Behavior Maintained under Second-Order Schedules of Intravenous Morphine Injection in Squirrel and Rhesus Monkeys

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Abstract. Under second-order schedules of morphine injection, high rates of responding by squirrel and rhesus monkeys were maintained when morphine was injected intravenously only at the end of each session. Every 30th key-pressing response during a 60-min interval produced a 2-s light; the first 30-response component completed after 60 min produced both the light and intravenous injection of morphine. A mean rate of approximately one response per second was maintained by doses of morphine ranging from 0.75-1.5 mg/kg. A pause in responding after each light presentation was followed by rapid responding until the light was produced again; pauses became shorter as the 60-min interval progressed. When brief light presentations were omitted, but morphine was still injected, response rates decreased and patterns of responding were altered. When saline injections were substituted for morphine injections, but the brief light was still presented, responding decreased markedly within three to five sessions and patterns of responding were altered.

Key words: Morphine — Second-order schedules — Drug-seeking behavior — Self-administration — Squirrel monkeys — Rhesus monkeys

Although behavior of experimental animals can be maintained by response-dependent injections of morphine, rates of responding usually are lower than those maintained by other consequent events. A wide range of morphine doses has been studied under fixed-ratio (FR) schedules of intravenous morphine injection, where each injection follows the occurrence of a constant number of responses (usually less than 30); long pauses in responding usually occur at the start of individual fixed ratios and mean rates of responding seldom exceed 0.09 responses per second [e.g., maximal rates of 0.06 to 0.09 response per second at 0.025 mg/kg/injection of morphine in rhesus monkeys (Hoffmeister and Schlichting, 1972; Hoffmeister and Goldberg, 1973)]. In contrast, when behavior is maintained by such consequent events as presentation of food or termination of a stimulus associated with periodic electric shocks, at response requirements of 50 or less, FR performance is generally characterized by a brief pause at the start of each ratio followed by an abrupt change to a constant high rate of responding until the ratio is completed and mean rates of responding usually exceed one per second (e.g., Ferster and Skinner, 1957; Kelleher and Morse, 1968).

Under FR schedules of intravenous morphine injection, the frequency of injection is directly related to the rate of responding and the experimental subject can produce repeated injections of morphine throughout each session. Since pretreatment with morphine can markedly suppress responding maintained under FR schedules of food presentation (Downs and Woods, 1976; Goldberg et al., 1976b) or of intravenous codeine or cocaine injection (Hoffmeister and Schlichting, 1972; Wilson and Schuster, 1973), the failure to maintain characteristic FR performance under FR schedules of morphine injection often is attributed to the cumulative effects of repeated injections of morphine in suppressing responding. Such effects will persist because of morphine's long duration of action (e.g., Hoffmeister and Schlichting, 1972).

The suppressant effects of morphine on behavior can be minimized by using schedules in which morphine is administered infrequently. In the present experiments, squirrel monkeys and rhesus monkeys were
studied under a second-order schedule in which every 30th response during a 60-min interval produced a 2-s light; the first 30-response FR component completed after 60 min produced several consecutive pairings of the light with an intravenous injection of morphine. Since morphine was injected only at the end of each experimental session, and at least 23 h elapsed before the start of the next session, this second-order schedule allowed a separation of the effects of morphine in maintaining behavior during the session from its other behavioral effects.

METHODS

Subjects and Apparatus

Squirrel Monkeys. Three male squirrel monkeys (*Saimiri sciureus*) weighing 800 to 1100 g were subjects. During anesthesia with mixtures of halothane and oxygen, a polyvinyl chloride catheter (inside diameter 0.38 mm and outside diameter 0.76 mm) was implanted by way of the right or left external jugular vein into the superior vena cava. Surgical procedures, catheters and apparatus were generally similar to those reported by Herd et al. (1969) and Goldberg (1973).

During experimental sessions, monkeys were individually restrained in a Lucite chair by a waist lock. The chair was enclosed in a sound-attenuating isolation chamber (Model AC-3, Industrial Acoustics Co., Bronx, New York). Extrinsic sounds were further masked by continuous white noise. The implanted venous catheter was connected by polyvinyl tubing to a motor-driven syringe located outside the isolation chamber. The syringe was driven by a 1/10-hp a.c. motor which could be energized by automatic programming equipment; the motor was held braked by a small d.c. voltage before and after being energized. Injection duration was approximately 200 ms; volume of each injection was 0.18 ml.

A response key (Lehigh Valley Electronics rat lever, no. 1352) was mounted on a transparent Lucite wall in front of the monkey. When the monkey pressed the key with a force of 0.28 n or more, there was an audible relay click and a response was recorded. Two green and two amber 6-watt bulbs, mounted at eye level behind the transparent Lucite wall, could be illuminated and used as visual stimuli. Between experimental sessions, monkeys were kept in individual home cages and had free access to food and water.

Rhesus Monkeys. Two male rhesus monkeys (*Macaca mulatta*) weighing 4.0 kg and 5.5 kg were used for studies of behavior maintained by morphine injections. The methods were generally similar to those used with squirrel monkeys. The catheter (inside diameter 0.64 mm and outside diameter 1.75 mm) was implanted by way of the right or left internal jugular vein into the superior vena cava. The catheter connections, motor-driven syringe system and injection volume and duration were the same as those used with the squirrel monkey. During experimental sessions, the monkeys were individually restrained in a Lucite chair by a neck and waist lock (Dews and Herd, 1974). The chair was enclosed in a sound-attenuating isolation chamber (Model AC-5, Industrial Acoustics Co., Bronx, New York), and white noise was continuously present. A response key of the same type used with the squirrel monkeys was mounted at eye level on a transparent Lucite panel in front of the monkey. Illumination in the chamber was provided by two red 25-watt bulbs mounted on the transparent Lucite panel above the response key or by a 15-watt white bulb mounted on top of the chair.

Between experimental sessions, monkeys were kept in individual home cages where water was always available and food was available in sufficient amounts (about 60 g/day) to maintain body weights.

One male rhesus monkey (M-681) was used for studies of behavior maintained by food presentation. This monkey lived in a primate cage enclosed in a sound-attenuating chamber. A response key and two 25-watt bulbs (white and red) were mounted on a transparent Lucite panel in the front wall of the cage. The isolation chamber and response key were of the same type used for the rhesus monkeys in the morphine study. Water was always available and the door of the isolation chamber was closed only during experimental sessions. Before the start of the experiment, the monkey's free-feeding weight was 11.5 kg; when food was limited during experiments to approximately 100 g (20 pellets) of Purina Monkey Chow per day, the monkey's weight stabilized at 10 kg.

Procedure

Before the present experiments, the squirrel monkeys had been studied under various schedules of intravenous morphine or cocaine injection; training techniques were generally similar to those described by Goldberg (1973) and Goldberg and Kelleher (1976). In the present experiments, the schedule of drug injection was changed to a second-order fixed-interval (FI) schedule of intravenous morphine injection with fixed-ratio (FR) components. The rhesus monkeys had no drug or experimental history prior to the present experiments. During initial training, a white light went on at the start of each daily session and every nth response (FRn) during a fixed interval of time (FI) changed the light to amber (squirrel monkeys) or red (rhesus monkeys) for 2 s; during brief presentations of the amber or red light, responding had no programmed consequence. The first FR component completed after the FI elapsed turned off the green or white light and produced 5 to 15 consecutive injections of 0.1 or 0.2 mg/kg morphine. After responding was initiated, the number of responses required to produce each light change and morphine injection was raised to 3 or 10 (FR 3 or FR 10). Each daily session ended after approximately 50 injections or 1 h. Once responding was maintained, the schedule was changed to a second-order FI schedule with FR components.

Under the second-order schedules, each squirrel and rhesus monkey was tested once a day, Monday to Friday. A green light (squirrel monkeys) or white light (rhesus monkeys) went on at the start of the session, and every nth response (FRn) during a fixed interval of time (FI) changed the light to amber (squirrel monkeys) or red (rhesus monkeys) for 2 s; during brief presentations of the amber or red light, responding had no programmed consequence. The first FR component completed after the FI elapsed turned off the green or white light and produced 5 to 15 consecutive injections of morphine. With the squirrel monkeys, the FR requirement was increased gradually from 3 or 10 responses to 30 responses. Using the nomenclature of Kelleher (1966a, b), the final second-order schedule can be designated as FI 60 min (FR 30: S) to indicate that there was a brief stimulus change (S) at completion of each FR 30 component. Whenever a morphine injection was raised to 3 or 10 (FR 3 or FR 10). Each daily session ended after approximately 50 injections or 1 h. Once responding was maintained, the schedule was changed to a second-order FI schedule with FR components.

After performance stabilized, the total dose of morphine injected at the end of each session was increased and decreased over a range from 0 (saline) to 6.0 mg/kg. The dose was regulated by varying the concentration of the morphine solution (squirrel and rhesus monkeys) or the number of injections in the series (rhesus monkeys). Each dose of morphine was studied for eight to 16 ses-