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# Behavioral Effects of Enantiomers of Dizocilpine Under Two "Counting" Procedures in Rats

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GALBICKA, G., M. A. KAUTZ AND T. JAGERS. *Behavioral effects of enantiomers of dizocilpine under two "counting" procedures in rats.* PHARMACOL BIOCHEM BEHAV **49**(4) 943-948, 1994.—Stereoisomers of the *N*-methyl-D-aspartate antagonist dizocilpine (MK-801) were studied to determine whether behavioral effects on complex operants depend on reinforcement loss accompanying behavioral disruption. Rats earned food pellets if the run of consecutive left-lever presses preceding a trial-terminating right-lever press approximated a target of 12. A percentile schedule reinforced any run closer to the target than two-thirds of the runs on the most recent 24 trials. Once the sequence was learned, half the subjects were shifted to a procedure that yoked reinforcement for each length run to the probability that length generated pellets during asymptotic percentile performance. Although these two procedures generate similar control run and reinforcement distributions, disrupting behavior reduced reinforcement probability far more under the yoked than the percentile procedure. Despite this difference in drug-induced reinforcement loss, both enantiomers produced similar dose-related decreases in run length and response rate under both procedures, with the (−) isomer approximately one log unit less potent than the (+) isomer. The absence of differential effects under these procedures diminishes the likelihood that reinforcement loss contributes to dizocilpine's effects, indirectly bolstering claims that dizocilpine directly affects learning.

Dizocilpine  Operant behavior  Run length  Response rate  Reinforcement density  Reinforcement loss
Counting  Percentile schedules

SEVERAL lines of evidence suggest that the *N*-methyl-D-aspartate (NMDA) receptor complex is involved in the acquisition of new behavior (i.e., learning). For example, newly acquired behaviors under a variety of paradigms appear more readily disrupted by dizocilpine (MK-801), an NMDA antagonist, than previously learned tasks [e.g., (4,12,15)]. To many, such differences are indicative of differential drug effects on the behavioral processes of learning (i.e., response acquisition) vs. performance (i.e., response maintenance), because nonspecific effects or effects on stimulus control in general would be expected to affect both learning and performance [cf.,(4)]. In addition, the types of errors made following administration of dizocilpine appear to differ from those following injection of the cholinergic antagonist scopolamine (2,3), suggesting an independence of glutamanergic and cholinergic involvement in learning processes.

Many of the comparisons offered in support of drug-specific effects on learning vs. performance, however, confound differences in reinforcement density. Learning a new task usually generates less frequent reinforcement than performing a well-learned one. This provides at least two potential mechanisms other than the learning/performance distinction per se that might be responsible for differential drug effects. First, drug effects could directly be modulated by different control levels of reinforcement, in much the same way that the effects of some drugs appear to differ depending on the control rate of responding [cf., (17)]. Alternatively, different reinforcement densities, measured either as a rate (e.g., pellets/min) or a probability (e.g., pellets/response or pellets/trial), may only indirectly modulate a drug's effects, by establishing different degrees of reinforcement loss that may be incurred as a function of behavioral disruption induced by drug. That is, if reinforcement delivery is contingent on responding, as is typical of operant procedures, and drug administration disrupts responding, reinforcement rate and/or probability generally will decrease. Several authors have sug-

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gested that such reinforcement loss under acute [e.g., (6,19)] and chronic drug administration [e.g., (8,11)] motivates the learning of responses that compensate for the drug's initial effects, restoring reinforcement density to levels approaching control values.

Reinforcement loss is an example of a behavioral mechanism of drug action [cf., (1,21)], because an analysis of the drug's effect in terms only of how it modifies physiological function would be incomplete without further specifying how that change affects the resulting interaction between behavior and the external environment. Recognizing behavioral mechanisms of drug action, alternatively, may provide a common explanation to otherwise disparate effects. For example, if reinforcement loss is a factor in determining the effects of some drugs, its degree of effectiveness should relate to the ease of determining whether reinforcement density has been altered. In a situation where responding is only very infrequently reinforced under control conditions, the loss of additional reinforcement following drug may not provide a very salient discriminative stimulus. Conversely, if reinforcement was previously highly likely under control conditions, very short periods of nonreinforcement may be sufficient to motivate compensatory behavior. This may explain why lean reinforcement schedules appear more sensitive to drug effects than ones providing more frequent reinforcement [e.g., (13,14)], to the extent that reinforcement loss may more likely be detected under the latter, generating responses that compensate for that loss. Similarly, smaller drug effects on a well-learned vs. a newly acquired behavior may represent differential operation of competing compensatory responses that restore the relatively higher reinforcement density generally associated with performing the former. This potential confound suggests a need to investigate directly contributions reinforcement loss may make to the modulation of drug effects.

We have previously used percentile schedules and a yoked comparison procedure to assess drug effects in the absence or presence, respectively, of concurrent changes in reinforcement probability incurred as a result of drug-induced behavioral disruption [e.g., (6,8,16)]. In the present study, a counting task was used to provide a behavioral baseline potentially sensitive to changes in overall response output (resp/s) as well as response accuracy (i.e., the correspondence between the target behavior and that emitted). The target behavior was a sequence of 12 left-lever presses followed by a single, trial-terminating right-lever press. The percentile schedule shaped and maintained a pattern approximating this ideal by providing a food reinforcer at the end of any trial during which the run of consecutive left-lever presses was closer to 12 than two-thirds of the runs during the immediately preceding 24 trials (i.e., if the current run was in the third of the distribution of runs closest to the target of 12). Hence, absolute run length does not directly determine whether reinforcement is provided—only the relative relation between the current run and recent runs is important. A run of six left-lever presses might produce a pellet early in training when most runs are shorter than six, but with extended training as runs more consistently approach 12, a run of six may no longer be considered in the third of the distribution closest to the target and, hence, may go unreinforced. Programming reinforcement in this fashion fixes the expected reinforcement probability during acquisition and maintenance, as well as following any disruption produced by drug, at a constant value, here 0.33 (i.e., the third of the distribution closest to the target). The comparison procedure yokes reinforcement probabilities for each particular length run to those obtained during prior exposure to a percentile schedule, to generate practically identical control response and reinforcement patterns while providing the more typical coupling of behavior and reinforcement density. That is, because specific run lengths have fixed reinforcement probabilities under the yoked procedure, and these probabilities peak at the target and rapidly decrease with increasing displacement above or below the target, runs comparable to those under the preceding percentile condition will generate reinforcement with an overall probability similar to that under the percentile schedule (i.e., 0.33). Changing the distribution of runs, for example by administering a drug, will decrease reinforcement probability, however, because both shorter and longer runs generate reinforcement with a probability lower than runs near the target. Hence, although percentile and yoked procedures provide very similar control probabilities of reinforcement, the former maintain that probability of reinforcement in the face of behavior change, the latter do not. Hence, the pair of procedures are ideally suited for studying any role reinforcement loss resulting from drug-induced behavioral disruption may play in determining the effects of drugs.

Using these two procedures, Galbicka and colleagues (6) reported that acute effects of amphetamine were more pronounced under the percentile than the yoked procedure, and that tolerance developed more readily to the behavioral effects on the latter (8). They suggested that this differential sensitivity is a function of drug-induced reinforcement loss incurred under the yoked but not the percentile procedure. According to this interpretation, behavioral disruption following drug administration decreases reinforcement density under the yoked procedure, and this, in turn, motivates learning responses that restore reinforcement density to control levels. This can only be accomplished under the yoked procedure by emitting runs in the vicinity of the target (i.e., by recovering baseline patterns of behavior). Under the percentile procedure, conversely, behavioral disruption is not correlated with reinforcement loss and, hence, behavioral effects of drugs are not altered by compensatory changes in behavior.

The present experiment extended this analysis to the effects of stereoisomers of dizocilpine, to determine the degree to which changes in reinforcement probability contribute to dizocilpine's behavioral effects on a complex operant. Although both enantiomers of dizocilpine have been reported to disrupt simple operants (10) as well as more complex ones [e.g., (15)], the contribution of reinforcement loss to these behavioral effects remains to be determined.

## METHOD

### *Subjects and Apparatus*

Ten Sprague-Dawley rats, maintained at 350 g via restricted feeding of chow, served as subjects. Each was individually housed with continuous access to water in acrylic cages lined with pine bedding. Experiments were conducted in five identical modular operant conditioning units configured for rats. The instrument panel of each chamber contained two levers mounted symmetrically around a pellet trough centrally located on the wall. A pellet dispenser behind the front wall could deliver 45-mg food pellet reinforcers into the trough. The force required to operate the levers was not calibrated across chambers, however, each rat's chamber assignment remained fixed throughout the study; hence, requirements remained consistent for each subject. Above the feeder trough near the ceiling was a houselight providing general illumination, and directly above each lever was a set of three stimulus

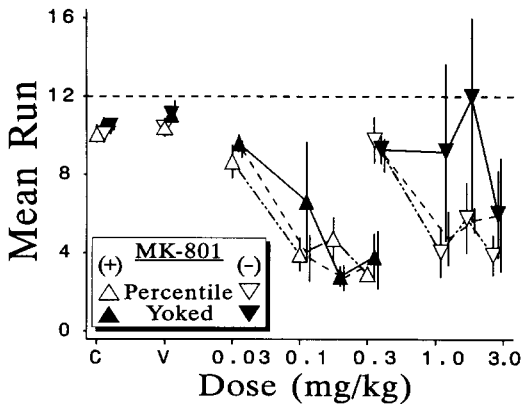


FIG. 1. Group mean runs during control sessions (points above C) and following vehicle (V) or doses of drug. Percentile data are indicated by open upright [(+)-dizocilpine] or inverted triangles [(−)-dizocilpine] connected by alternating dots and dashes. Solid triangles connected by solid lines illustrate effects on the yoked group, again with upright and inverted triangles distinguishing the two isomers as for the open symbols. The line comprised of long dashes without symbols offset just to the right of the yoked group represents that group's data excluding Subject 53. Points and vertical bars represent means ± SEM of individual subject means during the sessions indicated (standard errors for points without vertical bars are encompassed by the point). Points have been slightly horizontally displaced to decrease overlap. The horizontal dashed line represents the target value of 12.

lights. A heavy-duty relay mounted behind the front panel above the food trough produced an audible click with each effective press on either lever. Parallel metal rods comprised the floor of each chamber, which was itself housed inside a light- and sound-attenuating cubicle. Fans in each cubicle, as well as white noise continuously present in the room, helped mask extraneous sounds. Stimuli were presented and data collected by a PDP® 11/73 minicomputer operating under the SKED-11 operating system (20).

*Behavioral Procedure*

The pretraining procedures [see (7), for a detailed description] culminated in a baseline condition of trials signaled by illuminating the houselight and a green cue lamp above each lever. At least one left-lever press was required per trial, after which a right-lever press produced a pellet with a probability of 0.33 and started a 3-s intertrial blackout. Pressing the right lever prior to the left had no consequences. After 11 baseline sessions, the percentile procedure was instituted [cf., (5,9), for detailed descriptions of percentile procedures]. The percentile schedule determined whether the current run was above or below the target (12 in the present study), then compared it to all runs within the most recent 24 trials that, likewise, were above (or below) the target. Each run in this comparison memory was sequentially compared to the current run to determine whether it was closer to, equally removed, or farther from the target. If the run was closer to the target than two-thirds of the comparison runs, it produced a pellet. Otherwise, it did not. As a result, the closest third of all runs produced a pellet. In an attempt to increase the symmetry of responding around the target, one additional adjustment was made to this criterion. Provided at least 4 of the most recent 24 runs were on the opposite side of the target from the current run, the probability the current run was considered criterional was set to 0.33 ($12/m$), where $m$ is the number of comparison runs on the same side of the target. Hence, as $m$ increasingly exceeded 12, the probability was progressively reduced, until $m \geq 20$ (i.e., less than five runs on the opposite side), and as $m$ decreased, the probability increased gradually, to 1 at $m \leq 4$. Hence, reinforcement probability was adjusted to increase runs on the currently nonpreferred side of the target. In all cases, only after all comparisons were complete did the current run replace the oldest run in the memory (i.e., comparisons comprised runs from the most recent 24 trials, excluding the current one). Comparison distributions were carried across control sessions (i.e., the first response of one session was compared to the last 24 responses of the preceding control session), but were cleared at the beginning of all sessions involving vehicle or drug administration.

Once all subjects showed stable responding in the vicinity of the target, they were ranked according to overall mean run length during the last 10 sessions, and then odd and even ranks were assigned to the yoked and percentile group, respectively. For each subject in the yoked group, runs from the immediately preceding five sessions under the percentile schedule were combined into a single distribution, and the ad hoc probability of pellet delivery was determined for each length run in the distribution. These probabilities were subsequently used to program reinforcement for particular-length runs under the yoked procedure (e.g., if the distribution of runs contained 200 runs of eight presses, and 150 of these produced a pellet under the percentile procedure, then runs of eight produced food with a probability of 0.75 under the yoked procedure). Subjects were exposed to their assigned procedure for 13 additional sessions before drug administrations began. Sessions were conducted 5 days a week and terminated after 100 trials or 30 min, whichever came first.

*Drugs*

Stereoisomers of dizocilpine (Research Biochemicals, Natick, MA) were each dissolved in saline and injected IP in a volume of 1 ml/kg 30 min prior to the session. Each of four doses of the two isomers was administered twice to each subject in random order. Subjects also received two injections of vehicle, for a total of 18 injections. Injections preceded sessions on Tuesdays and Fridays, with the previous day's session serving as the noninjection control performance. Effects were

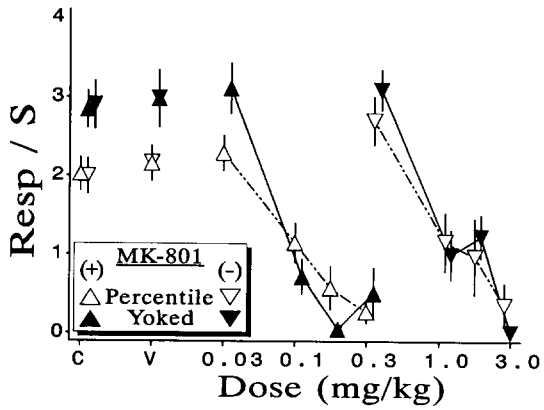


FIG. 2. Dose-effect curves for overall response rate (resp/s). Plotting conventions are the same as in Fig. 1.

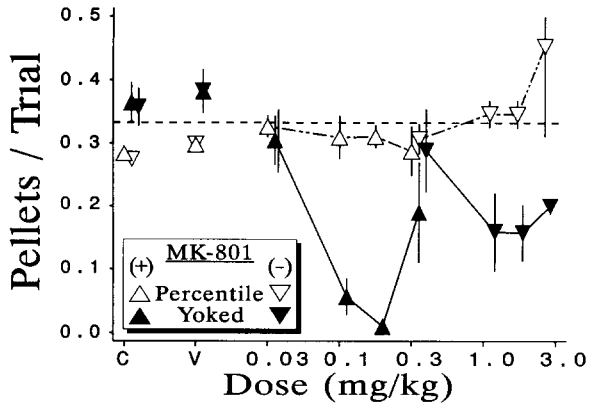


FIG. 3. Dose-effect curves for reinforcement probability (pellets/trial). Plotting conventions are the same as in Fig. 1, except the horizontal dashed line represents the programmed probability of reinforcement.

considered reliable if the standard errors of the mean of individual subject means following vehicle and following drug did not overlap.

## RESULTS

During the last five sessions of the baseline condition (i.e., prior to shaping), the group mean run length approximated 4.0 (range = 1-8). Instituting the targeted percentile procedure increased mean run length for all subjects to a value closer to, but generally just short of the target value of 12. Figure 1 shows asymptotic group mean run length under control conditions (C) for both groups, as well as following vehicle (V) or drug administration. Control run lengths under the two procedures did not reliably differ, with mean run length equal to approximately 10.5. Vehicle injection produced no discernible effect on run length, while increasing doses of either enantiomer of dizocilpine generally decreased mean run length. The means for yoked subjects were generally higher, and the standard errors larger, than for percentile subjects [compare filled and unfilled symbols, particularly following administration of (−)-dizocilpine]. This reflects the influence of a single subject's data from the yoked group. Values obtained after excluding his data (shown by the long dashed line with no symbol, displaced just to the right of the yoked-group data) evidence means more in keeping with the percentile group data, and much reduced standard errors. The two isomers produced similar effects, except the (+) isomer appeared approximately one log unit more potent than the (−) isomer.

Control response rates (see Fig. 2) exceeded two resp/s, and were, thus, relatively high for both groups. Unlike run length, however, response rates reliably differed between groups, with the yoked group showing consistently higher rates. Again, vehicle injections did not affect rates, both enantiomers generally produced dose-related decreases in response rate, and the (+) isomer was approximately one log unit more potent in reducing response rate that its (−) counterpart. The lowest dose of the (−) isomer actually increased response rate modestly but reliably under the percentile but not the yoked procedure. Note that the data presented in Fig. 2 (and all remaining figures) includes data from the subject whose run lengths were atypical. The measures in Figs. 2-4 were analyzed with this subject's data excluded; however, no systematic effects were noted on any of these measures. Hence, separate dose-effect curves for the subset of subjects were not presented.

Control reinforcement probabilities under both procedures approximated the nominally programmed value of 0.33 (see Fig. 3), with a small but reliable underestimation (percentile) or overestimation (yoked) in each group. Although mean runs were drastically and equally disrupted under both procedures, reinforcement probability under the percentile schedule did not greatly differ from the programmed value except at the largest dose of the (−) isomer, while under the yoked procedure it was drastically suppressed at all but the lowest dose of either isomer.

Reinforcement rate (see Fig. 4) under these procedures was jointly determined by the probability of reinforcement and the rate of trial completion. For the percentile subjects, the probability of reinforcement remained roughly constant even when run length was shortened by drug administration. Because shorter runs require less time to complete, reinforcement rate often increased at doses that decreased mean run under this procedure [e.g., 0.1 mg/kg of (+)-dizocilpine and 1.0 mg/kg (−)-dizocilpine]. For the yoked group, conversely, reinforcement rate was only suppressed by increasing doses of either isomer of dizocilpine.

## DISCUSSION

The present results replicate many previously reported effects of dizocilpine on behavior. Increasing doses of either enantiomer decreased run length under both of the present procedures. The decreases correspond to decreases in accuracy of performance reported under other discrimination procedures at comparable doses [e.g., (3,4,15,21)], to the extent that shorter runs represent a decrease in control by the trained target value. The decreases in response rate observed at all doses under the yoked procedure and at all but the lowest dose under the percentile procedure also replicates effects reported by others [e.g., (10,18)] when control rates of responding are relatively high, as they were in the present study. For both run length and overall response rate, the (+) isomer was more potent than the (−) isomer, by approximately one log unit. This potency difference also closely parallels results obtained by others [e.g., (4,10)].

Control performances under the present two procedures were similar but not identical. The aspect of responding explicitly differentiated, run length, was indistinguishable in the

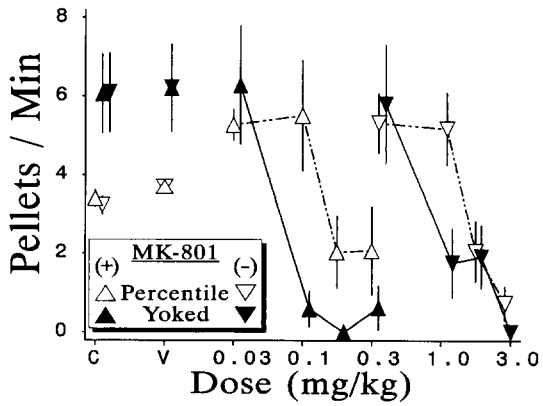


FIG. 4. Dose-effect curves for overall reinforcement rate (pellets/min). Plotting conventions are the same as in Fig. 1.

two groups during nondrug and vehicle sessions. Control reinforcement probabilities were also similar under the two procedures, although small differences did exist between groups. These differences represented deviations in either direction of only 10–15% from the nominally programmed value, however, and are probably not cause for concern. This difference was, in part, due to the symmetry routine programmed for the percentile group, which decreased reinforcement probability below the value programmed by *w* in response to the consistent bias towards runs just short of the target [see procedure, and (6), for a more detailed analysis of this effect], and was, in part, due to slight improvement across time on the part of the yoked group.

Control response rates maintained under these procedures were also qualitatively very similar, in that relatively high rates (greater than two resp/s) were maintained by both. The yoked group's rates, however, were reliably higher than the percentile group's. There is no procedural reason for this discrepancy. Previous research has reported nearly identical response rates for the two groups (6,16), or an unreliable tendency for lower rates in the percentile group (8) attributable almost entirely to a single subject's unusually low rate (less than one resp/s). The present results are the first report of a systematic difference in response rate between the two groups, and most likely arose from group assignment based on matching overall run length and not overall response rate. This difference in control response rate also lead to differences in overall control reinforcement rate, because the latter is a direct function of the former when overall reinforcement probability is controlled as it was in the two groups here.

The experimental rationale and procedural design dictated that behavioral disruption would greatly decrease reinforcement probability under the yoked but not the percentile procedure. Percentile reinforcement probability significantly deviated from the scheduled value only at the highest dose (see open symbols in Fig. 3), where several subjects completed just a few trials and, hence, provided a very small sample size from which to derive reinforcement probability. Conversely, yoked reinforcement probabilities were significantly reduced at all doses that reliably altered run length (compare closed symbols in Fig. 3). Despite this substantial difference in the effects of both enantiomers on reinforcement probability under the two procedures, there was no indication that the effects on run length (Fig. 1) or response rate (Fig. 2) differed under the two procedures. Hence, it is unlikely that reinforcement loss, at least measured by changes in reinforcement probability, contributed to modulate the effects of dizocilpine. This contrasts with previous investigations of *d*-amphetamine (6,8) and ketanserin (16), where drug effects did vary under the two procedures. The absence of an effect attributable to reinforcement loss indirectly strengthens claims that dizocilpine may directly disrupt learning and/or memory. It does not seem likely that the differential results observed in studies directly comparing dizocilpine's effects on learning vs. performance result from differential reinforcement loss associated with the higher-density reinforcement under the performance procedure/component, because such differential results would have been expected here between the two groups. No significant differences were obtained, however, and even the suggestion of a possible difference in the severity of effects on run length under the two procedures was removed by eliminating the data for the one discrepant subject. Excluding this subject's data appears warranted by the fact that all other subjects under both procedures behaved similarly at all doses of drug (i.e., standard errors of dependent measures for the group were generally small after excluding this subject, except when at the highest dose the number of trials completed was minimal). The factors responsible for this one subject's divergent results remain unclear. Visual observation during drug sessions revealed a tendency to press several times and then turn toward the wall, rear, then turn back to the front of the chamber and press again, starting a new cycle. Perseveration errors have been reported for dizocilpine under response-sequence procedures (3), and this may be an example of one. Conversely, the same report noted that with four-response sequences, dizocilpine increased the probability of all types of errors (i.e., perseveration, skipping one response, skipping to the end, and reinitiating the sequence), as if subjects were no longer controlled by their previous behavior. If that is the case, then both perseveration and shorter runs might be expected here.

In summary, the complex behavioral pattern maintained under the present two procedures was equally disrupted by administration of dizocilpine, with the (+) isomer roughly one log unit more potent than the (−) isomer in producing behavioral effects. Drug-induced disruption in reinforcement density did not modulate either enantiomer's effects. Thus, it appears that differential effects of dizocilpine on learning and performance reported previously may not depend on differences in baseline reinforcement density and/or the concomitant differences in the degree of reinforcement loss induced by drug administration. It would be of interest to compare the effects of dizocilpine on acquisition, rather than performance, of percentile schedule responding, because any deficit obtained would not be confounded with reinforcement loss. As such, acquisition deficits could not be attributable to motivational variables, but would more likely represent direct interference with the processes by which behavior comes under control of previous behavior.

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