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Effects of dextromethorphan on rats' acquisition of responding with delayed reinforcement

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Abstract

Separate groups of 16 rats received 0, 40, 60, or 80 mg/kg dextromethorphan prior to a 2-h response-acquisition session during which responses on one lever produced food (reinforcement lever, RL, responses) after a 15-s resetting delay and responses on the other lever cancelled food deliveries earned by RL responses, but otherwise had no programmed consequences. When compared to the 0 mg/kg dose, the 40, 60, and 80 mg/kg doses significantly decreased the latency to the tenth RL response, which has been used previously as an index of response acquisition [Pallares, MA, Nadal, RA, Silvestro, JS, Ferre, NS. Effects of ketamine, a noncompetitive NMDA antagonist, on the acquisition of the lever-press response in rats. Physio Behav 1995; 57:389–392.]. Only the 80 mg/kg dose, however, significantly reduced the total number of food pellets earned, the total number of RL responses, or the total number of rats that met the criterion for response acquisition. The present results indicate that dextromethorphan can disrupt initial response acquisition (i.e., learning) with positive reinforcement, although the dose that did so depended on the measure used to index performance. Moreover, the effects of the drug did not appear to reflect specific learning impairment, but rather more general disruption of behavior.

Keywords: Response acquisition; Learning; Delayed reinforcement; Dextromethorphan; Rats

1. Introduction

Dextromethorphan (93-methoxy-17-methylmorphinan, DM) is the dextrorotary isomer of levomethorphan, a codeine analog of the morphinan derivative levorphanol. At low doses DM is an effective antitussive that lacks most opioid-like activity and is considered to be a safe over-the-counter cough suppressant (Jaffe and Martin, 1990). Higher doses have been studied for treating pain and various neurodegenerative conditions but the drug is rarely used for these purposes (Ikjaer et al., 1997; Nicholson et al., 1999), in part because such doses produce unpleasant subjective effects similar to those produced by the dissociative anesthetics phencyclidine (PCP) and ketamine (Dematteis et al., 1998; Kim et al., 1996). These effects include agitation, confusion, slurred speech, ataxia, increased perceptual awareness, altered time perception, floating sensations, unusual facial movements, and hallucinations (Darobe, 1996; Darobe et al., 1996; Narin and Diaz, 2001; Wolf and Caravati, 1995). The PCP- and ketamine-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 and, like the dissociative anesthetics, acts as a noncompetitive antagonist by blocking the Ca^{2+} channel coupled to these receptors (Nicholson et al., 1999).

Although DM can produce unpleasant effects and is not a controlled substance, sporadic abuse of the drug has been reported in several areas of the world (Cranston and Yoast, 1999). DM is cheap and readily available and therefore is especially appealing to young recreational drug users (Nevin, 2004). Because young people are frequently exposed to DM, there is good reason to examine the effects of the drug on learning and memory and a few studies have used animal models to do so. Two studies have shown that DM disrupted memory as indexed by a passive avoidance task. Sierocinska et al. (1991) reported that none of the DM doses they examined (3, 11, 22 mg/kg IP) significantly affected performance immediately after training, but 2 days after training rats that

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received 22 mg/kg entered a chamber in which they had previously been shocked significantly faster than control subjects. In a similar study, Murata and Kawasaki (1993) reported that DM injected into the ventricles of rats at concentrations that produced motor incoordination and a reduction in muscle tone also disrupted performance in a passive shock-avoidance task.

Studies using water mazes also have demonstrated DM-induced behavioral disruption. Bane et al. (1996) found that DM at 30 and 40 mg/kg produced a significant impairment in rats' learning and relearning in such an apparatus, and Dematteis et al. (1998) reported that DM at 40 mg/kg interfered with several measures of performance. In both studies, lower doses produced inconsistent effects.

Interestingly, all of the studies showing DM-induced impairment of learning and memory involved negative reinforcement, that is, conditions under which behavior was controlled by escape from or avoidance of aversive stimulation. No studies of the drug's effects on learning or memory in assays involving positive reinforcement, where animals respond to produce a reward, have appeared, although Taskin (1996) reported that IM injections of DM (10, 20, and 40 mg/kg) produced dose-dependent decreases in rats' rates of responding under a fixed-interval 45-s schedule of milk delivery. The purpose of the present study was to examine the effects of DM in rats exposed to a learning assay involving the initial acquisition of lever-press responding with positive (i.e., food) reinforcement. A previous study (Pallares et al., 1995) reported that ketamine (4, 8, and 12 mg/kg) produced dose-dependent disruption in rats' acquisition of a lever-press response, although these doses did not significantly affect motor performance. If the behavioral effects of DM are primarily produced by its metabolite, DR, which has neurochemical actions similar to those of the dissociative anesthetics, it is reasonable to hypothesize that DM and ketamine should affect response acquisition in similar fashion.

Previous studies from our laboratory and elsewhere have used response-acquisition procedures to examine the effects of chlorpromazine (Byrne et al., 1997; Stolerman, 1971a,b), chlordiazepoxide (Stolerman, 1971a,b), *d*-amphetamine (LeSage et al., 1996), pyridostigmine and permethrin (van Haaren et al., 1999, 2000), and 3,4-methylenedioxymethamphetamine (MDMA) (Byrne et al., 2000) on learning with immediate and delayed reinforcement. The results of these studies suggest that the procedure is more sensitive when reinforcement is delayed than when it is immediate, and researchers from our laboratory and elsewhere have proposed that response acquisition with delayed reinforcement is a sensitive and meaningful index of drug-induced learning disruption (Snycerski et al., 1998, 2004; van Haaren et al., 1999, 2000). The procedure also appears to be sensitive to gender differences in rats (van Haaren et al., 1992) and strain differences in mice (Baron and Meltzer, 2002).

2. Methods

2.1. Subjects

Eighty experimentally naïve male Sprague–Dawley rats, purchased from Charles River (Portage, MI) and approximately 50 days old at the beginning of the study (mean weight = 155 g) were used. They were housed in pairs in plastic cages (24 cm long × 31.5 cm wide × 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 each experimental session. Food was available immediately after magazine training and response-acquisition sessions. This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals promulgated by the National Research Council (1996) and was approved by the Institutional Animal Care and Use Committee at Western Michigan University.

2.2. Apparatus

Experimental sessions were conducted in commercially available operant conditioning chambers, each 31.5 cm long × 25.5 cm wide × 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 of the chamber. An aperture located 2 cm above the floor in the middle of the response panel allowed access to a food cup. A beam of infrared light passed through the aperture; when it was broken, a head-entry (HE) response was recorded. When scheduled, 45 mg food pellets (BioServ, Frenchtown, NJ) were delivered into the food cup. An overhead 28-V light provided ambient illumination throughout experimental sessions. Each chamber was housed in a sound- and light-attenuating shell equipped with an exhaust fan that provided masking noise and ventilation. Experimental events were controlled and data were recorded by MED-PC software operating on an IBM-compatible personal computer.

2.3. Magazine training procedure

Sixteen rats were randomly assigned to a No Food Control group while the remaining 64 rats were assigned at random to one of four experimental groups, each comprising 16 animals. All experimental groups were treated identically, save for the kind of injection (vehicle or DM) administered prior to the response-acquisition session. 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, a variable-time 15-s schedule was initiated. Under this schedule, 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. Rats received 1 h access to food following the magazine training sessions.

2.4. Pharmacological procedure

Twenty-one hours after the second magazine training session, each rat received an IP injection of DM or vehicle

(distilled water). The No Food Control group and one of the four experimental groups received distilled water, while the other three experimental groups received 40, 60, and 80 mg/kg DM, respectively. If the procedure used in the present is as sensitive as other commonly used assays, DM at 40 mg/kg IP should interfere with learning, because similar or lower doses disrupted rats' learning and memory in prior studies (Bane et al., 1996; Dematteis et al., 1998; Murata and Kawasaki, 1993; Sierocinska et al., 1991). Drug testing in the present study began at 40 mg/kg. Because this dose disrupted some, but not all, measures of performance, two higher doses (60, 80 mg/kg) subsequently were examined. Dextromethorphan hydrobromide (Sigma Labs, St. Louis, MO) was dissolved in distilled water and all injections were given at a volume of 1 ml/kg.

2.5. Response-acquisition procedure

Thirty minutes after injection the rats were placed in the chambers for a 2-h response-acquisition session. This session length ensured that declining drug levels over time would not complicate the analysis of results, because levels of DM (and its behaviorally active metabolite, DR) rise rapidly in the brain and plasma of Sprague–Dawley rats and remain consistently high up to 3 h after IP injection (Wu et al., 1995). Testing began with the No Food group, after which the 0, 40, 60, and 80 mg/kg groups were tested, in that sequence.

During the response-acquisition session a two-lever resetting/cancellation procedure was arranged as described elsewhere (Byrne et al., 2000; Sutphin et al., 1998). During this session, the chambers contained two levers. One lever was designated the reinforcement lever (RL) and the other was designated the cancellation lever (CL). A tandem fixed-ratio 1 differential-reinforcement-of-not-responding 15-s schedule was arranged on the RL. Under this schedule, presses on the RL were followed by food after a delay of 15 s, while presses on this lever during a delay reset the interval. Therefore, obtained delays were equal to programmed delays. 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.

For the rats 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 food strengthened a given rat's responding, so that it acquired lever-pressing, that rat should have responded more than rats in the No-Food Control group (where responses did not produce food). Therefore, comparing the performance of groups that received drug to that of 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 rats that received vehicle injections (0 mg/kg DM) under the response-acquisition procedure determined whether doses of DM affected performance relative to that of untreated rats given the opportunity to learn.

2.6. Data analysis

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. Very few Cancels occurred in any group, therefore, these data are not reported. Data for RL responses, CL responses, Pellets, and Resets were analyzed via one-way ANOVAs followed by Tukey HSD tests.

Previous studies of *d*-amphetamine (LeSage et al., 1996) and gamma-hydroxybutyrate (Laraway, 2003) indicated that these drugs slowed the onset of responding under response-acquisition procedures at doses that did not affect measures of performance across the entire session. To determine whether DM produced similar effects, the latency from the onset of the session to the emission of the first, fifth, and tenth RL response was recorded for each rat. Because some rats did not emit sufficient RL responses for analysis, precluding the use of a conventional ANOVA, latency data were analyzed via Kruskal–Wallis one-way analysis of variance followed by Dunn's Multiple Comparison tests.

3. Results

3.1. DM effects on acquisition

Rats in the No Food Control group emitted few responses; the mean number of responses on both levers for rats in this group was 29. A given rat in one of the experimental groups was assumed to have acquired the RL response if a) it emitted at least 36 responses on that lever (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 b) it responded a greater number of times on the RL than on the CL. Using these criteria, 11, 6, 5, and 1 rats acquired the response in the 0, 40, 60, and 80 mg/kg groups, respectively. 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 0 mg/kg and 40 mg/kg (4, $N=32$, $p>0.05$) or 60 mg/kg (4, $N=32$, $p>0.05$) groups.

3.2. DM effects on RL responses, CL responses, pellets, and resets

Fig. 1 shows the mean number of RL responses, CL responses, Pellets, and Resets for each of the four experimental groups. For RL responses, CL responses, Pellets, and Resets, measures were highest in the 0 mg/kg group and lowest in the 80 mg/kg group. One-way ANOVAs revealed significant differences in RL responses ($F=3.14$, $p<0.04$), CL responses ($F=3.35$, $p<0.03$) and Pellets ($F=5.23$, $p<0.03$) across experimental groups. Tukey HSD tests revealed significant differences between the 0 mg/kg group and DM 80 mg/kg group

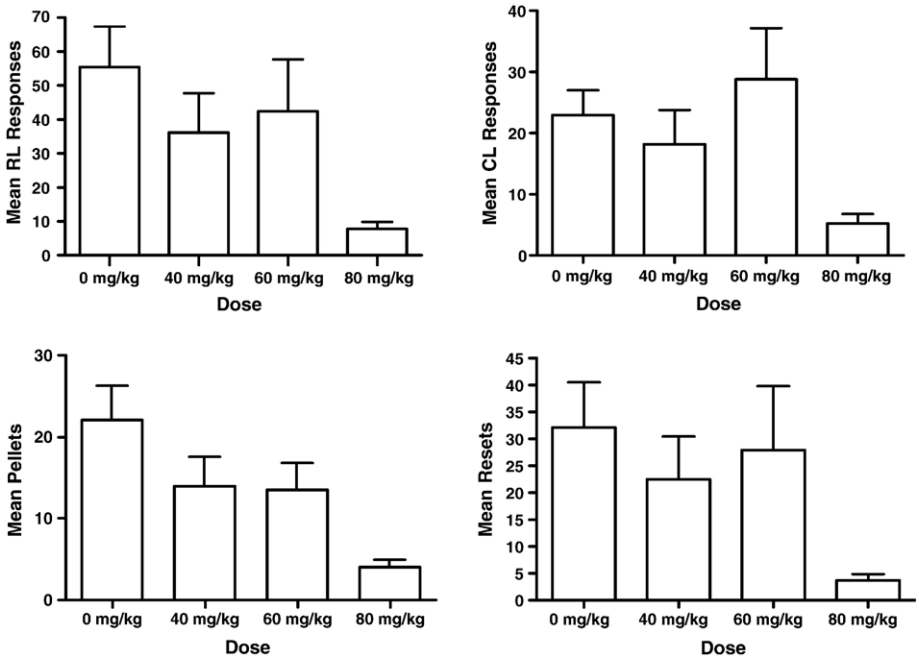

Fig. 1. The mean (±1 SE) number of RL responses, CL responses, Pellets, and Resets for each of the four experimental groups. Data reflect performance during a single 2-h response acquisition session.

in RL responses ($q=4.20$, $p<0.05$) and Pellets ($q=5.59$, $p<0.05$). One-way ANOVAs revealed no significant differences between groups in Resets ($F=2.28$, $p>0.09$).

3.3. DM effects on latency to respond

Fig. 2 shows the mean latency to the first, fifth, and tenth response for all of the experimental groups. Kruskal–Wallis one-way analysis of variance revealed a significant difference across groups in latency to the first ($H=15.74, p<0.0013$), fifth ($H=26.90$, $p<0.0001$) and tenth ($H=26.21$, $p<0.0001$) RL response. Dunn's Multiple Comparison tests revealed significant differences in the latency to emit the first RL response between the 0 mg/kg and 40 (difference in rank sum 18.53, $p<.05$), 60 (−19.38, $p<.05$), and 80 mg/kg (−24.22, $p<.05$) groups. Such tests also revealed significant differences between these respective groups in the latency to emit the fifth (−24.25, $p<.01$; −18.57, $p<.05$; −32.53; $p<.001$) and tenth (−22.00, $p<.01$; −19.88, $p<.05$; −31.50, $p<.001$) RL response.

4. Discussion

Previous studies have shown that DM can interfere with learning and memory (Bane et al., 1996; Dematteis et al., 1998; Murata and Kawasaki, 1993; Sierocinska et al., 1991) and the present results are consistent with these findings, because DM disrupted the initial acquisition of a lever-press response with delayed reinforcement. DM is rapidly converted to DR, which produces neurochemical effects similar to those of PCP and ketamine (Nicholson et al., 1999) and it is probable that the behavioral effects observed in the present study were due primarily to DR, not DM. However, Pallares et al. (1995) reported that ketamine (4, 8, and 12 mg/kg) produced dose-dependent disruption in rats' acquisition of a lever-press response, although these doses did not significantly affect motor

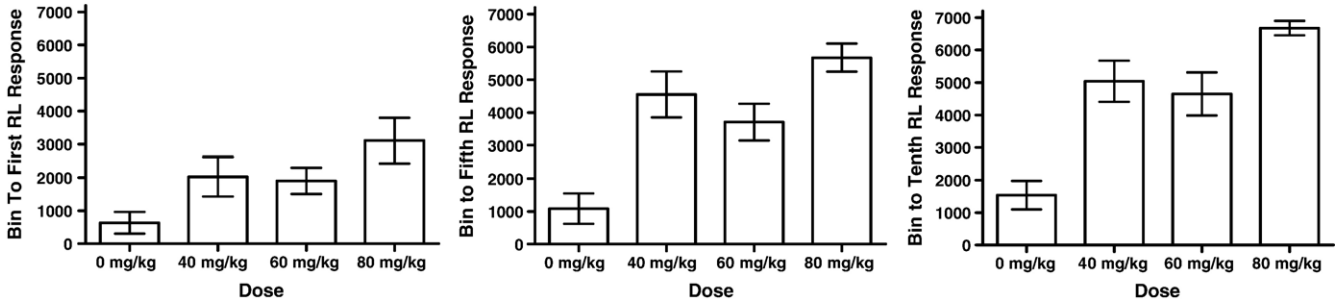

Fig. 2. The mean (±1 SE) latency to the first, fifth, and tenth response for each of the four experimental groups during the 2-h response-acquisition session. Each bin was 5 s in duration.

performance. Such results were not obtained with DM in the present study.

The minimum dose at which learning was disrupted in the present study depended on the measure of performance. For example, all doses significantly increased the latency to the first, fifth, and tenth RL response. Latency to the first response is not an indication of the drug's effects on learning, because learning under operant conditioning procedures reflects a strengthening of behavior due to its historical consequences. Therefore, at least one response must be emitted before learning can begin to occur. Pallares et al. (1995) defined response acquisition as the emission of 10 responses on a single lever, and if this definition is used, data from the present study indicate that DM disrupted response acquisition at doses of 40, 60, and 80 mg/kg. Previous studies using maze procedures have reported DM-induced disruptions of learning and memory at doses of 30 and 40 mg/kg (Bane et al., 1996; Dematteis et al., 1998). If latency to the fifth or tenth RL response is used as the response measure in the present study, then the response acquisition with delayed reinforcement procedure appears to be similar in sensitivity to more commonly used water maze procedures.

If, however, other tenable measures of performance are used, such as the percentage of rats that acquired RL responding, the mean number of RL responses emitted, or the mean number of pellets earned, only the highest dose of DM tested in the present study (80 mg/kg) produced statistically significant disruption. This dose is higher than the minimum dose that interfered with learning and memory under other procedures. Moreover, visual inspection revealed that 80 mg/kg produced general behavioral impairment. Rats that received this dose appeared sedated, fell on their sides, made awkward and jerky movements when walking, and had difficulty walking on the metal bars of the chamber floor. Such gross disruptions were not seen at lower doses; their presence suggests that the effects of 80 mg/kg on response acquisition did not involve selective impairment of learning or memory processes. In fact, unless latency to the fifth or tenth RL response is used to index learning, the present findings suggest that lower doses of DM, where motor involvement apparently is not a factor, have no effect on learning. Findings with water mazes have, however, demonstrated learning impairment at relatively low doses (Bane et al., 1996; Dematteis et al., 1998), although Murata and Kawasaki (1993) reported that DM disrupted performance in a passive shock-avoidance only when it also produced motor incoordination and a reduction in muscle tone. Further research is needed to delineate the conditions under which DM produces learning impairment at doses that do not generally disrupt behavior.

Response-acquisition procedures similar to those used in the present study have been used previously to examine the effects of several drugs (Byrne et al., 1997, 2000; LeSage et al., 1996; Pallares et al., 1995; Stolerman, 1971a,b; van Haaren et al., 1999, 2000), as well as gender (van Haaren et al., 2000), genetic variables (van Haaren et al., 1992), and motivational variables (Lattal and Williams, 1997). Performance under such procedures appears to be more sensitive to disruption by drugs when reinforcement is delayed, rather than when it is immediate (e.g., Byrne et al., 1997; Laraway, 2003), but the specific delay that is most sensitive has not been determined. It would be interesting to examine the effects of DM at delays shorter and longer than the 15-s that was used in the present study, and it is certainly possible that there are delays at which relatively low doses would disrupt all measures of learning.

Response acquisition with delayed reinforcement procedures have been described as especially sensitive and meaningful indices of drug-induced learning impairment (Snycerski et al., 1998, 2004; van Haaren et al., 1999, 2000). Seemingly small procedural differences can, however, affect performance under such procedures (e.g., Dickinson et al., 1992; Sutphin et al., 1998; Wilkenfield et al., 1992). For example, results can differ depending on whether responses on a single lever are analyzed, or whether responses on a lever that produced food (or water) and a lever than did not do so are compared (Byrne et al., 1997; Sutphin et al., 1998; Wilkenfield et al., 1992).

Two-lever procedures have been claimed to provide a means of disentangling nonspecific drug effects from specific learning impairment (Snycerski et al., 1998), but such procedures complicate the definition of response acquisition. Moreover, recent research has indicated that both response–reinforcer relations and response generalization may contribute to responding on a lever that does not produce food (Keely et al., accepted for publication). Therefore, levels of responding on the two levers are not necessarily independent and comparing these levels is not the best index of response acquisition with delayed reinforcement, or of drug effects thereon. A yoked-control arrangement, in which experimental rats' presses on a single lever produce food after a resetting delay and lead to food delivery for yoked-control rats, for which presses have no programmed consequences, appears to be the best procedure for studying drug effects on response acquisition, and we recommend that procedure for future studies. This variation of the procedure may be more sensitive than the one used in the present study which, depending on the measure of response acquisition used, was similarly or less sensitive to the disruptive effects of DM than other commonly used procedures (water mazes, passive avoidance).

Unlike those procedures, which involve established responses (swimming, walking) coming under the control of new variables (the location of a platform, the delivery of shock in a particular location), procedures similar to those used in the present study allow for an investigation of drug effects on the initial establishment of a form of responding (lever pressing) not previously in the animal's repertoire. In 1992, Evans and Wenger noted that the initial establishment of a new response topography is an important form of learning that researchers had largely ignored, and called for the development of "behavioral models to assess the effects of drugs and toxic chemicals on the acquisition of new behavior" (p. 55). Modest efforts in this direction have been made in the ensuing years and it appears that procedures similar to those used in the present study hold promise A problem with such procedures, however, is substantial variability across subjects exposed to the same experimental conditions, which makes it harder to detect possible effects of drugs and other independent variables (Snycerski

et al., 2004). Using a single lever in response-acquisition studies may reduce variability and, as suggested previously, increase sensitivity. Arranging more magazine training sessions than the two used in the present experiment may do likewise, because a recent study demonstrated that acquisition with reinforcement delayed 15 s was more consistent when rats received 5 magazine training sessions than when they received 0 or 1 (Snycerski et al., 2004). With further refinement, procedures that examine response acquisition with delayed reinforcement may provide a convenient and useful animal model for scientists interested in learning and related phenomena.

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