**DRUG-BEHAVIOR INTERACTION HISTORY:
MODIFICATION OF THE EFFECTS OF
MORPHINE ON PUNISHED BEHAVIOR**

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Squirrel monkeys were trained to respond under a multiple fixed-interval, fixed-interval schedule in which the first response after 5 min terminated a visual stimulus in the presence of which electric shocks could occur. During one component of the schedule, correlated with one color of stimulus lights, every 30th response also produced electric shock; responding was suppressed during this component to approximately 10 to 12% of that occurring in the alternate component in which responding was not punished. In contrast to previous research, morphine (0.03 to 1.0 mg/kg) increased punished responding. Unpunished responding, however, was either not affected or decreased at doses of morphine that increased punished responding. Increases in rate of punished responding also occurred when the single-schedule punishment condition was studied alone in these animals. Subsequent experimentation, which systematically analyzed the development of the rate-enhancing effects of morphine on punished responding, involved the study of drug effects in additional monkeys trained initially under a single-schedule punishment condition. The effects of morphine on punished responding were studied before, after, and then during exposure to the multiple schedule that included a component in which responding was not punished. Increases in response rate with morphine did not occur until it was administered during exposure to the multiple schedule that included a component in which responding was not punished. As with the other monkeys, once the rate increases in punished responding occurred under the multiple schedule, these effects of morphine persisted, even when the multiple schedule was removed. These findings indicate that the behavioral effects of a drug can depend on the combined influence of that drug and the specific circumstances under which it is studied. Neither the behavioral experience alone nor exposure to the drug was sufficient to alter morphine's effects. Once this drug-behavior interaction occurs, however, the behavioral effects of that drug can be changed substantially.

Key words: behavioral pharmacology, punishment, morphine, fixed interval, behavioral history, stimulus-shock termination, escape, lever press, squirrel monkeys

The behavioral effects of drugs are known to be influenced by a variety of nonpharmacological factors. Such factors include the schedule-controlled rate and pattern of responding, the type of maintaining event, conditions existing in an alternate component of a multiple schedule, and the prior behavioral history of the organism (see reviews by Barrett, 1985; Barrett & Witkin, 1986; McKearney & Barrett, 1978). In many cases, these conditions can directly influence the qualitative effects of a particular drug, by determining whether the drug will increase rates of behavior or whether it will decrease them.

Thus, some of the defining characteristic effects of drugs can be influenced to a significant extent by behavioral variables.

During the course of experiments designed to investigate behavioral interactions under multiple schedules using noxious stimuli, we administered a number of drugs that, because of the schedules employed, could have had potentially interesting effects. The study reported here describes the effects of morphine. This compound was examined initially on behavioral performances of squirrel monkeys maintained under a two-component schedule in which responding in each component terminated a stimulus correlated with shock (Azrin, Holz, & Hake, 1962; Morse & Kelleher, 1966). During one component, however, responding was also punished by the delivery of shock; responding was not punished during the alternate component. Morphine was studied under this multiple schedule because, when examined under single-component schedules, it has been shown to increase

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unpunished responding maintained by stimulus-shock termination (McKearney, 1975), and to decrease punished responding maintained under these schedules (Glowa & Barrett, 1983). When we found substantial increases in punished responding under the multiple schedule with morphine, these effects were studied systematically in an effort to identify the factors responsible.

METHOD

Subjects

The subjects were 4 experimentally naive adult male squirrel monkeys. Each was caged individually and had unrestricted access to food and water.

Apparatus

During experimental sessions, individual monkeys were seated in a Plexiglas chair that provided loose restraint at the waist. The chair was equipped with a response lever (BRS/LVE Model 121-05) that, when depressed with a force exceeding 0.2 N, registered a response and produced the click of a relay mounted behind the front panel. Three pairs of colored lamps were also mounted behind the front panel. The monkey's tail was shaved at its distal end and was held immobile by a small stock. Two brass electrodes rested on the shaved portion of tail which, prior to each session, was massaged with EKG sol electrode paste. Electric shock consisted of the application of a 200-ms, 650-V ac, 7-mA pulse delivered through series resistance to the electrodes. The shock was monitored continuously by a Simpson Model 1253 milliammeter.

Procedure

Experiments were first conducted with 2 monkeys (MS-9 and MS-25) initially trained to postpone regularly scheduled shocks delivered under an avoidance schedule (Sidman, 1953). Under this schedule, shocks were delivered every 5 s in the absence of a response. The occurrence of a response postponed the next scheduled shock for 30 s. After approximately 2 weeks under this procedure, the avoidance schedule was replaced by a stimulus-shock termination schedule. White stimulus lamps illuminated the chamber during both of these phases. Under the stimulus-shock termination schedule, shocks occurred every

3 s after a 30-s fixed interval (FI) had elapsed. A response at any time after the 30-s FI elapsed terminated the prevailing visual stimulus, prevented further shocks, and produced a 30-s timeout period during which there were no scheduled consequences. Also, during these sessions, a second component was added, correlated with the illumination of red stimulus lamps. Over a 1-week period, the length of the FI in both components was increased in 30-s steps to 5 min, where it remained for the remainder of the experiment. Under these conditions shocks were scheduled to recur every 3 s after the 5-min FI had elapsed; a response at any time after the FI elapsed terminated the visual stimulus (either red or white), prevented further shocks, and produced the timeout. During this phase the timeout period was lengthened to 1 min. Performances were maintained under the multiple FI schedule for 2 to 3 weeks. A 30-response fixed-ratio (FR) schedule of response-produced shock was then added to the component correlated with the red stimulus lamps. Under this component the first response after 5 min terminated the red stimuli and prevented shocks; in addition, every 30th response produced shock (punishment). The FR was reset at the beginning of each punishment component.

Morphine was administered when performances had been maintained for at least 30 sessions under the multiple schedule of unpunished and punished responding. The components were scheduled in strict alternation, and a daily session was comprised of five components each (a total of approximately 60 min). Drug effects were also studied subsequently under the punishment schedule alone, which consisted of daily exposure to 10 components of the stimulus-shock termination schedule plus FR 30 shock.

A second pair of monkeys (MS-87 and MS-93) was trained under an avoidance schedule identical to that described above. Subsequently, these monkeys were shifted to the stimulus-shock termination schedule and responding was established following procedures used with the previous monkeys. However, a multiple schedule was not used initially. Once responding stabilized under the single-component schedule in the presence of red stimuli, the 30-response shock-presentation schedule was added. Drug effects were first

studied under the punishment schedule alone, after which the second component was added, accompanied by white lights; responding in the presence of the white lights did not produce shock. Morphine was not administered at this time when responding was maintained under the multiple schedule. After responding stabilized under the multiple schedule (within 12 to 30 sessions), the component in which responding was not punished was discontinued. Drug effects were then reassessed under the single-component punishment schedule after exposure (without morphine) to the multiple schedule. The multiple schedule was then reintroduced and, after 7 to 17 sessions, drug effects were assessed under the multiple schedule. Finally, drug effects were reexamined on responding maintained under the punishment schedule alone.

The experimental sequence for all 4 monkeys is summarized in Table 1. In brief, the sequences used with Subjects MS-87 and MS-93 were employed to evaluate drug effects under different phases of the schedule to determine whether the procedure alone, experience with the drug, or the combination of drug plus procedure contributed to the modification of the effects of morphine.

Drug Procedure

Morphine sulfate (Merck and Co.) was dissolved in 0.9% sterile saline solution and was administered intramuscularly into the calf immediately before the session. Typically, morphine was administered on Tuesdays and Fridays, except when performances on the preceding day were not within the range of performances maintained prior to drug administration. Also, if high doses of morphine (3.0 mg/kg) were administered, another dose was not given for 7 days. Each dose was usually administered at least twice, with the injection volume 1.0 mL/kg. Doses are expressed as the salt.

Data Analysis

Data were collected from impulse counters and running-time meters to provide measures of response rate (responses per second). Drug effects are expressed as percentage changes from control response rates calculated from Thursday sessions or from sessions on Tuesday or Friday when saline rather than morphine was administered.

Table 1

Summary of experimental sequences (excluding initial training under the avoidance schedule or under the stimulus-shock termination schedule alone prior to the introduction of punishment). Asterisks denote those phases during which morphine was administered.

Monkeys	Procedures
MS-9 & MS-25	Multiple FI FI (plus punishment)* FI (plus punishment)*
MS-87 & MS-93	FI (plus punishment)* Multiple FI FI (plus punishment) FI (plus punishment)* Multiple FI FI (plus punishment)* FI (plus punishment)*

RESULTS

Control performances of the 2 squirrel monkeys (MS-9 and MS-25) responding under the multiple stimulus-shock termination schedule were comparable to those reported when these schedules are studied separately (McKearney, 1976; Morse & Kelleher, 1966). Prior to the introduction of the FR 30 shock presentation schedule, response rates were essentially equivalent in the two components and patterns of responding resembled those often reported under FI schedules (Ferster & Skinner, 1957). With the introduction of the punishment procedure, response rates in that component decreased to approximately 10 to 12% of control levels (Table 2). Figure 1 (top left) shows control performances under the termination schedule for Monkey MS-25. High response rates were maintained in the component where responding did not produce shocks under the FR 30 schedule. The rates of responding maintained in the alternate component were much lower. Addition of the FR 30 schedule lengthened the initial pause in the punishment components and produced overall lower rates that occasionally were negatively accelerated throughout the interval.

Under the multiple schedule, administration of morphine (0.03 to 0.1 mg/kg for MS-25 and 0.3 to 1.0 mg/kg for MS-9) produced large increases in punished responding (Figure 2). All determinations at these doses fell outside the range of control values. For Monkey MS-25, these same doses either did not affect or decreased unpunished responding in the alternate component; for MS-9, unpunished responding was increased slightly across

Fig. 1. Cumulative response records of control performance and drug effects for one monkey (MS-25) under the multiple fixed-interval stimulus-shock termination schedule (left panel) and under the single-component punishment schedule. Under the multiple schedule (left panels), the first response after 5 min terminated stimuli in the presence of which shocks occurred 3 s after the interval elapsed. In addition, during one component, denoted by the deflection of the event pen beneath the record, every 30th response produced shock. The pens reset at the end of each fixed-interval and the paper did not run during the timeout period. Shocks delivered under the fixed-ratio schedule are indicated by displacements of the response pen. The punishment schedule was also studied alone (right panels). Termination shocks are indicated by the displacement of the lower event line (none shown). Ordinates: cumulative responses; abscissae: time. Note that morphine increased punished responding under both schedule conditions.

a range of morphine doses (0.03 to 0.3 mg/kg). The highest dose of morphine, 1.0 (MS-25) or 3.0 (MS-9) mg/kg, decreased unpunished responding considerably but left punished rates at control levels, although they were on the descending limb of the dose-effect curve. Figure 1 (bottom, left) shows detailed patterns of responding of MS-25 under a 0.1 mg/kg dose of morphine. Although response rate in the first component (unpunished) was elevated, unpunished rates in the remaining cycles were near or slightly below control levels. In contrast, consistent increases in punished responding occurred with this dose of morphine, although patterns remained comparable to those occurring under control conditions.

Increases in punished responding continued to occur when this behavior was studied alone, after the alternate component was deleted (Figures 1 and 2). Response rates under the single-component schedule did not differ substantially for these monkeys when punished responding was studied alone (Table 2). The peak of the dose-effect curve for Monkey MS-25 shifted from 0.1 to 1.0 mg/kg but was unaffected for MS-9.

The increases in punished responding produced by morphine, both under the multiple schedule and after experience under the multiple schedule, then prompted studies with the two additional monkeys (MS-87 and MS-93). The effects of morphine on performances throughout the various experimental phases are shown in Figures 3 and 4; control response rates are given in Table 2. As with Monkeys MS-9 and MS-25, control rates of punished responding were approximately 10 to 15% of those that occurred initially under the nonpunished condition. When administered prior to any training under the multiple schedule, morphine (0.01 to 1.0 mg/kg) produced only dose-dependent decreases in punished responding (Figures 3 and 4, left panels); rates and patterns of responding changed little from control (Figure 3, left, top and middle). After a history of training under the multiple schedule, unaccompanied by morphine administration, morphine continued to produce decreases in responding under the punishment condition alone (Figures 3 and 4, left panel). However, these effects were attenuated somewhat in that, at most doses, re-

sponding was decreased less after multiple-schedule exposure than before training under this condition (Figure 4, left panels; triangles).

When the effects of morphine were studied under the multiple schedule, increases in punished responding occurred (Figures 3 and 4, middle panels). These effects were slight with MS-87 and occurred only at the 0.1 mg/kg dose, whereas the entire dose-effect curve was shifted upward with MS-93. All administrations of the 0.1 mg/kg dose, however, yielded data beyond the range of control values for both monkeys and with MS-93 these effects occurred across the 0.01 to 0.1 mg/kg dose range. Doses of morphine (0.3 and 1.0 mg/kg) produced large decreases in unpunished responding; in the punishment component, morphine did not alter or produced smaller proportional effects on response rates.

With discontinuation of the component in which responding was not punished, morphine continued to produce increases in punished responding (Figures 3 and 4, right panels). For Monkey MS-87, increases with morphine were greater under the punishment schedule alone than under the multiple schedule, but increases still occurred at only one dose. The peak rate-increasing effect of morphine shifted from 0.1 mg/kg under the multiple schedule to 0.03 mg/kg under the punishment schedule alone (Figure 4, right panel). Again, for both monkeys all determinations of this dose fell beyond the control ranges.

DISCUSSION

In previous studies of the effects of morphine on punished responding maintained by the termination of stimuli correlated with electric shock delivery, administration of this substance has been shown to decrease responding (Glowa & Barrett, 1983). When first studied under the multiple schedule in the present experiment, however, morphine produced substantial increases in punished responding. Because this drug can increase unpunished responding under single-component stimulus-shock termination schedules (McKearney, 1975; see also a review by Barrett & Katz, 1981), it seemed possible that interactions between components of the multiple schedule may have contributed to the rate-increasing effects of morphine. This possibil-

Fig. 2. Dose-response curves for two monkeys MS-25 (top) and MS-9 (bottom) under the multiple-schedule and single-schedule conditions. Unconnected points on the left represent control performances under the respective schedule procedures ± 1 SE (SE not shown when less than the diameter of the depicted point). The dashed horizontal line represents the locus of no change from control levels. Effects are expressed as a percentage of control (nondrug and saline injection) performances. Vertical lines on the dose-effect curve denote the range of observations. Left panels show morphine effects under the multiple schedule in which responding was and was not punished. Curves on the right represent effects under the punishment procedure alone.

ity also seemed likely because, except for small increases with MS-9, morphine did not produce characteristic large increases in unpunished responding maintained under the multiple schedule of stimulus-shock termination. Previous research has demonstrated that such "contextual" features can modify the effects of *d*-amphetamine on punished responding maintained by food. For example, *d*-amphetamine decreased punished responding of squirrel monkeys when this performance alternated with a component in which responding had no scheduled consequences (extinction). When the extinction condition was replaced with an avoidance schedule, however, *d*-amphetamine produced large increases in punished responding (McKearney & Bar-

Fig. 3. Cumulative response records for one monkey (MS-87) under the various experimental phases. Details of the recording are identical to those in Figure 1. Left panels show control performances and the effects of morphine before and after exposure to the multiple schedule in which responding was punished and when it was unpunished. Morphine did not increase responding under these procedures. Middle panels show control performances and drug effects under the multiple schedule. Note that morphine increased punished responding under the multiple schedule. Panels on the right show that increases in punished responding continued to occur even when the component in which responding was not punished was deleted.

rett, 1975). Thus, the behavioral effects of *d*-amphetamine depended not only on the specific behavior under study, but also on the total environmental context in which that behavior occurred.

When the altered effects of morphine on

punished responding were analyzed systematically in the present experiment (by selective introduction of the component in which responding was not punished), modification of the effects of morphine was shown to depend on both exposure to the multiple schedule and

Table 2
Response rate (responses per second) under the experimental procedures. Figures are averages based on approximately 7 to 10 noninjection or saline control sessions. Numbers in parentheses are 1 SD.

Procedure	Monkey			
	MS-9		MS-25	
	Unpunished	Punished	Unpunished	Punished
Multiple FI FI (plus punishment)	0.706 (0.110)	0.066 (0.031)	1.236 (0.193)	0.155 (0.012)
FI (plus punishment)	—	0.096 (0.016)	—	0.144 (0.015)
Procedure	MS-87		MS-93	
	Unpunished	Punished	Unpunished	Punished
	Unpunished	Punished	Unpunished	Punished
FI (plus punishment)	—	0.086 (0.005)	—	0.048 (0.003)
Multiple FI FI (plus punishment)	0.85 (0.02)	0.17 (0.01)	0.33 (0.03)	0.016 (0.004)
FI (plus punishment)	—	0.079 (0.012)	—	0.033 (0.003)
Multiple FI FI (plus punishment)	0.62 (0.04)	0.13 (0.006)	0.31 (0.03)	0.003 (0.0003)
FI (plus punishment)	—	0.123 (0.002)	—	0.032 (0.003)

on the administration of morphine while that condition was in effect. That is, the effects of morphine on punished responding were not modified substantially by training alone under the multiple schedule that included the unpunished condition. However, when morphine was administered under the multiple schedule, increases in punished responding occurred and these effects persisted even when the unpunished condition was then removed. Thus, the behavioral effects of morphine were reversed by exposure to that drug under a particular environmental setting.

The importance of currently operative behavioral variables in determining drug action have been known for some time. For example, Dews (1955) found that the effects of pento-barbital depended on whether responding was maintained under fixed-ratio or fixed-interval schedules. Similar results were also obtained with *d*-amphetamine (Dews, 1958). Much research in behavioral pharmacology has demonstrated the importance of the ongoing rate and pattern of responding in determining the effects that a number of drugs will have on behavior (Kelleher & Morse, 1968). Recently, it has been found that conditions that have occurred in the past, such as exposure to a particular schedule of reinforcement, can have a significant influence on the specific behavioral effects of a drug (see reviews by Barrett & Witkin, 1986; McKearney, 1979). Such experience can be important even though the effects of that history are not apparent in current behavior.

In the present study, the effects of morphine were altered by exposure to that drug only under the multiple-schedule condition. Although an interaction between behavior under the two components in which responding was and was not punished seems likely, further clarification of conditions responsible for this effect remains necessary. Inasmuch as morphine did not increase unpunished responding consistently or in all monkeys, the rate-increasing effects under the punishment component did not appear to stem from direct induction. It is possible that there is some "contrast" effect: Morphine has been shown to increase unpunished responding under stimulus-shock termination schedules (McKearney, 1975); the failure to do so in the present study, or the fact that morphine occasionally even decreased this responding, is

Fig. 4. Dose-effect curves for two monkeys, MS-87 (top panels) and MS-93 (lower panels), under the various experimental procedures. Details are the same as those in Figure 2. Note that morphine did not increase responding before or after exposure to the multiple schedule (left panels) but did produce increases when administered under the multiple schedule. Increases with morphine continued to occur under the punishment schedule alone (right panels).

also interesting and may suggest that the increases in punished responding are attributable to the absence of such increases in the alternate component. Regardless of the eventual explanation for this outcome, it is clear that the combined exposure to a drug and a particular type of behavioral experience can produce a dramatic and apparently enduring alteration in the effects of that drug.

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