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Effects of Morphine Sulfate on Operant Behavior in Rhesus Monkeys

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SCHULZE, G. E. AND M. G. PAULE. *Effects of morphine sulfate on operant behavior in rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **38**(1) 77–83, 1991.—The acute effects of morphine sulfate were assessed using a battery of complex food-reinforced operant tasks that included temporal response differentiation (TRD, n=5), delayed matching-to-sample (DMTS, n=6), progressive ratio (PR, n=9), incremental repeated acquisition (IRA, n=9), and conditioned position responding (CPR, n=7) tasks. Performance in these tasks is thought to depend upon specific brain functions such as time perception (TRD), learning (IRA), short-term memory and attention (DMTS), color and position discrimination (CPR), and motivation to work for food (PR). Morphine sulfate (0.1–5.6 mg/kg IV), given 15 min presession, produced significant dose-dependent decreases in the number of reinforcers obtained in each task. Response accuracy was significantly decreased at doses ≥1.0 mg/kg for TRD when compared to saline injections. Accuracy was not consistently affected in any other task in the test battery. Response rates decreased or response latencies increased significantly at doses of 1.0 mg/kg and above for the PR task, at 3.0 mg/kg and above for the IRA and TRD tasks, and only at the highest dose 5.6 mg/kg in the CPR and DMTS tasks. Percent task completed was decreased following doses of 1.0 mg/kg and higher for the IRA, PR and TRD tasks, at doses of 3.0 mg/kg and higher for the DMTS task, and at the high dose of 5.6 mg/kg for the CPR task. These results indicate that in monkeys, the performance of operant tasks designed to model learning ability (IRA), time perception (TRD) and motivation (PR) are more sensitive to the disruptive effects of morphine than is performance in tasks designed to model short-term memory and attention (DMTS). The task which models color and position discrimination (CPR) was the least sensitive to disruption by morphine.

Monkeys Operant behavior Test battery Learning Memory Morphine Drug effects
Delayed matching-to-sample Temporal response differentiation Progressive ratio Incremental repeated acquisition
Conditioned position responding Motivation Time perception Color discrimination Position discrimination

MORPHINE, the classical centrally acting opiate agonist, is clinically prescribed for its analgesic activity. Additionally, morphine produces a state of euphoria which is related to its abuse potential in humans. It produces its therapeutic and behavioral effects by interacting with central opiate receptors, and is typically classified as a prototypic mu opiate agonist (5, 13, 17) producing analgesia, miosis, hypothermia, and euphoria (13, 17, 18). The behavioral, reinforcing and discriminative stimulus properties of morphine have been well documented in humans and experimental animals (14, 17, 18, 33, 36).

In animals, the effects of morphine on operant behavior maintained by simple schedules of reinforcement has been extensively studied (7, 9, 10, 12, 15, 16). Generally, morphine produces dose-related decreases in the overall rate of responding in pigeons, rats and primates (3, 7, 9, 17) with the possible exception of the chimpanzee where rate increasing effects have been reported (2). The effects of opiates on behavior maintained by more complex schedules of reinforcement have been studied in pigeons, rats and monkeys (9, 24, 27, 34). In general, under complex schedules of reinforcement, morphine produces slight decrements in the accuracy of responding only at doses which simultaneously produce response rate suppressions.

Most studies in the literature have focused upon morphine's effects on a single behavior rather than upon its effects on a battery of different behaviors. In evaluating the neurobehavioral effects of delta-9-tetrahydrocannabinol, marijuana smoke and other psychoactive drugs in monkeys (28–32), a complex operant test battery (OTB) was used allowing multiple complex behaviors to be monitored sequentially. Multiple sequential measures (test batteries) can be used to clarify the differential sensitivity of the variables under study to insult by a particular drug or toxicant. Thus the correlated results from a study examining multiple behavioral measures provide a powerful assessment of the relative sensitivities of different indices to disruption by the agent being studied. Multiple measures are essential to a thorough study of the effects of chemical agents on CNS function, and the results

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of such studies can be fruitfully compared with neurochemical, neuropathological, neurophysiological, and pharmacokinetic data (19).

The present experiment was one of several studies designed to validate the use of an OTB for assessing neurobehavioral toxicity. One approach to validating the OTB is to use relatively well-characterized, reversibly acting drugs as reference compounds (21,28). Selective behavioral effects of these reference compounds in monkeys can then be compared to their known effects in humans and other animal species. Eventually such data can be compared with that produced by drugs or environmental toxicants with unknown mechanisms of action (6). Human performance in the OTB has also been recently examined using children as subjects (26), and it has been observed that the OTB performance of well-trained monkeys is generally indistinguishable from that of human children (Paule et al., unpublished observation). Such observations serve to further validate the use of OTB performance in laboratory animals.

The effects of intravenous morphine sulfate in monkeys, as measured by performance in the OTB, were established here in order to further investigate the utility of this approach. Morphine doses (0.1–5.6 mg/kg) were chosen for study based on literature reports and the criteria that the highest dose grossly affected most behavioral endpoints and the lowest dose was without significant effects. The behavioral tasks contained in the OTB were temporal response differentiation (TRD), delayed matching-to-sample (DMTS), progressive ratio (PR), incremental repeated acquisition (IRA), and conditioned position responding (CPR). Morphine was chosen for study because of the reversibility of its effects after acute administration and its relatively well characterized mechanism of action (13,17) allowing it to serve as a prototypic mu opiate agonist (5,11).

METHOD

Subjects

Nine male rhesus monkeys (*Macaca mulatta*) between three and six years of age (10–20% of maximal achievable lifespan) and weighing from four to nine kilograms at the beginning of the study served as subjects. All animals had been previously trained under the schedules in the OTB for approximately two years and had been used in previous studies of acute marijuana smoke, THC, diazepam, and *d*-amphetamine administration (29–32). During this study, all nine animals exhibited stable (less than 15% variability over one month) preexposure baselines for the IRA and PR tasks, seven for the CPR task, six for the DMTS task and five for the TRD task. Each animal was tested in the OTB, but only data from those animals exhibiting stable preexposure baselines are presented and were used for statistical analysis. Animal housing, feeding, etc., were as described previously (29). Access to food (Purina Hi Protein Monkey Chow, Ralston Purina, St. Louis, MO) supplemented with fresh fruit and chewable multi vitamins with iron (Arkansas Cooperative Assoc. Inc., North Little Rock, AR), given after daily behavior sessions was restricted such that animals gained approximately 0.0–0.1 kg/month.

Apparatus

The apparatus have been described in detail elsewhere (29) and consisted of portable restraint chairs, sound-attenuated behavioral chambers, operant panels and computer consoles. The operant panel was equipped with three press plates that had to be pushed to effect a switch closure and four retractable levers that operated a switch when depressed. The press plates and levers were aligned horizontally with the press plates above the levers. A trough for reinforcer (banana-flavored pellet) delivery was located below the levers [see (29) for details].

Operant Schedules

The use and description of the operant tasks contained in the OTB have been detailed elsewhere (26,27). A brief description follows.

Temporal response differentiation (TRD). For this task, only the far left retractable lever (extended) was used, and subjects were required to hold the lever in the depressed position for a minimum of 10 seconds but no longer than 14 seconds. Releasing the lever too early or too late started another trial.

Delayed matching-to-sample (DMTS). For the DMTS task only the press-plate manipulanda were used. At the start of each trial, one of seven white on black geometric symbols (the sample) was projected onto the center plate (side plates were dark). The subject was required to make an "observing" response to the center plate indicating observation of the "sample." After the observing response was made, the center plate was extinguished for one of six time delays presented pseudorandomly. After the various time delays, all three plates were illuminated, each with a different geometric symbol, only one of which matched the sample. A response to the "match" then resulted in reinforcer delivery, whereas nonmatching responses were followed by a 10-second time-out period (all plates darkened) and then initiation of another trial with either the same or a different sample (randomly presented). Of the six animals showing stable performance in this task, one was presented time delays of 1, 2, 4, 8, 16 and 32 seconds, three were presented delays of 2, 4, 8, 16, 32 and 48 seconds, and two were presented delays of 2, 8, 16, 32, 48, and 64 seconds. Presentation of time delays was based upon individual performance such that accuracy from the shortest delay declined by approximately 20–25% at the longest time delay producing a "memory" decay curve.

Progressive ratio (PR). Animals were required to increase the amount of work (number of lever presses) required for each reinforcer. Only the far right retractable lever (extended) was used in this task. Initially, one or two lever presses (depending upon the individual subject) resulted in reinforcer delivery. After each reinforcer was delivered, the response requirement was increased by the initial number (a fixed ratio) of lever presses required for the first reinforcer. Thus if the initial requirement was two lever presses, the second reinforcer was obtained after four lever presses, the third after six lever presses, etc. Ratios were chosen such that responding generally declined or was abolished (breakpoint) during each 10-minute PR session.

Incremental repeated acquisition (IRA). The IRA task immediately followed the PR task and required subjects, using all four response levers (extended), to acquire a new sequence of lever presses each test session. IRA began with the presentation of a one-lever response sequence (IRA1). Each response on the correct lever resulted in reinforcer delivery and after 20 correct response sequences (criterion performance), a one-minute time-out period was followed by the presentation of an 'incremented' two-lever sequence (IRA2), such that a response on a different lever was required before a response on the original lever produced food. After the 20th errorless two-lever sequence (i.e., no errors were made between the first and last correct lever presses of the required sequence), the task was incremented to a three-lever sequence and so on, up to six-lever sequences or until 35 min had elapsed.

Conditioned position responding (CPR). In the CPR task only the press-plates were used. At the start of a trial, only the center plate was illuminated with either a red, yellow, blue, or green

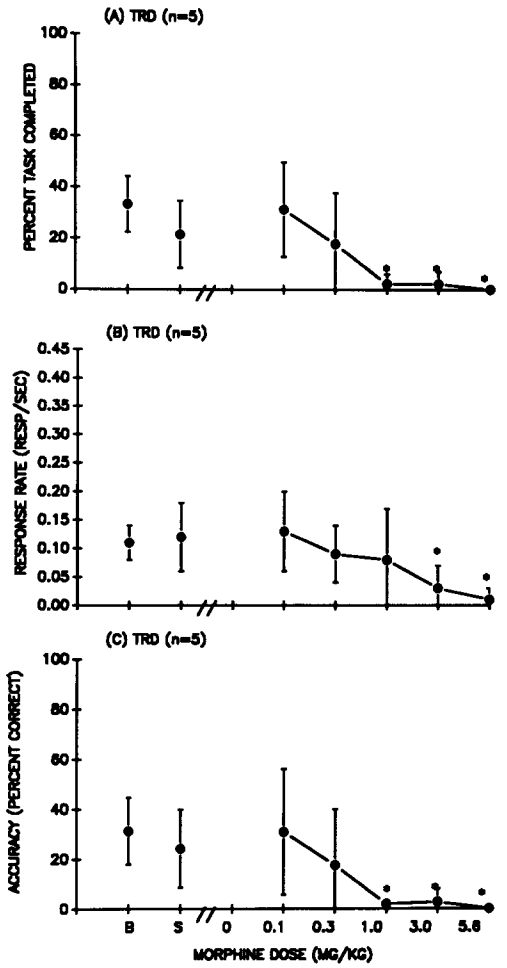

FIG. 1. Effects of morphine on temporal response differentiation (TRD) percent task completed (A), mean response rate (B) and response accuracy (C), n = 5. Each point represents the mean ± SE. On the abscissa, the letter B represents the preexposure baseline of performance and the letter S represents saline control performance determined for five observations. Asterisks represent significant differences from saline controls as determined by Fisher's (LSD) *t*-test ($p<0.05$).

color. Subjects made observing responses to the center plate, indicating observation of the color, after which it was extinguished and the two side plates were immediately illuminated white. If the center plate had been either blue or green, responding to the right plate resulted in reinforcer delivery. If the center press plate was illuminated red or yellow, responding to the left plate resulted in reinforcer delivery. Responding at the wrong position initiated a 10-second time-out period followed by initiation of another trial. The sequence of color presentation was yellow, blue, green, red, but the initial color which began each session was randomly presented.

Procedure

Behavioral sessions were conducted daily, Monday through Friday, and lasted approximately 50 min. Subjects were rotated through 12 behavior chambers such that no monkey was placed in the same chamber for two consecutive test days in order to avoid disruption of ongoing large-scale chronic behavioral studies. Behavioral schedules alternated daily. For example, the temporal response differentiation (TRD 20-min) and delayed matching-to-sample (DMTS 30-min) tasks were presented on one Monday; progressive ratio (PR 10-min), incremental repeated acquisition (IRA 35-min), and conditioned position responding (CPR 5-min) tasks were presented the Tuesday; TRD and DMTS were presented on Wednesday and so forth. The sequence of behavioral tests given on a single day was fixed and presented in the order described above.

Drugs and Dosing Procedure

Morphine sulfate (National Institute on Drug Abuse, Rockville, MD) was dissolved in sterile bacteriostatic (0.9% benzyl alcohol) saline (Elkins-Sinn Inc, Cherry Hill, NJ) for an injection volume of 0.1 ml/kg. The purity of the morphine was determined to be 95.5% by in-house HPLC analysis using a UV detector set at 230 nm. Doses of morphine (0.1, 0.3, 1.0, 3.0 and 5.6 mg/kg, IV) were administered in a randomized order. Generally, morphine injections were given on Tuesdays and Fridays while saline injections were given on Thursdays. Due to the daily alternation of behavioral tasks, all doses were given twice to provide dose-response data for each set of operant tasks. Approximately 15 min following injections, subjects were placed into operant chambers and behavioral sessions began one min later.

Data Analysis

The endpoints measured in each task have been described in detail elsewhere (28,29). Three fundamental measures are monitored for each task and include percent task completed, response rate or response latency, and response accuracy. The percent task completed data are measures of a predetermined arbitrary criteria of performance (i.e., earning 60 reinforcers represents the performance maximum for the CPR task) and are functions of both response rate and response accuracy. Percent task completed is calculated by dividing the total number of reinforcers earned in a given session by the total number of reinforcers possible for a given session and multiplying this quotient by 100. The total number of reinforces possible for a given task was chosen based upon the length of the test and the task difficulty. The percent task completed is a convenient and comprehensive measure showing intraanimal stability and is useful for comparing drug effects on performance across tasks (26–32). Since no predetermined criteria of performance exists for the PR task (i.e., each individual determines its own performance maximum) the percent task completed endpoint is not applicable for this task. For the TRD task, mean duration and temporal distribution of lever holds, and for the PR task the breakpoint (the magnitude of the last ratio completed for which the animal earned a reinforcer) were also measured.

Statistical Analysis

The overall effect of drug treatments on performance in the various tasks was determined using a one-way repeated measures analysis of variance [ANOVA; (35)]. If overall significance was evident ($p<0.05$), then performance at each dose was compared to vehicle control performance by Fisher's least significant difference (LSD) multiple *t*-tests (20). For DMTS group accuracy data, significance was assigned to those group means falling outside the ninety-five percent confidence intervals constructed from vehicle control observations at each time delay.

RESULTS

Overall Effect of Saline Vehicle

Saline vehicle injections produced no statistically significant

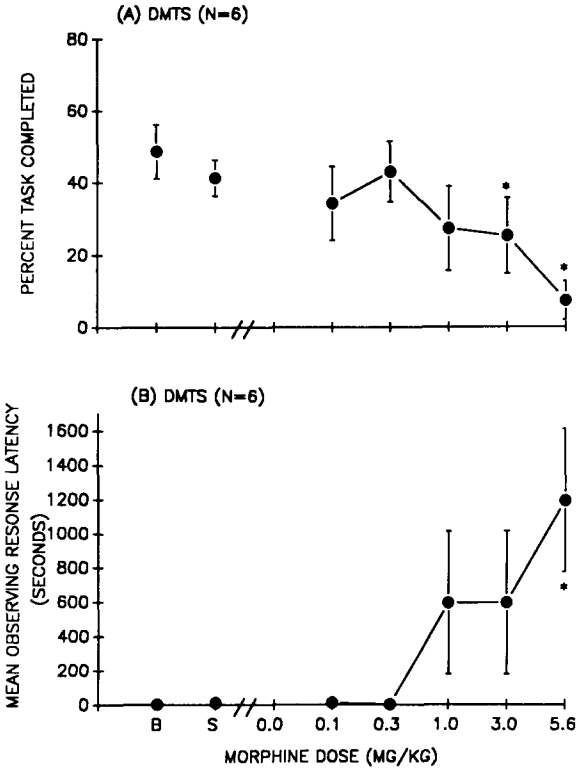

FIG. 2. Effects of morphine on delayed matching-to-sample (DMTS) percent task completed (A) and mean observing response latency (B), n = 6. Data presented as described in Fig. 1.

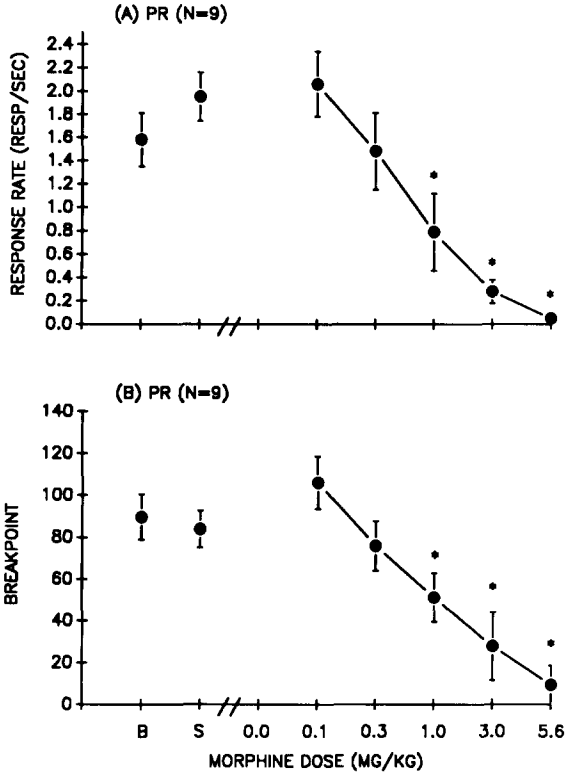

FIG. 3. Effects of morphine on progressive ratio (PR) response rate (A) and breakpoint (B), n = 9 unless indicated otherwise. Data presented as in Fig. 1.

group effects on performance in any of the endpoints examined when compared to noninjected baseline data.

Temporal Response Differentiation (TRD)

Morphine produced significant dose-dependent decreases in TRD percent task completed, response accuracies and mean response rates (Fig. 1). Under control conditions, the TRD schedule generates low response rates (0.11–0.13 resp/s), response accuracies averaging 28–32% and percent task completed values of 22–37% for this 20-min task (120 reinforcers possible). Compared to saline controls, significant decreases were observed in percent task completed and response accuracy following the 1.0, 3.0 and 5.6 mg/kg doses. Significant decreases in mean response rates occurred at doses of 3.0 and 5.6 mg/kg. As noted for the TRD response accuracy and percent task completed measures, the mean duration (in s) that the lever was held in the depressed position by the group was also significantly decreased by morphine administration at doses of 3.0 and 5.6 mg/kg (data not shown) thus contributing to the accuracy decreases.

Delayed Matching-To-Sample (DMTS)

Morphine produced significant dose-dependent decreases in DMTS percent task completed following doses of 3.0 and 5.6 mg/kg and significantly increased mean observing response latencies following a dose of 5.6 mg/kg (Fig. 2). Under control conditions, the DMTS schedule generates low response latencies (2.0–5.6 s/resp), response accuracies averaging 85–64% (depending upon delay), and percent task completed values of 45–50% for this 30-min task (120 reinforcers possible). In some animals, increases in mean observing response latencies occurred at the 1.0 and 3.0 mg/kg doses leading to elevated group means and larger standard errors for these doses but they did not attain statistical significance. No evidence of morphine-induced changes was found for response accuracy as a function of time-delay (data not shown).

Progressive Ratio (PR)

Morphine produced significant dose-dependent decreases in PR breakpoint and response rates (Fig. 3) following doses of 1.0, 3.0, and 5.6 mg/kg. Slight increases in PR break points occurred after 0.1 mg/kg doses of morphine but they failed to reach statistical significance. The PR schedule, under control conditions, generates high response rates (1.6–2.0 resp/s), and breakpoints averaging 85–90 responses (i.e., the last ratio completed which resulted in reinforcer delivery).

Incremental Repeated Acquisition (IRA)

Morphine administration produced significant dose-dependent decreases in IRA percent task completed (Fig. 4A) at the 1.0, 3.0 and 5.6 mg/kg doses. Similarly, dose-dependent decreases in mean response rates for IRA-2 (Fig. 4B) and for the IRA1 and IRA3 components (data not shown) were evident but significance occurred only at the 3.0 and 5.6 mg/kg doses, while no significant increases or decreases in response accuracy occurred for the IRA2 component (Fig. 5C) or for any other IRA component. Under control conditions, the IRA schedule generates moderate re-

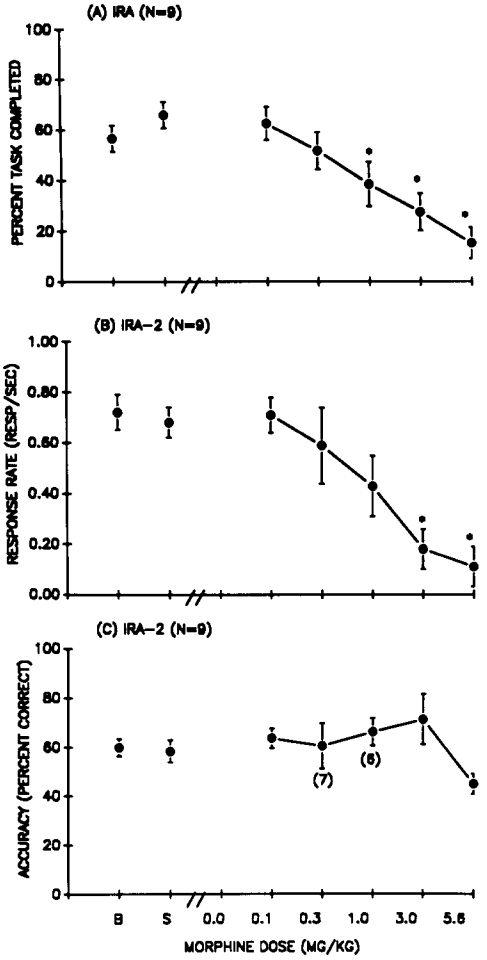

FIG. 4. Effects of morphine on incremental repeated acquisition (IRA) percent task completed (A), response rate for IRA2 (B) and accuracy for IRA2 (C), n = 9 unless indicated otherwise. Data presented as described in Fig. 1.

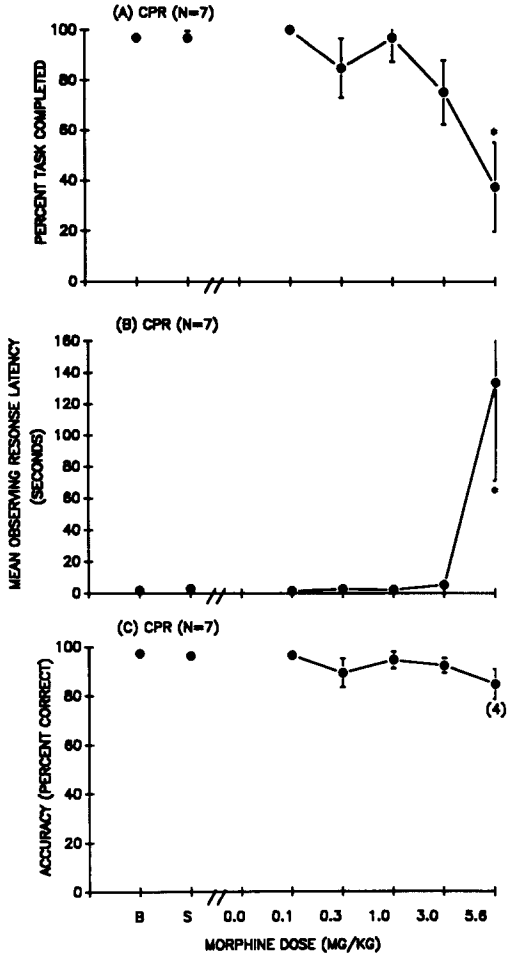

FIG. 5. Effects of morphine on conditioned position responding (CPR) percent task completed (A), mean observing response latency (B) and response accuracy (C), n = 7 unless indicated otherwise. Data presented as in Fig. 1.

sponse rates for a two-lever sequence (0.7–0.75 resp/s), response accuracies averaging 58–65%, and percent task completed values of 48–65% for this 35-min task (120 reinforcers possible).

Conditioned Position Responding (CPR)

Morphine produced dose-dependent decreases in CPR percent task completed and increases in mean observing response latencies which reached significance only at 5.6 mg/kg (Fig. 5). No clear effects were observed on any CPR parameters at doses below 3.0 mg/kg. The accuracy of responding in the CPR task was not significantly affected by morphine at the doses employed in this study (Fig. 5C). Under control conditions, the CPR schedule generates low response latencies (1.5–1.8 s/resp), high response accuracies averaging 96–98%, and percent task completed values of 95–97% for this 5-min task (60 reinforcers possible).

DISCUSSION

Intravenous morphine administration to monkeys produced differential disruption of performance in the behavioral tasks contained in the operant test battery used in this experiment. The order of task sensitivity to morphine disruption was TRD = IRA = PR > DMTS > CPR. Sensitivity here is reported in terms of the lowest dose needed to significantly alter performance in a given test. Of the five tasks studied, TRD was the only task in which morphine produced significant decrements in response accuracy. In general, the percent task completed measure was more sensitive to the effects of morphine than were response rate or latency or response accuracy (except TRD). This probably represents the combined effects of morphine to decrease response rate and accuracy to yield a significant decrease in percent task completed at the lower 1.0 mg/kg doses.

The effects of delta-9-tetrahydrocannabinol (THC), marijuana smoke, diazepam (Valium®), and *d*-amphetamine in these same animals performing in the same operant test battery (29–32) were quite different. Unlike diazepam, marijuana smoke and THC, morphine produced significant dose-dependent decrements of response rate and breakpoint in the PR task, an effect also produced by *d*-amphetamine administration (32). Morphine produced significant increases in DMTS response latencies but no observable effects on matching accuracy at any delay, an effect quite different from that of diazepam, THC or *d*-amphetamine. These observations support the hypothesis that differential effects on complex

operant performance are produced by drugs which act through different CNS mechanisms (6).

In general, performance in the OTB under nondrug conditions indicated strong schedule control. Morphine produced response rate decreases (or increased response latencies) in tasks having low, moderate and high baseline response rates. Interestingly, those tasks which use lever manipulanda (IRA, TRD, PR) showed equal sensitivity to the disruptive effects of morphine, and were more sensitive to morphine than those tasks using press plate manipulanda (DMTS, CPR). This finding suggests that for morphine, response topography may be a greater determinant of drug effect than baseline response rates.

The effects of morphine on delayed matching performance have received little experimental attention. Similar to our findings in monkeys, morphine produced no effects on matching performance of pigeons at doses less than 3 mg/kg, while larger doses produced decreases in response rates (increases in latency) and small inconsistent decreases in accuracy (15). These findings suggest that morphine produces a general effect on motor function at these doses rather than a specific effect on matching accuracy. This would indicate that morphine does not disrupt short-term memory processes in rhesus monkeys, an observation that is consistent with morphine's effects on passive avoidance responding in rats (4).

The depressive effect of morphine on PR response rates and break point observed in this experiment are similar to those findings reported for performance maintained by a fixed ratio schedule of food presentation in monkeys (3), pigeons (7), and rats (15). One distinct species difference in the behavioral response to morphine is known. Unlike the rhesus monkeys in this experiment, morphine produces increases in fixed ratio responding (as much as 160%) in chimpanzees at doses ranging from 0.1–1.0 mg/kg (2).

The morphine-induced decrease in the IRA percent task completed correlated primarily with decreases in response rates. The effects of morphine on IRA performance are consistent with the effects reported for morphine using traditional (i.e., nonincremented) repeated acquisition procedures in pigeons (34), and monkeys (25), and incremented procedures in rats (27). In general, the mu opiate agonists have little or no effect on accuracy of responding in monkeys across a range of doses which decrease response rate (22). These morphine-induced response rate suppressions appear to be the result of increased periods of pausing, rather than changes in running rate (23,25).

The CPR task was relatively insensitive to the acute effects of morphine with significant effects occurring on percent task completed and response latency measures only at the highest dose tested. These findings are consisted with reports that the accuracy of performance of conditional discriminations in monkeys is less sensitive to disruption by morphine than repeated acquisition performance of response chains (25). Interestingly, the CPR task has proven to be the least sensitive task in the OTB for detecting the effects of other centrally active drugs including amphetamine and diazepam (31,32).

The morphine-induced decreases in TRD percent task completed correlated with both changes in response rate and response accuracy. Morphine produced response rate suppressions while simultaneously decreasing the mean duration of lever holds. This resulted in a decrease in the total number of responses and a decrease in response duration, therefore decreasing both response rate and response accuracy. One report indicates that low doses of morphine increase response rates and high doses decrease response rates of rats performing under a differential reinforcement of low-rate schedule of reinforcement (8). We found no such increases in response rates in monkeys performing in the TRD task as did another report in rats performing under a DRL schedule (1).

In the present experiment, morphine was shown to differentially affect performance in a battery of complex operant tests. The relative sensitivities of these tasks for detecting morphine's behavioral effects were IRA = TRD = PR > DMTS > CPR. Furthermore, the acute effects of morphine reported here are notably different than the acute effects of THC, *d*-amphetamine or diazepam when given to the same animals performing the same tasks. The present study suggests that morphine, a prototypic mu agonist, has a greater influence over CNS processes modulating IRA (''learning''), PR (''motivation'') and TRD (''time-perception'') behaviors than over those processes modulating responding in the DMTS (''short-term memory'' and ''attention'') task and the least influence over CPR (''color and position discrimination'') responding based upon their sensitivity to disruption by morphine. In addition, morphine affected response rates rather than response accuracy in the majority of tasks, suggesting a general effect on motor function similar to reports in humans indicating that morphine produces sedation, and muscular incoordination at high doses rather than specific disruption of cognition (9,13). These results serve to further the validation of specific operant test methods for use in behavioral pharmacology/toxicology by providing evidence that performance in these tasks is selectively disrupted by reference compounds. This approach provides behavioral data (i.e., profiles) which may ultimately suggest possible mechanisms or brain processes involved in the effects produced by compounds with unknown mechanisms of action.

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