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Prior Behavioral Experience Can Reverse the Effects of Morphine

J. E. Barrett and J. A. Stanley

Department of Psychiatry, School of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814, USA

Abstract. Morphine administration typically decreases responding of squirrel monkeys trained to avoid electric shock. However, the rate-decreasing effects of morphine on avoidance responding were reversed after either concurrent or prior exposure to a condition in which responding was maintained by shock presentation. These findings demonstrate that behavioral experience can play a significant role in determining the behavioral effects of drugs and that specific types of environmental conditions can completely reverse the usual effects those drugs have on behavior.

Key words: Morphine – Behavioral history – Schedule-controlled behavior – Drugs and noxious stimuli – Avoidance – Behavioral experience – Experience – Squirrel monkeys

The behavioral effects of many drugs often depend on characteristic features of ongoing behavior and on the environmental circumstances which exist at the time the drug is administered. For example, the effects of abused drugs, as well as many drugs with psychotherapeutic efficacy, can be influenced by the rate at which the behavior normally occurs (Dews and DeWeese 1977; Dews and Wenger 1977; Kelleher and Morse 1968; Sanger and Blackman 1976), by the type of consequences that control responding (Barrett and Katz 1981), by direct changes in behavior produced by the drug itself (McKearney 1979), and by other conditions present in the environmental setting in which the drug is administered (McKearney and Barrett 1978; Siegel et al. 1982). Although these more immediate factors can play a significant role in altering the behavioral effects of many drugs, certain drug effects can also depend on conditions which have existed previously but are no longer present in the current environment or apparent in ongoing behavior. For example, the rate-decreasing effects of *d*-amphetamine on punished responding of squirrel monkeys can be changed to rate-increasing effects after relatively brief exposure to an avoidance schedule (Bacotti and McKearney 1979; Barrett 1977). Thus, a drug may affect behavior differently depending on the prior behavioral experience of the organism. At the present time, very little is known about the classes of drugs which may exert qualitatively different effects, about the types of behavioral experiences capable of altering drug effects, or about the types of behavior which may be susceptible to the influence of previous experience.

In the present experiment the effects of morphine were first examined on separate behavioral performances of squirrel monkeys that were maintained simultaneously (concurrent schedule) by the presentation and postponement of electric shock (Barrett and Stanley 1980). Morphine has been reported to produce opposite effects on these behaviors when studied in isolation: for example, morphine decreases responding of squirrel monkeys maintained under shock-postponement schedules (Dworkin and Branch 1982; Holtzman 1976; Houser 1978; Houser and Cash 1975), but increases responding maintained by shock presentation (McKearney 1974). Under the concurrent schedule studied in the present experiment, however, morphine increased responding under both the shock-presentation and shock-postponement schedules. Further systematic examination of these atypical effects of morphine under the shock-avoidance schedule demonstrated that either concurrent or previous exposure to a condition in which responding is maintained by response-produced shock can markedly and durably reverse the behavioral effects of morphine.

Materials and Methods

Four experimentally naive mature male squirrel monkeys (*Saimiri sciurea*) were housed individually with unrestricted access to food and water. All monkeys weighed approximately 1 kg. None of the monkeys had previously received drugs.

The monkeys were studied during daily 1-h sessions while seated in a Plexiglas primate chair (Hake and Azrin 1963). The chair was equipped with differently colored stimulus lights and a response lever (BRS/LVE 121-05) mounted behind the transparent front wall. A depression of the lever of 0.20 N or more activated a feedback relay and was recorded as a response. During certain phases of the experiments a chain was also present. The 16 cm chain was attached to a Gerbrands G-6312 lever mounted at the top left of the panel beyond the monkey's reach. A pull on the chain with a downward force exceeding 0.85 N counted as a response and also activated the feedback relay. The distal end of the monkey's tail was shaved and, during experimental sessions, was held motionless in a small stock. The tail was coated with EKG electrode paste just prior to the session to ensure low-resistance contact with two brass electrodes that rested on the shaved region of the tail. Electric shock presentation consisted of the delivery of a 10 mA, 200-ms, 650 V AC, 60 Hz

Offprint requests to: J. E. Barrett

pulse delivered through a variable resistor in series with the tail. During experimental sessions the chair was placed in a sound-attenuating enclosure equipped with white masking noise and an exhaust fan.

Procedure. Initial studies with morphine were conducted with two squirrel monkeys (MS-46 and MS-47) performing under a schedule in which responding was simultaneously maintained by both the presentation and postponement of electric shock (concurrent schedule). Under this condition, each chain-pulling response postponed or avoided shock for 45 s; otherwise, avoidance shocks were delivered every 5 s. Simultaneously, the first lever press after 3-min had elapsed, either from the start of the session or the last response-produced shock, resulted in the delivery of shock [fixed-interval (FI) 3-min schedule]. These performances were established by first training the monkeys under the shock-postponement schedule and then under the schedule of response-produced shock (Barrett and Stanley 1980).

After studying the effects of morphine under the concurrent shock-presentation shock-postponement schedule, morphine's effects were then examined under the shock-postponement schedule after the FI shock-presentation schedule was deleted (extinction), while the lever was still present. Finally, morphine dose-effect curves were determined when the lever was removed and only the postponement schedule was in operation. Throughout all phases, responding was allowed to stabilize until there were no trends in response rates (at least 14 daily sessions).

The effects of morphine were also examined in two additional monkeys (MS-68 and MS-75) initially trained only under the shock-postponement schedule using the chain-pulling response. There was no lever present during this phase. All other details were identical to those of the other two monkeys. After the effects of morphine were determined, the shock-postponement schedule and chain were removed and responding was established on the lever under the FI 3-min schedule of response-produced shock. Exposure to each of these conditions lasted approximately 1 month. Morphine was not administered during the time the shock-presentation schedule was in effect. In the last phase of this study the lever and shock-presentation schedule were removed and responding was reestablished under the chain-pull avoidance schedule. Morphine was administered after approximately 2 weeks under this condition.

Drug Administration. Morphine sulfate (Sigma, St. Louis, MO, USA) was dissolved in 0.9 % saline and was injected IM into the calf muscle immediately before the session. Doses (0.01 – 3.0 mg/kg), expressed as the total salt, were given in a solution of 1.0 ml/kg body weight. Each dose of morphine was given at least twice, with test sessions typically occurring on Tuesdays and Fridays. Thursday's session or a Tuesday or Friday in which saline rather than morphine was administered provided measures of control performance.

Results

The inset in Fig. 1 shows characteristic performances maintained under the concurrent shock-postponement shock-presentation schedule (MS-46 and MS-47). Response rates were positively accelerated during the FI schedule, resulting in shock presentation (lever) while, simultaneously, responding occurred at a steady rate under the shock-postponement schedule (chain pulling). These performances with squirrel monkeys are similar to those obtained when these schedules were studied in isolation (Barrett and Stanley 1980; McKearney 1968; Morse and Kelleher 1970, 1977). Rates of responding under the two schedules during this phase (condition 1) and subsequent phases are given in Table 1.

Table 1. Response rates (responses/s) under the different experimental conditions. The effects of morphine were determined under all conditions except the shock-presentation schedule (condition 2) for MS-68 and MS-75. Data in parentheses are 1 SE

Schedule conditions	Monkeys	
	MS-46	MS-47
1. Concurrent		
Shock avoidance	0.291 (0.01)	0.166 (0.01)
Shock presentation	0.416 (0.03)	0.780 (0.03)
2. Concurrent		
Shock avoidance	0.149 (0.01)	0.142 (0.02)
Extinction	0.134 (0.01)	0.234 (0.02)
3. Shock avoidance	0.233 (0.03)	0.473 (0.03)
	MS-68	MS-75
1. Shock avoidance	0.157 (0.01)	0.540 (0.03)
2. Shock presentation	0.824 (0.03)	0.613 (0.04)
3. Shock avoidance	0.160 (0.01)	0.486 (0.06)

Intermediate doses of morphine (0.3 – 1.0 mg/kg) increased responding substantially under the shock-avoidance schedule (Fig. 1). Small increases also occurred under the shock-presentation schedule at lower morphine doses (0.03 – 0.1 mg/kg). Responding maintained by shock presentation was decreased at the 1.0 mg/kg morphine dose that increased responding under the shock-avoidance schedule. The 3.0 mg/kg dose of morphine decreased responding under both schedules.

Since morphine does not usually increase shock-avoidance behavior in squirrel monkeys, it seemed that increased avoidance responding in the present study may have resulted from the simultaneous maintenance of responding under the shock-presentation schedule. Increases in this latter behavior by morphine may also have engendered increases in avoidance responding by a process of induction. However, when the FI schedule of response-produced shock was deleted (extinction) and the effects of morphine were redetermined, intermediate doses of morphine continued to increase responding under the shock-avoidance schedule (Fig. 1). The reduced rates of responding on the lever were also increased, even though shocks no longer occurred following responses on that manipulandum. When the lever was subsequently removed and only the shock-avoidance schedule was in effect (Table 1), morphine continued to increase avoidance responding (Fig. 1).

Increases in shock-avoidance responding persisted for months after the removal of the lever and the shock-presentation schedule, suggesting that a history of exposure to the initial response-produced shock condition was responsible for the atypical (i.e., rate-increasing) effects of morphine. This possibility was examined in the two ad-

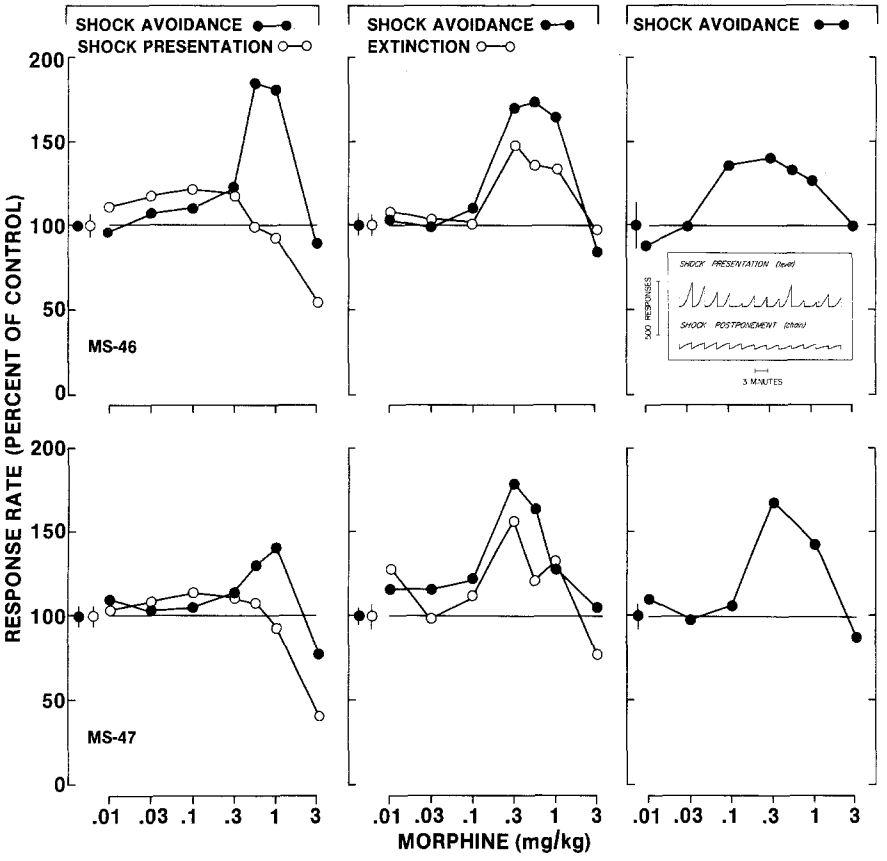

Fig. 1
Effects of morphine sulfate on behavior of two squirrel monkeys (MS-46 *top*, MS-47 *bottom*). The *left panels* show the effects of morphine when responding was maintained simultaneously by a concurrent schedule of shock-postponement and response-produced shock. The inset in the *right panel* shows cumulative response records of characteristic control (nondrug) performances under this schedule. The recording pens reset after each response-produced shock. The *middle panels* show the dose-effect functions for morphine when the response-produced shock schedule was removed and lever responding had no consequence (extinction): the avoidance schedule was still in effect. The *right panels* show effects of morphine on avoidance responding alone. Unconnected points on the left of each figure denote control performances ± 1 SE based on at least seven nondrug or saline injection sessions

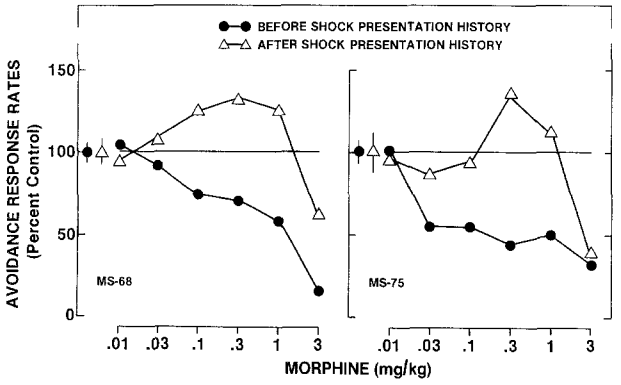

Fig. 2. Effects of morphine sulfate on shock-avoidance responding before (●) and after (△) exposure to a condition under which responding was maintained by response-produced shock. Morphine decreased responding prior to a history of response-produced shock, but increased responding after exposure to this condition. Unconnected points on the left of each panel denote control performances ± SE based on at least seven nondrug or saline injection sessions

ditional squirrel monkeys (MS-68, MS-75) trained initially only to avoid shock using the chain-pulling response. Control response rates for these monkeys under this and subsequent phases are given in the lower half of Table 1. In contrast to the effects obtained with monkeys studied under the concurrent schedule, morphine (0.03 – 3.0 mg/kg) only decreased avoidance responding in the monkeys having no prior experience with response-produced shock (Fig. 2). After training under the shock-presentation schedule (Table 1), however, intermediate doses of morphine increased avoidance responding (Fig. 2). Thus, the additional experience of response-produced shock reversed the effects of morphine on shock-avoidance responding.

Discussion

The effects of morphine on responding under a shock-postponement (avoidance) schedule depended on whether monkeys had either concurrent or sequential exposure to a condition in which responding was maintained by response-produced shock. In the absence of such a history, morphine decreased avoidance responding, a finding consistent with previous studies (Dworkin and Branch 1982; Holtzman 1976; Houser 1978). However, after responding had been maintained under a schedule of shock presentation, morphine increased responding under the avoidance schedule.

Changes in the effects of morphine on responding under the avoidance schedule were not due to changes in response rate which, under some conditions, can influence the behavioral effects of drugs (Dews and Wenger 1977; Kelleher and Morse 1968; McKearney and Barrett 1978). Rates of avoidance responding were comparable across most conditions for monkeys studied initially under the concurrent schedule (MS-46 and MS-47) and were not systematically related to the effects of morphine (Table 1). Rates of avoidance responding were nearly identical throughout all experiments with monkeys studied only under the single-schedule conditions (MS-68 and MS-75). Thus, exposure to particular behavioral conditions can dramatically alter the effects of morphine, even when behavior itself does not appear to change as a result of those conditions.

In addition to the importance of behavioral history, previous research has also demonstrated that prior pharmacological experience can also alter the behavioral effects of drugs. For example, previous exposure to morphine prevented the rate-increasing effects of pentobarbital on punished responding of squirrel monkeys maintained under a stimulus-shock termination schedule (Glowa and Barrett 1983). Experience with morphine in the present study may also have contributed to the modified effects of this drug on avoidance responding during subsequent phases. However, this is unlikely in view of the fact that doses were determined over a 3–4 month period without noticeable changes in the effects of repeated determinations. Further, studies with chronic morphine (Dworkin and Branch 1982; Houser and Cash 1975) have not reported any modification in morphine's effects on avoidance responding comparable to those reported here. Thus, it would appear that mere experience with morphine is not sufficient to reverse the effects of morphine on avoidance behavior.

The importance of behavioral history as a determinant of the behavioral effects of drugs has been shown previously with *d*-amphetamine (Bacotti and McKearney 1979; Barrett 1977). In those studies, exposure to an avoidance schedule reversed the rate-decreasing effects of *d*-amphetamine on punished behavior. In the present study, the effects of morphine on behavior maintained under an avoidance schedule were reversed by experience under a schedule of response-produced shock. The influence of behavioral experience in determining drug effects does not appear limited to one type of behavior or to a single class of drugs. Based on these findings, it would appear that perhaps the behavioral effects of abused drugs may be determined in significant ways by environmental and/or experiential factors. Further, if the likelihood that a drug will be abused depends on the particular effects that drug has on behavior, then factors such as behavioral experience, which alter those effects, may be significant in determining whether a drug will ultimately be abused. The effects a drug will have on behavior clearly do not depend solely on static pharmacological properties of the drug. An understanding of those experiential variables which influence the particular effects a drug has on behavior will considerably broaden our knowledge of factors involved in drug abuse.

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