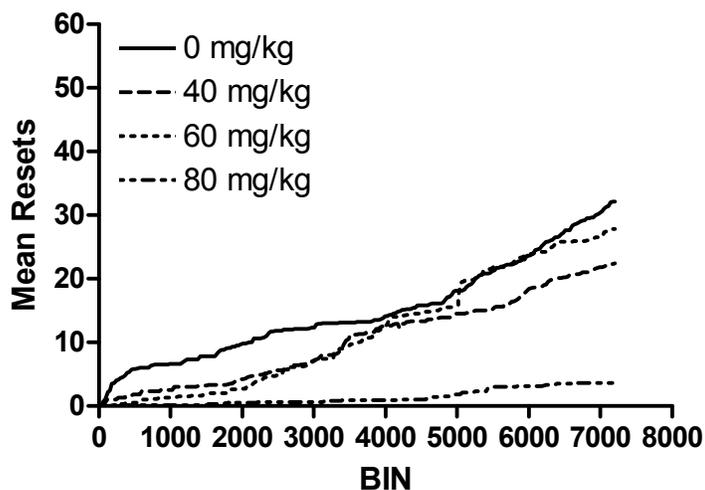


Figure 5. Cumulative records of mean Resets.

Subjects in the DM 0 mg/kg, DM 40 mg/kg, and DM 80 mg/kg groups showed a dose-dependent decrease in mean total responses on each lever, Pellets, Cancels and Resets. However, the DM 60 mg/kg group produced more responding on each lever Cancels and Resets than did the other drug groups. The DM 60 mg/kg group surpassed the vehicle group in CL responses and Cancels. Figures 6, 7, 8, 9, and 10 show the average RL, CL, Pellets, Cancels and Resets, respectively. Figure 9 has been rescaled to best display the data. A one-way ANOVA revealed significant differences in RL responses ($F = 3.14, p < 0.04$), CL responses ($F = 3.35, p < 0.03$) and Pellets ($F = 5.23, p < 0.03$) between the doses of drugs. A Tukey HSD revealed significant differences between the vehicle group and the DM 80 mg/kg group in RL responses ($q = 4.20, p < 0.05$) and Pellets ($q = 5.59, p < 0.05$) and between 60 mg/kg and 80 mg/kg in CL responses ($q = 4.30, p < 0.05$). One-way ANOVAs revealed no significant differences between groups in Cancels ($F = 0.95, p > 0.42$) and Resets ($F = 2.28, p > 0.09$).

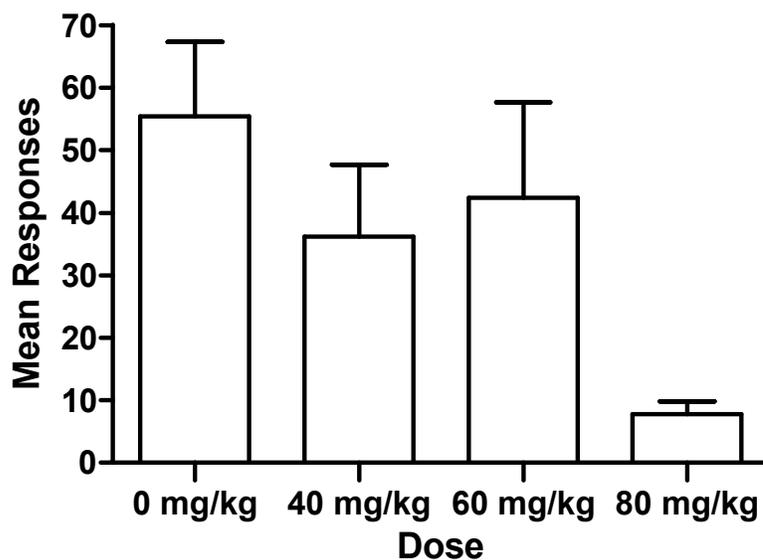


Figure 6. Average RL responses for each group. The bars represent standard errors.

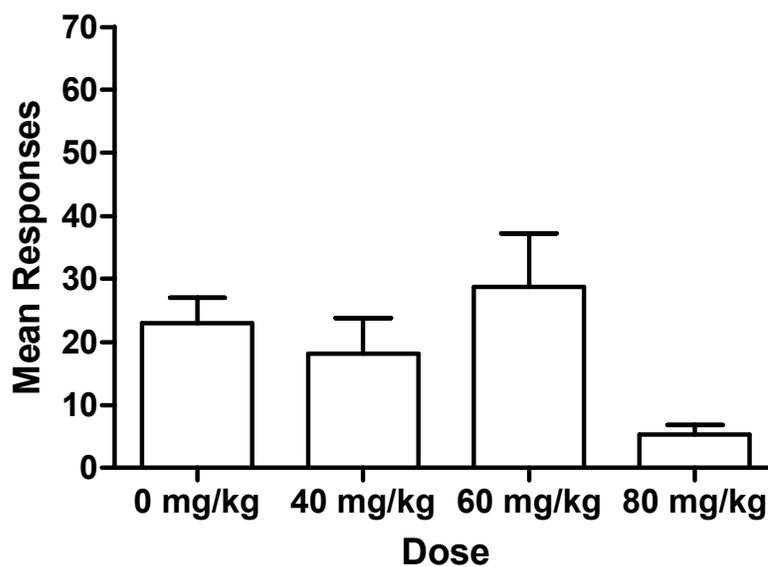


Figure 7. Average CL responses for each group. The bars represent standard errors.

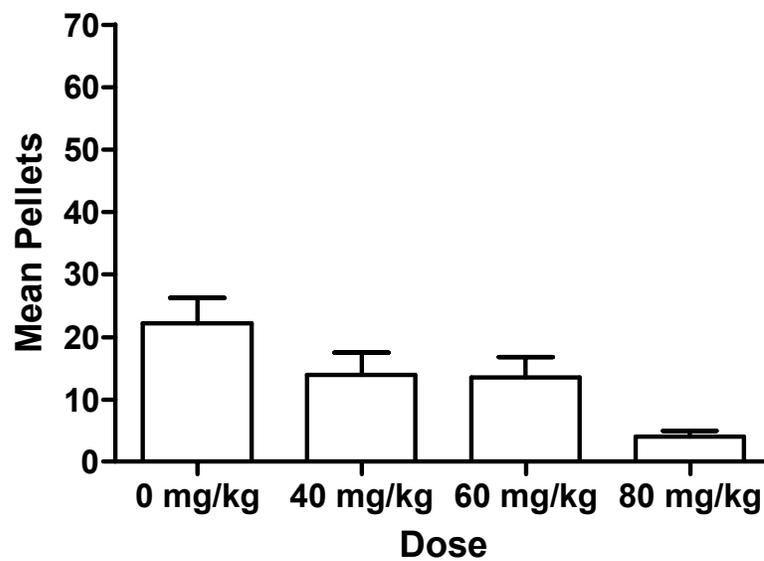


Figure 8. Average Pellets for each group. The bars represent standard errors.

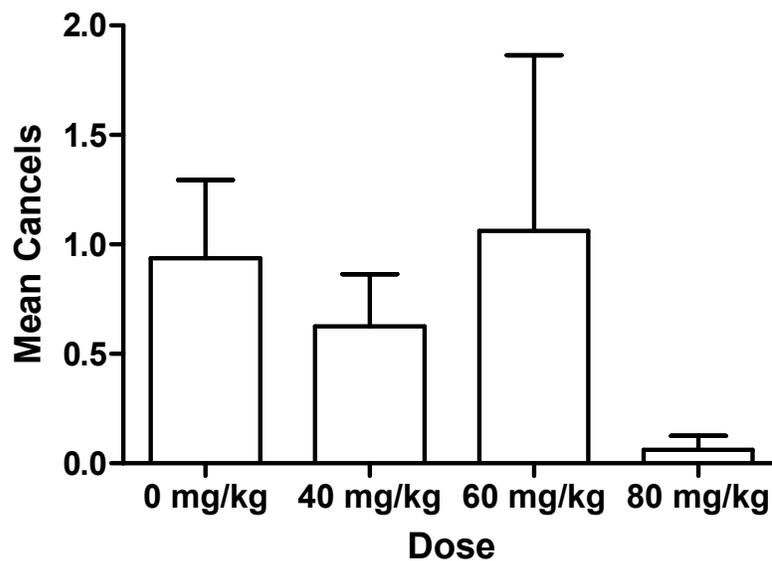


Figure 9. Average Cancels for each group. The bars represent standard errors.

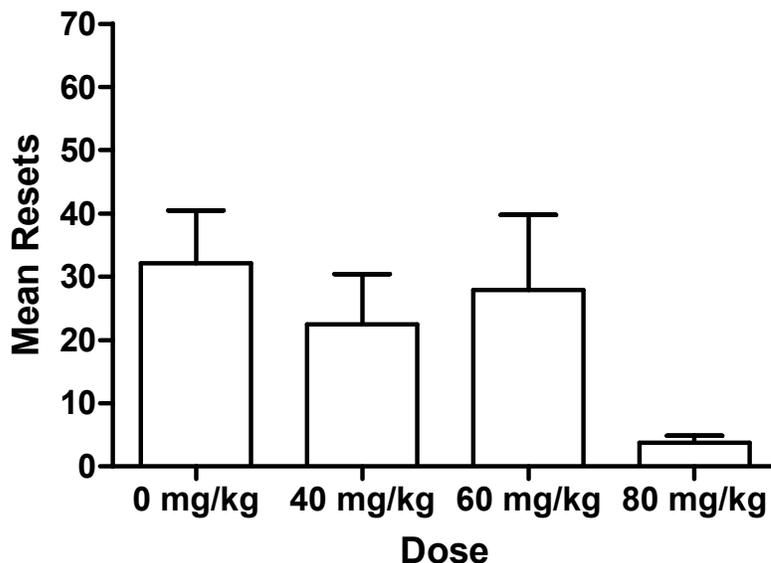


Figure 10. Average Resets for each group. The bars represent standard errors.

The percent of total responses emitted on the RL was computed for each rat [i.e., Percent = $(RL / (RL + CL)) \times 100$] during the acquisition session. This measure of response efficiency quantifies the degree to which the RL exerts stimulus control over the lever-press response. Furthermore, this measure is not influenced by the rate of behavior. The majority of responses were emitted on the RL for all conditions. A one-way ANOVA revealed that DM did not significantly affect the Percent ($F = 1.27$, $p > 0.29$).

A given dose of drug can affect learning by either reducing the total number of rats that acquired a lever-press response or by slowing the rate of acquisition. Therefore, two calculations were used to assess the number of rats that acquire the RL response. The subjects in each experimental group that were determined to have

acquired the RL response met both of the following conditions: 1) Subjects emitted at least 36 total responses, the upper limit of the 95% confidence interval around the mean number of responses on both levers by the No Food Control group ($M = 29$, upper limit = 7), and 2) subjects responded a greater number of times on the RL than the CL (e.g., Snyderski, Laraway, & Poling, 2005). Figure 11 shows the number of subjects in each group that acquired a lever-press response. A Fisher's Exact test revealed that significantly fewer rats injected with 80 mg/kg DM acquired responding than did subjects that were injected with vehicle ($4, N = 32, p < 0.0006$). There were no significant differences between the DM 0 mg/kg and DM 40 mg/kg ($4, N = 32, p > 0.05$), and DM 60 mg/kg ($4, N = 32, p > 0.05$) groups.

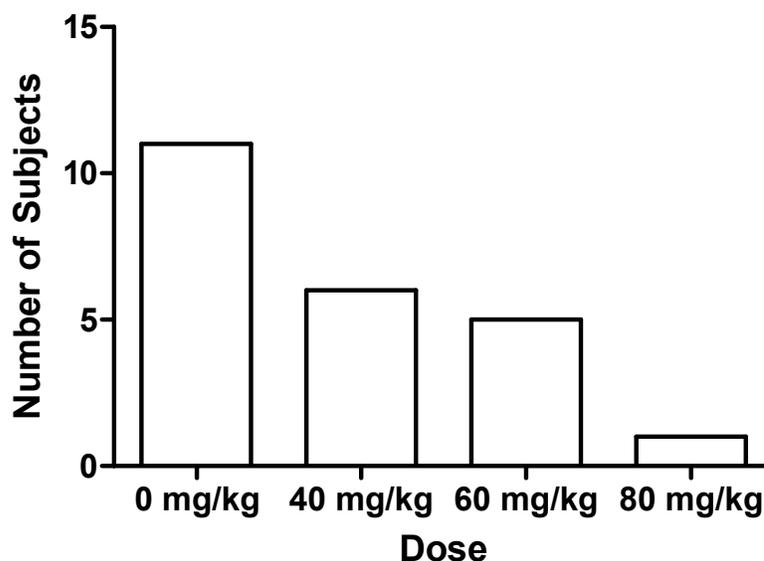


Figure 11. The number of subjects that acquired the lever-press response in each group.

A given dose of drug may impair learning by producing side effects that are incompatible with the lever-press response. Responding on both levers (RL + CL = Total) was calculated to assess the overall rates of lever pressing in each subject. A one-way ANOVA revealed a significant difference in Total ($F = 3.53, p < 0.02$). A Tukey HSD revealed significant differences between the vehicle group and the DM 80 mg/kg group in Total ($q = 4.20, p < 0.05$). Figure 12 shows average Total for all groups.

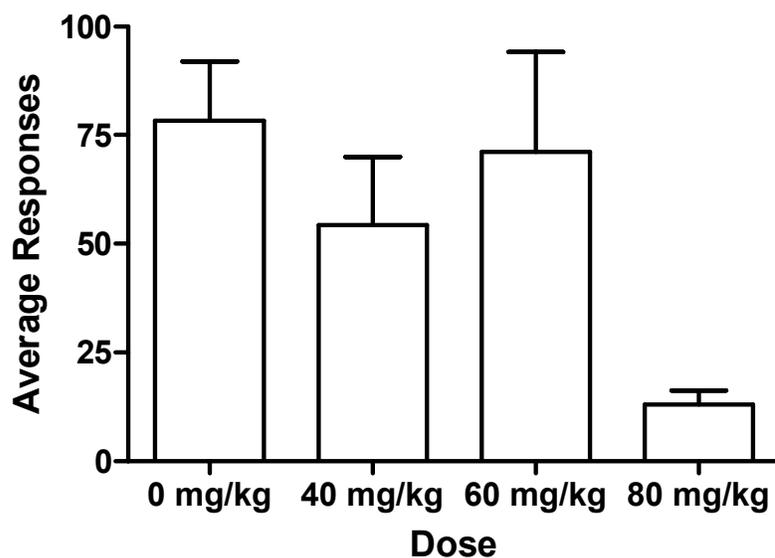


Figure 12. Average total responses on both levers for each group. The bars represent standard errors.

Variability across subjects may be an indication of differences in the rate that those subjects metabolized DM. Figures 13 through 16 show cumulative RL data for all subjects injected with DM at 0, 40, 60, and 80 mg/kg respectively. Figure 16 has been rescaled to best display the data. There was a wider range of RL responses in the DM 40 mg/kg and 60 groups than in the DM 80 mg/kg group.

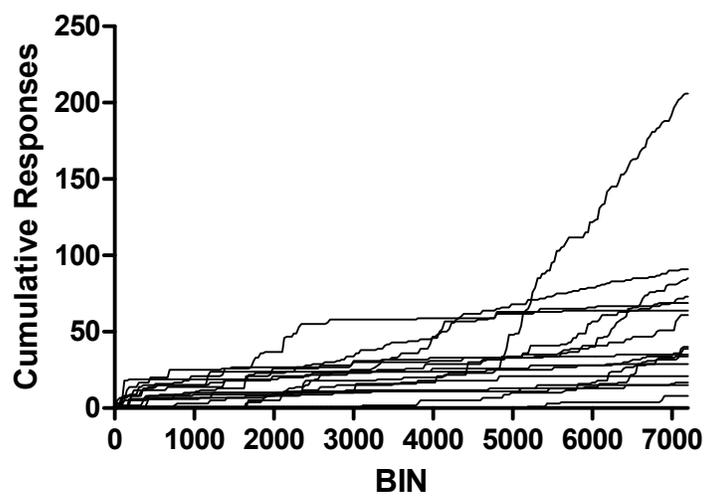


Figure 13. Cumulative RL responses the DM 0 mg/kg group.

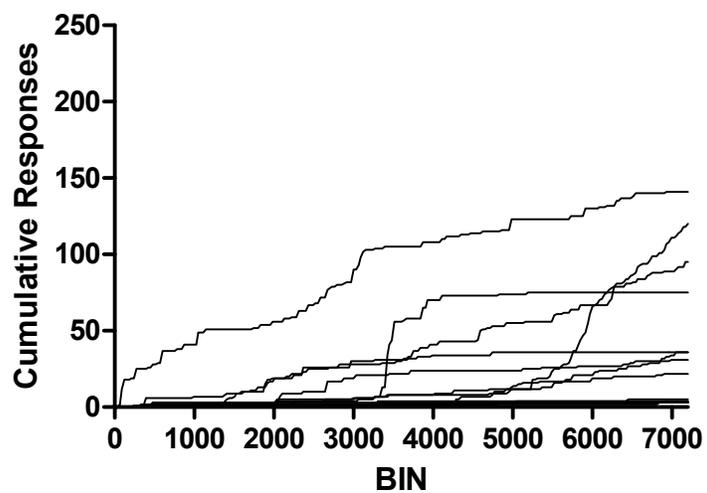


Figure 14. Cumulative RL responses the DM 40 mg/kg group.

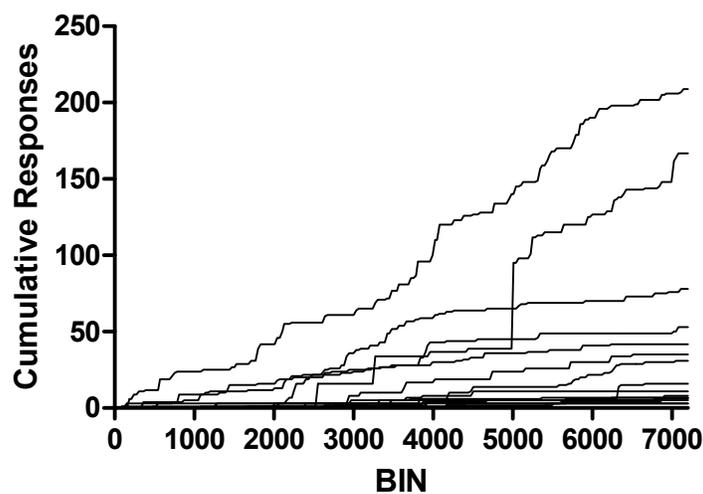


Figure 15. Cumulative RL responses the DM 60 mg/kg group.

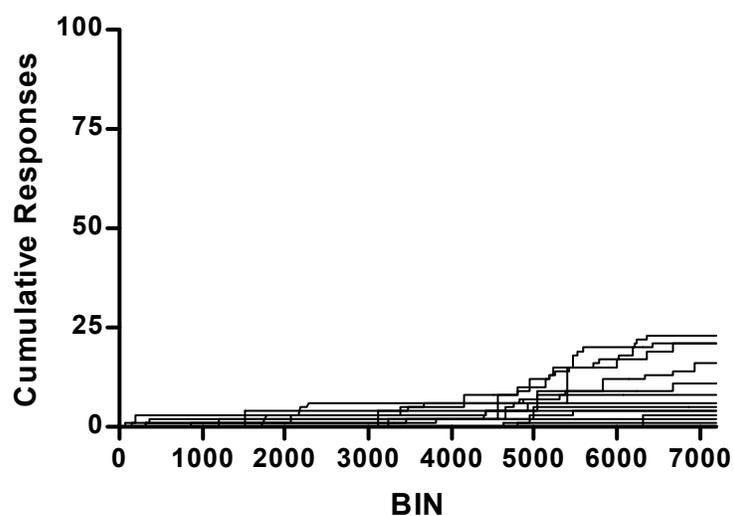


Figure 16. Cumulative RL responses the DM 80 mg/kg group.

A given dose of drug may affect behavior by increasing latency to respond (Latency). The measure of Latency used in the current study is the number of 30-s bins that passed before the Nth RL response was emitted. Latency to the first, fifth and tenth response were used in the current study. Figures 17, 18, and 19 show

average Latency to the first, fifth and tenth response, respectively. A Kruskal-Wallis one-way analysis of variance revealed a significant difference in Latency to the first response across groups ($H = 15.74$, $p < 0.0013$), 5th response across groups ($H = 26.90$, $p < 0.0001$) and the 10th response across groups ($H = 26.21$, $p < 0.0001$).

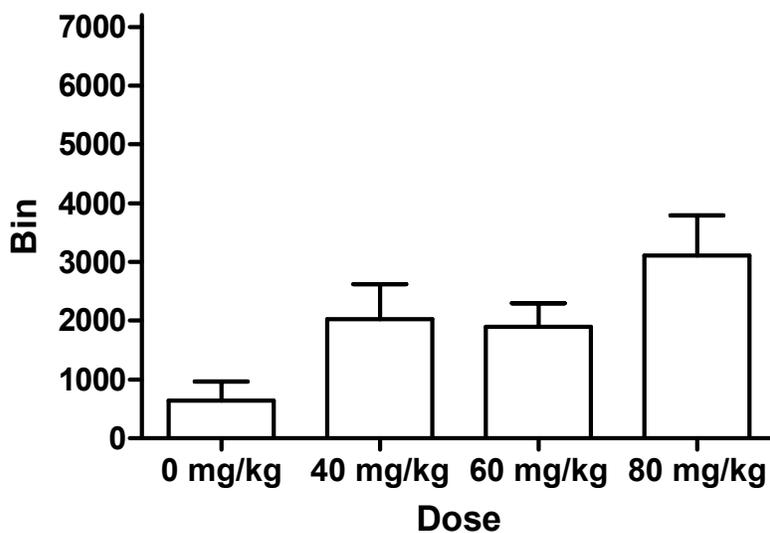


Figure 17. Mean latency to emit the first response. The bars represent standard errors.

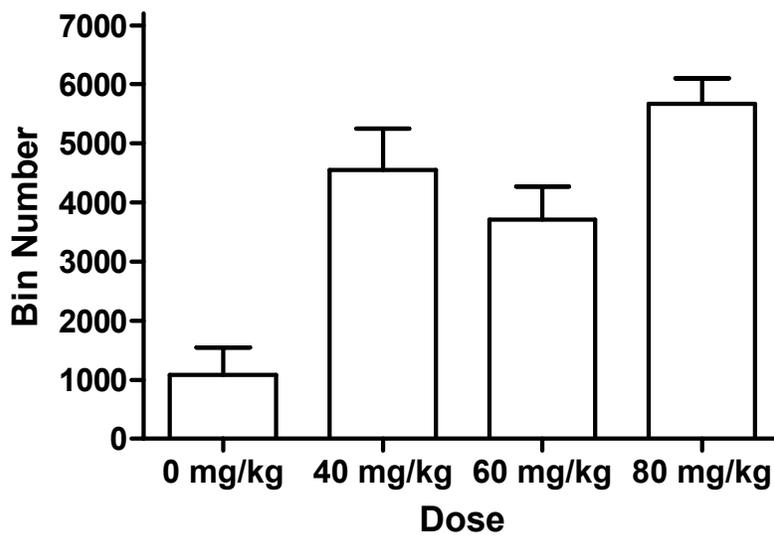


Figure 18. Mean latency to emit 5 responses. The bars represent standard errors.

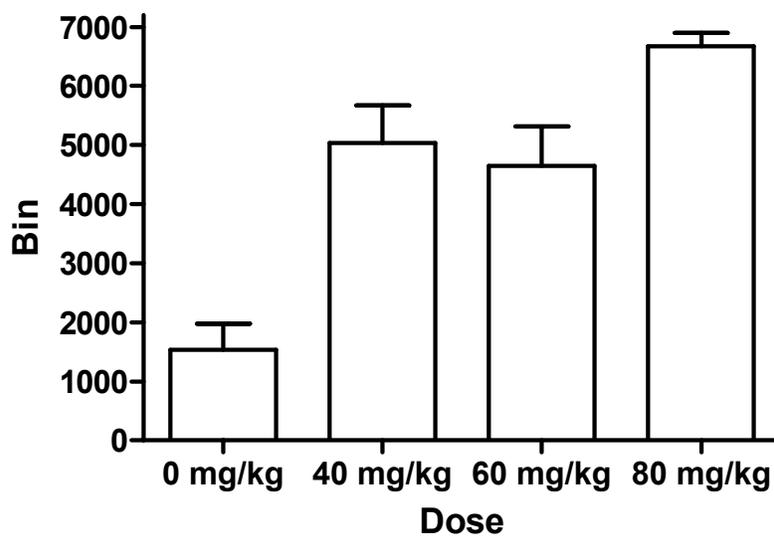


Figure 19. Mean latency to emit 10 responses. The bars represent standard errors.

Dunn's multiple comparison tests revealed significant differences in Latency to the fifth response between the vehicle group and the DM 40 mg/kg group; the vehicle group and the DM 60 mg/kg group; and the vehicle group and the DM 80 mg/kg group. Tables 1, 2 and 3 show the results of the Dunn's Multiple Comparison tests for the latency to the first, fifth and tenth response respectively.

Table 1

Dunn's Multiple Comparison tests for the latency to the first response.

<u>Dunn's Multiple Comparison Test</u>	<u>Difference in rank sum</u>	<u>P value</u>
DM 0 mg/kg vs. DM 40 mg/kg	-18.53	P < 0.05 *
DM 0 mg/kg vs. DM 60 mg/kg	-19.38	P < 0.05 *
DM 0 mg/kg vs. DM 80 mg/kg	-24.22	P < 0.01 *
DM 40 mg/kg vs. DM 60 mg/kg	0.84	P > 0.05
DM 40 mg/kg vs. DM 80 mg/kg	-5.69	P > 0.05
DM 60 mg/kg vs. DM 80 mg/kg	-4.84	P > 0.05

Significant differences are marked with an asterisk.

Table 2

Dunn's Multiple Comparison tests for the latency to emit 5 responses.

<u>Dunn's Multiple Comparison Test</u>	<u>Difference in rank sum</u>	<u>P value</u>
DM 0 mg/kg vs. DM 40 mg/kg	-24.25	P < 0.01 *
DM 0 mg/kg vs. DM 60 mg/kg	-18.97	P < 0.05 *
DM 0 mg/kg vs. DM 80 mg/kg	-32.53	P < 0.001 *
DM 40 mg/kg vs. DM 60 mg/kg	5.281	P > 0.05
DM 40 mg/kg vs. DM 80 mg/kg	-8.281	P > 0.05
DM 60 mg/kg vs. DM 80 mg/kg	-13.56	P > 0.05

Significant differences are marked with an asterisk.

Table 3

Dunn's Multiple Comparison tests for the latency to emit 10 responses.

<u>Dunn's Multiple Comparison Test</u>	<u>Difference in rank sum</u>	<u>P value</u>
DM 0 mg/kg vs. DM 40 mg/kg	-22.00	P < 0.01 *
DM 0 mg/kg vs. DM 60 mg/kg	-19.88	P < 0.05 *
DM 0 mg/kg vs. DM 80 mg/kg	-31.50	P < 0.001 *
DM 40 mg/kg vs. DM 60 mg/kg	2.13	P > 0.05
DM 40 mg/kg vs. DM 80 mg/kg	-9.50	P > 0.05
DM 60 mg/kg vs. DM 80 mg/kg	-11.63	P > 0.05

Significant differences are marked with an asterisk.

CHAPTER IV

DISCUSSION

Latency to Respond

The present study was conducted to assess the effects of DM on the initial acquisition of a lever-press response with delayed reinforcement. All doses of drug interfered with learning by significantly increasing Latency and in that sense the study was successful in extending the use of this procedure to the study of opioids. All three measures, Latency to first, fifth and tenth response, were affected by all doses of DM. However, because the first response had not been previously reinforced, latency to the first response is not an indication of learning. Latency to the fifth and tenth responses is, however, a valid measure of learning.

Comparing the Response-Acquisition Procedure to Other Assays

Other research methods examining the influence of DM on learning showed effects at smaller doses than those that significantly affected the dependent measures, other than Latency, in the current study. For example, Taskin (1986) showed that DM at 20 and 40 mg/kg disrupted response rates under an FI-45 schedule of reinforcement. Bane et al. (1996) showed that DM at 30 and 40 mg/kg produced a

significant impairment of spatial learning. Finally, Dematteis et al. (1998) demonstrated that DM at 40 mg/kg produced impairment in the performance of a place learning procedure on a water maze task. The aforementioned assays examined the acquisition of negatively reinforced behavior and any effect of DM could be due to the anxiolytic action of DR (Dematteis et al., 1998). However, as mentioned above, none of these studies examined the initial acquisition of positively reinforced behavior.

The detrimental effects of DM on the acquisition of positively reinforced behavior is of particular concern since the typical recreational users of the drug are adolescents and young adults and disruption of learning is particularly important during these years. In humans, drug use during adolescence has been shown to disrupt the acquisition of cognitive skills that may be important to functioning in interpersonal and intrapersonal domains (Schier & Botvin, 1995).

Behavioral Disruption

Only the highest dose of DM produced significant effects on RL responses, CL responses, Pellets, and Acquisition, a dose that also produced noticeable behavioral disruption throughout the session. Visual inspection revealed subjects in the DM 80 mg/kg group demonstrated obvious signs of ataxia (awkward and jerky movement, falling on side and difficulty walking on bars in the experimental chamber). These disruptions were not seen after injections of the lower doses. It is reasonable to assume that the PCP-like activity of DR affected subjects in the current study given

that DM was administered via IP injection with a 30-m post injection period. As mentioned above, in Sprague-Dawley rats, brain concentrations of DR rise rapidly and remain consistently high 3 h after IP administration of DM at 30 mg/kg (Wu et al., 1995). Dematteis et al. (1998) documented similar effects on a water-maze task after injections of high doses of DM and DR. Rats injected with DM 40 mg/kg and DR 20 and 40 mg/kg showed only slight to moderate levels of behavioral disruption, as measured in an open field experiment. However, these subjects exhibited noticeable disruption (floating before swimming, jumping off the escape platform, swimming along the sidewalls and attempting to run up sidewalls) when performing on a water maze task. The authors attributed this to ataxia and the anxiolytic action of DR (which may reduce motivation to find the escape platform), as well as sedation produced by DM.

Sedation produced by DM may also contribute to the significant effects observed at the highest dose in the current study. DM is rapidly metabolized and only low concentrations of DM may have been active in subjects during experimental sessions in the current study. The fact that significant effects on RL, CL, Pellets, Cancels, Percent, and Acquisition were only seen at the 80 mg/kg dose may be due to the need to achieve a certain DM threshold concentration before an effect can be observed (A. Somogyi, personal communication, February 18, 2005).

Locomotor Activity

In the present study, a reduction in Total and increase in Latency was observed in the DM 40 mg/kg and 80 groups. However, subjects in the DM 60 mg/kg group demonstrated an increased Total and shorter Latency than other experimental groups, although the difference was not statistically significant. These findings may be related to the dose-dependent effects of DR, an active metabolite of DM, on locomotor activity. For example, Wu et al. (1995) showed a significant increase in locomotor activity in rats given IP injections of DM at 60 mg/kg compared to those given saline. No significant effects were observed after injections of lower doses (15 and 30 mg/kg). Dematteis et al. (1998) observed a reduction in locomotor activity after injections of DR at 20 and 30 mg/kg while 40 mg/kg increased locomotor activity. It is possible that DM at 60 mg/kg affected Total and Latency by producing an increase in locomotor activity in the current study. A dose of drug that increases locomotion, without producing side effects that are incompatible with responding, increases the probability that subjects will come in contact with the lever reducing Latency and increasing Total.

Lack of Effect at Lower Doses

As mentioned earlier, doses of DM that failed to disrupt acquisition significantly in the current study had been shown to produce low levels of behavioral

disruption in other studies. For example, injections of DM at 40 mg/kg produced slight motor disturbances in rats (Bane et al., 1996; Dematteis et al., 1998) and injections of DM at 30 to 60 mg/kg significantly reduced FR responding in substitution tests involving a saline vs. PCP discrimination (Nicholson, 1999). In the current study, subjects in the DM 60 mg/kg and 40 mg/kg groups did not exhibit the signs of ataxia observed in the DM 80 mg/kg group. Also, the responding of subjects in the DM 40 mg/kg and 60 mg/kg groups on RL, CL, Pellets, Cancels, Percent, and Acquisition did not significantly differ from the control group. There are two possible explanations for a lack of a significant effect at the lower doses tested. First, DM may not disrupt acquisition of RL, CL, Pellets, Cancels, Percent, and Acquisition at these doses. Second, the lack of statistical significance at the lower doses may be due to within-group variability in the rate that subjects metabolized DM.

Suggestions for Further Research

DM Combined with Other Drugs

DM is often abused in combination with other OTC substances. Nevin (2004) noted that the use of DM in combination with other drugs is the rule rather than the exception. DM has been used recreationally in combination with diphenhydramine (Jun, Thorndike & Schindler, 2004), pseudoephedrine (Narin & Diaz, 2001), and chlorpheniramine maleate (Nevin, 2004), typically because OTC preparations that contain DM also contain these substances.

DM also has been used in combination with MDMA. In a sample of street drugs sold as MDMA, the most common drug identified, other than MDMA, was DM (Baggott, Heifets, Jones & Mendelson, 2000). Occasionally, DM is mixed with heroin to increase its pharmacological effects (Cranston & Yoast, 1999).

The continued abuse of OTC drugs by humans and use of street drugs laced with DM warrants further study of the behavioral effects of combinations of these drugs. Research on the behavioral effects of DM in combination with other drugs may yield different results from findings generated by previous research examining this drug. For example, Jun et al. (2004) found that rats would self-administer DM and diphenhydramine in combination but not when either drug was given alone.

Route of Administration

The route of administration of DM may influence the behavioral response to this drug. Because the effects of DR resemble those of PCP, subjects that convert DM to DR more readily would be more likely to exhibit PCP-like effects (Dematteis et al., 1998; Funck-Brentano et al., 1992; Kerry, Somogyi, Mikus, & Bochner, 1993). DM eventually is metabolized to 3-hydroxymorphinan via two separate pathways. Kerry et al. (1993) describe this process:

The O-demethylation of DM to dextrorphan (DR) is catalyzed by the polymorphic CYP2D6 (cytochrome P4502D6) isozyme in humans. DR is further metabolized by N-demethylation to 3-hydroxymorphinan (3OHM) and both metabolites are then conjugated. DM is also N-demethylated to 3-

methoxymorphinan (3MM), which is further O-demethylated to 3OHM. (p. 833)

Variability across humans has been observed in the rate that DM is converted to DR. Pfaff, Briegel and Lamprecht (1983) observed average plasma levels of DR ranging from 11.7 to 690 ng/ml in adult human subjects 2 h after oral administration of DM (25 mg). Kennedy, Abdel-Rahman, Kashuba, and Leeder (2004) noted that the metabolic rates for DM of children between the ages 3 and 8 years, who were determined to be extensive metabolizers, did not stabilize until 4-h after oral administration. The authors noted that longer periods of time might be needed before metabolic rates stabilize in subjects who are poor metabolizers.

Differences in DM metabolism also have been documented in different strains of rats. For example, female Dark Agouti rats are deficient in the cytochrome P450 enzyme, which catalyses the O-demethylation of DM to DR in Sprague-Dawley rats (Ishmael, Franklin, & Murray, 1998). Dark Agouti and Sprague-Dawley rats are considered poor metabolizers and extensive metabolizers of DM, respectively. Kerry et al. (1998) observed a wide range in the rates that three Sprague-Dawley rats metabolized DM to DR (25.01 to 52.43 nanomoles formed per milligram of microsomal protein per hour). Although the extent that variation in the rate that subjects metabolize DM affects learning has not been assessed, it certainly is plausible that this variable affected the results of the present study.

The current study used the IP route of administration in order to enhance the biotransformation of DM to DR. The effects that administration of DM may have via

the SC route were not examined in the current study due to the limited availability of subjects. As mentioned above, the lack of an effect at the lower doses may be due to the need to achieve a certain threshold concentration of DM before an effect can be observed. Injecting DM via the SC route of administration produces a different metabolic pattern from the IP route, thus increasing the bioavailability of DM (Wu et al., 1995). Therefore, the use of the SC route of administration would likely produce different results from those of the current study.

APPENDIX A

A copy of the Institutional Animal Care and Use Committee is on file in The
Graduate College, Western Michigan University.

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