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Methohexital and Cocaine Self-Administration Under Fixed-Ratio and Second-Order Schedules

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SPEAR, D J , C MUTANER, S R GOLDBERG AND J L KATZ *Methohexital and cocaine self-administration under fixed-ratio and second-order schedules.* PHARMACOL BIOCHEM BEHAV **38**(2) 411–416, 1991 —Behavior maintained by either cocaine or methohexital was compared under two different schedules of drug delivery Under a fixed-ratio 10 schedule, each tenth response produced an injection and responding was characterized by pauses alternating with high rates that were sustained until the drug injection. Under a second-order schedule, each tenth response produced a brief visual stimulus, and the first sequence of ten responses emitted after the lapse of a ten-minute interval produced the stimulus and the drug injection Responding under the second-order schedule was characterized by an overall positive acceleration in responding that consisted of fixed-ratio response patterns terminating in the presentation of a brief stimulus Under either schedule, each drug maintained maximal rates of responding at intermediate doses. In most respects, rates and patterns of responding depended more on the schedule of drug delivery than on the particular drug maintaining responding.

Methohexital Cocaine Squirrel monkey Self-administration Fixed-ratio schedule Second-order schedule

BARBITURATES and psychomotor stimulants, drugs which are abused by man, have been found to function as reinforcers (i.e., to maintain IV self-administration behavior) in experimental animals (6, 13, 14). Early evidence suggested that there may be differences in the reinforcing effects of these two types of drugs. Comparable response rates were maintained in two groups of subjects (5,6) when each response resulted in an injection of pentobarbital (0.25–1.0 mg/kg/injection) or cocaine (0.015–0.2 mg/kg/injection). However, when the response requirement was increased to ten responses per injection (fixed ratio 10, or FR 10), rates of responding maintained by cocaine increased approximately tenfold, while rates of responding maintained by pentobarbital remained virtually unchanged (6).

Johanson (11), however, found little or no differences in rates of responding maintained by either pentobarbital or cocaine. Under one condition, a fixed-interval (FI) schedule arranged a drug injection (pentobarbital, 0.05–3.0 mg/kg/injections or cocaine, 0.0125–1.0 mg/kg/inj) to follow the first response emitted five minutes since the last injection. Under another condition, each tenth response (FR 10) produced a brief stimulus light and the first FR 10 sequence completed after the lapse of a five-min interval produced both the stimulus light and drug injection [second-order FI 5 min (FR 10:S) schedule]. Response rates under both schedules were dependent on drug dose, and schedule-appropriate response patterning was observed for both schedules and both drugs. Under the FI schedule, a period of no responding followed each injection, with increasing rates of responding as the interval progressed. Under the second-order schedule, each FR 10 sequence occurred at a high sustained rate and was preceded by a short pause in responding. As the interval progressed, the pauses preceding each FR 10 sequence decreased.

The present study was a further examination of the maintenance of behavior by injections of barbiturates or cocaine. Decreases in response rates of self-administration behavior are often observed with frequent injections or high doses of either barbiturates or cocaine (12). Such cumulative drug effects may be unrelated to the reinforcing effects of the drug and may be responsible for the discrepancy between pentobarbital and cocaine observed by Goldberg et al. Methohexital (Brevital), an ultra-short acting barbiturate which has been shown to maintain the behavior of rats, rhesus monkeys, and baboons (1, 3, 4, 13, 15), was the barbiturate selected for study since its short duration of action minimizes cumulative sedative effects when repeated injections occur within the experimental session. Four conditions were studied cocaine and methohexital were both compared under an FR 10 schedule and under an FI 10 (FR 10:S) second-order schedule. The second-order schedule further minimizes cumulative effects of the two drugs by maintaining responding with stimuli that were paired with drug injections that were delivered relatively infrequently (8).

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METHOD

Subjects

Ten male squirrel monkeys (*Saimiri sciurea*) weighing between 0.8 and 0.95 kilograms participated in some phase of the four conditions. Three subjects were used in each condition. Five squirrel monkeys (S-475, S-478, S-61, S-1886, and S-985) were experimentally and drug naive at the beginning of the study. The remaining subjects had histories of either food-maintained or shock-avoidance responding prior to this study. Although these subjects had experience with various drugs delivered IM, no subject had experience with drugs as reinforcing stimuli. One subject, S-080, died before completion of all second-order schedule conditions.

In each monkey, a polyvinyl chloride catheter for IV drug injections was surgically implanted under halothane anesthesia, in either the right or left jugular, femoral, or illiac vein and passed subcutaneously to the monkey's back where it exited the skin Surgical procedures are described more completely by Herd, Morse, Kelleher and Jones (10) Subjects wore nylon mesh jackets at all times to protect the catheters. Each weekday the catheters were flushed, refilled with saline (0.9% NaCl) and sealed with stainless steel obturators. When not in the experimental chamber, subjects were housed in individual stainless steel cages with free access to water. Subjects were fed enough Purina Monkey Chow at the end of each day to maintain them at 95–100% of their unrestricted feeding weights

Apparatus

During experimental sessions subjects sat in a Plexiglas chair, restrained in the seated position by a waist lock (9). The chair was enclosed in a sound-attenuating isolation chamber (Model AC-3, Industrial Acoustics Co , Bronx, NY). Extraneous sound was masked by white noise. A response lever (No 121-05, BRS/LVE Corp , Laurel, MD) was mounted on a transparent wall in front of the monkey Lever presses of a force greater than 15 g produced an audible click of a relay and were recorded as responses. Pairs of green, amber and red 6-watt bulbs, mounted at eye level behind the transparent wall, could be illuminated and used as visual stimuli. The catheter was connected to polyethylene tubing which passed out the bottom of the subject's jacket and out of the isolation chamber where it was attached to a motor-driven syringe The syringe was driven by a 110-V AC motor energized by automatic programming equipment and before and after being energized was held braked by a small DC voltage. Injection duration was approximately 200 ms at a volume of 0.18 ml. Experimental cubicles were connected to electromechanical and computer programming and recording equipment in a separate room.

Procedure

Experimental sessions were conducted Monday through Friday. Initially, during the illumination of green stimulus lamps, cocaine injections (12, 50, or 100 μg/kg/injection) were delivered response independently once per minute Each injection was accompanied by a two-s amber light. During subsequent sessions the green stimulus lights were illuminated and each lever-press response resulted in an IV injection of cocaine and a 2-s illumination of the amber lights Once responding was stable, each injection was followed by a 5-s timeout period during which the chamber was dark and lever presses had no scheduled consequences. The number of responses required to produce each injection and the length of the timeout period were increased over several sessions until responding was maintained under an FR 10 schedule with a one-minute timeout period following each injection

FR 10. When responding was stable, methohexital was substituted for cocaine for three squirrel monkeys (S-475, S-478, and S-61). Responding of three other subjects (S-985, S-280, and S-1886) was maintained under the FR 10 schedule with cocaine Based on previous studies of IV self-administration with frequent injections during the session (14,15), methohexital doses of 25, 50, 100, 200, and 400 μg/kg/inj and cocaine doses of 3, 6, 12, 25, 50, and 100 μg/kg/inj were chosen for study Drug dose was varied with each dose studied for 10 to 15 sessions. Response rates at a particular dose were occasionally determined more than once with redeterminations in effect for at least 3 sessions. Visual inspection of the data showed no consistent trends at this time On a few occasions stability could not be reached within 15 sessions and additional exposure was necessary. This occurred most frequently in drug-naive subjects under saline conditions. Experimental sessions lasted 100 minutes. Although number of injections varied across subjects, between 30 injections (saline and lowest/highest doses) and 70 injections (medium doses) occurred per session. A similar number of injections occurred under both drugs

Second-order. After responding stabilized for the remaining subjects, the schedule was changed to a second-order schedule Under the second-order schedule, green stimulus lamps were illuminated and each FR 10 response sequence completed during a ten-minute interval produced a two-s illumination of the amber lights The first FR sequence completed after lapse of the ten-minute interval produced the two-s amber light and drug injection. A one-min timeout period followed each injection. For three squirrel monkeys (S-782, S-482, and S-984) responding was maintained by cocaine injections (10, 30, 100, and 300 μg/kg/inj), while for the remaining squirrel monkey, S-080, responding was maintained by methohexital injections (300, 600, 1000, and 1800 μg/kg/inj). Intermediate cocaine doses of 56 and 180 μg/kg/inj were studied for S-782 in an attempt to define details of the unusually flat dose-effect curve The same doses of methohexital were studied with subjects S-782 and S-482 after completion of studies with cocaine. Drug doses were chosen as comparable to effective doses in previous studies with equally spaced injections (7, 13, 15) Each dose of each drug was studied for 10 to 15 sessions with redeterminations in effect for at least 3 sessions As under the FR schedule, there were occasions when stability could not be reached within 15 sessions and additional exposure was necessary. This occurred only for S-984 under two saline determinations, however. All sessions ended after 10 injections were delivered (a minimum length of 110 minutes) or the lapse of 2 5 hours.

The effects of the brief stimuli paired with injections were studied at each drug dose The effectiveness of these stimuli in maintaining responding was assessed by eliminating all but the stimuli that accompanied the injection Once performances stabilized, the brief stimuli were reintroduced For most drug doses, response rates were determined more than once for conditions under the second-order schedule

Analysis of Results

Mean response rates were computed for each session by dividing total responses in the presence of the green lights by the total time the green lights were present (that is, time excluding brief stimulus presentations and timeouts) Mean response rates during timeout periods were computed by dividing total responses occurring during timeout periods in each session by total time occupied by timeout periods When response rates at a particular dose were determined more than once, all determinations were averaged.

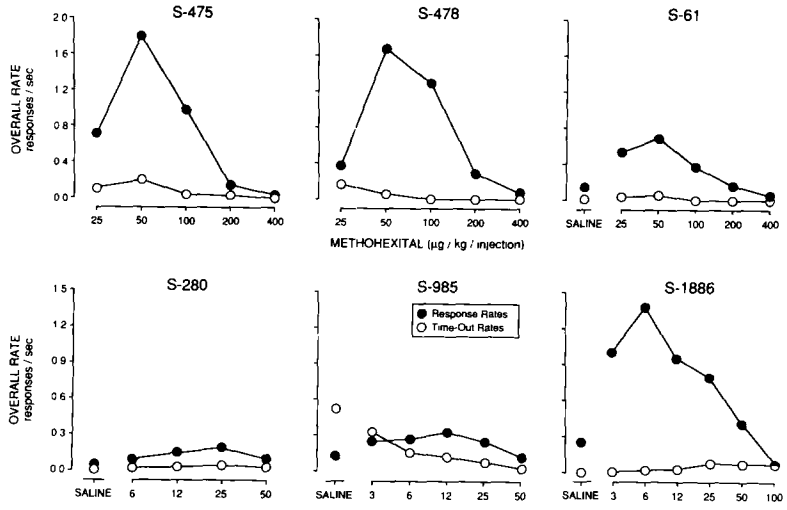

FIG. 1 Mean response rates during the last three days for individual subjects at each dose studied under the FR 10 schedule Top row of panels shows response rates for methohexital-maintained responding, bottom row of panels shows response rates for cocaine-maintained responding Filled symbols show rates when the stimulus light was green, open symbols show rates during timeout periods Note that the y-axis scale is different for methohexital- and cocaine-maintained responding

Drugs

Cocaine hydrochloride and methohexital sodium were dissolved and diluted with 0.9% saline solutions. Doses per injection are expressed as µg of the salt forms of the drugs per kg body weight of the subject

RESULTS

Mean overall rates of methohexital-maintained responding under the FR 10 schedule for each subject are shown in the top panels of Fig. 1 for all doses of methohexital studied Filled circles show rates of FR responding when the green light was on and responses could produce methohexital. Open circles show that typically very little responding occurred during timeout periods. As the dose per injection was increased, mean response rate first increased and then decreased. At the higher doses, a general anesthesia was observed during timeout periods The highest mean rate of lever pressing for all subjects was maintained at 50 µg/kg/inj of methohexital.

The bottom panels of Fig. 1 show mean overall response rates for cocaine-maintained responding as a function of dose. For all subjects responding first increased as dose was increased, with further increases in dose producing a decrease in mean response rate This dose-rate function was, however, much flatter for S-280 and S-985 than for S-1886. The cocaine dose which maintained the highest mean response rate was different for each subject (6, 12, or 25 µg/kg/inj for S-1886, S-985, and S-280, respectively). Saline injections maintained low mean response rates for S-985 and S-1886, and the lowest mean rates of responding for S-280. For S-985 relatively high rates during the timeout period were consistently maintained across multiple determinations with saline injections For the other subjects, cocaine injections generally maintained higher mean rates of responding during the green stimulus light than during timeout periods.

Figure 2 shows the patterns of responding of S-61 at three methohexital doses (25, 50, and 200 µg/kg/inj) as well as saline.

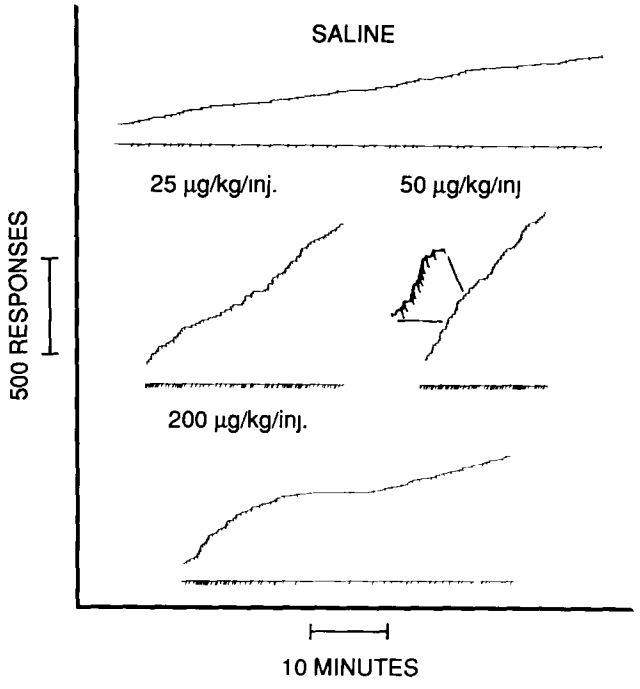

FIG 2 Sample cumulative records for saline and selected doses of methohexital injections (25, 50, and 200 µg/kg/inj) for S-61 under the FR 10 schedule The saline record shows the entire session, while the other records are from the first half of the session The paper advanced at a constant speed throughout the session but did not operate during timeout periods The upper response pen incremented with each lever press Drug injections are noted by downward deflections of the response pen and the lower event pen. The inset at 50 µg/kg/inj shows the indicated enlarged portion of the record

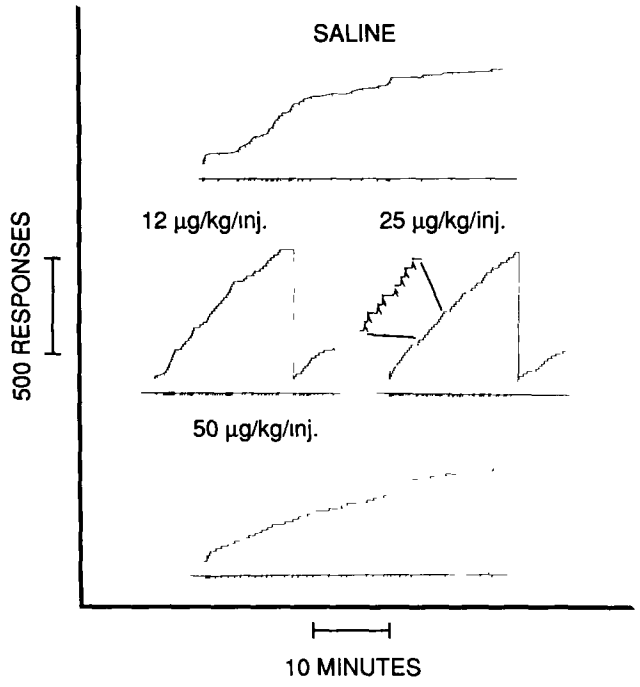

FIG 3 Sample cumulative records for saline and selected doses of cocaine injections (12, 25, and 50 µg/kg/inj) for S-280 under the FR 10 schedule The saline and 50 µg/kg/inj cocaine records show the entire session, records of 12 and 25 µg/kg/inj cocaine are from the first half of the session. The paper advanced at a constant speed throughout the session except the recorder did not operate during timeout periods The upper response pen incremented with each lever press Drug injections are noted by downward deflections of the response pen and the lower event pen. The inset at 25 µg/kg/inj shows the indicated enlarged portion of the record Pens were reset when the top of the paper was reached

The selected records are typical of responding for this subject under these conditions and are generally similar to the other subjects under comparable conditions. Saline injections resulted in erratic responding at a much lower rate than drug-maintained responding with no consistent FR response pattern. As methohexital dose was increased from 25 to 50 µg/kg/inj, overall response rate increased largely due to decreases in the duration of pause times. At these lower doses, responding was maintained at a fairly constant rate throughout the session, resulting in stable injection rates. Responding showed characteristic FR response patterns, a brief pause after each injection was followed by a high, steady rate of responding. This patterning can be seen clearly in the enlargement of responding at 50 µg/kg/inj. At 200 µg/kg/inj of methohexital, response rates and number of injections were high at the beginning of the session, but usually showed a marked decrease about halfway through the session.

Representative cumulative records for S-280 under the FR 10 schedule of cocaine self-administration are shown in Fig. 3. These records are typical of S-280 and all other subjects under similar conditions. When responses produced saline injections, rates of responding were not maintained consistently across the session and the FR response pattern was not usually observed. At low cocaine doses, fairly stable rates were maintained throughout the session. Increasing cocaine dose from 12 to 25 µg/kg/inj resulted in decreasing the length of the pause and thus increasing overall response rate. As with methohexital, the typical FR pattern of responding was observed with cocaine injections. The enlargement of responding at 25 µg/kg/inj shows the distinct FR response patterning. A further increase in dose to 50 µg/kg/inj produced lower overall response rates as a result of increases in pause times.

Mean response rates for individual subjects under the second-order schedule of methohexital injections are shown in the top panels of Fig. 4. Filled circles represent responding during sessions with brief stimulus presentations; open circles represent response rates for sessions without brief stimulus presentations. Methohexital injections during conditions with the brief stimulus

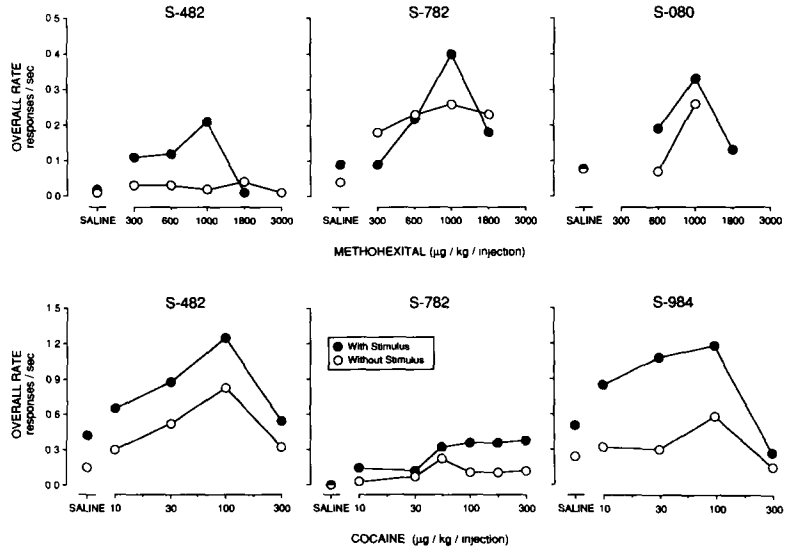

FIG 4 Mean response rates during the last three days for individual subjects at each dose studied under the second-order schedule. Top row of panels shows response rates for methohexital-maintained responding, bottom row of panels shows response rates for cocaine-maintained responding Filled symbols show rates when the brief stimulus followed each FR 10 completion, open symbols show rates when the brief stimulus was omitted Note that the y-axis scale is different for methohexital- and cocaine-maintained responding

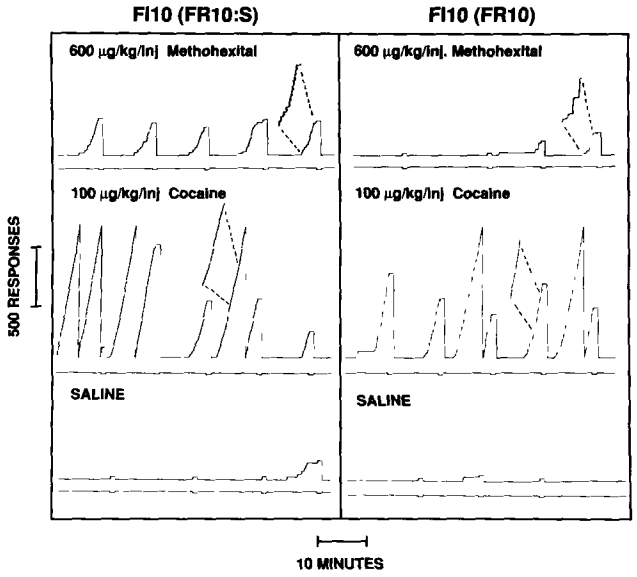

FIG 5 Sample cumulative records for 600 µg/kg/inj methohexital, 100 µg/kg/inj cocaine and saline under the second-order schedule for S-482 All records are from the middle to last half of the session The left column shows records from sessions when the brief stimulus followed each FR 10 completion, the right column shows records from sessions when the brief stimulus was omitted The upper response pen incremented with each lever press Brief stimulus presentations are marked by downward deflections of the response pen and drug injections are marked by downward deflections of the lower event pen and resetting of the response pen Pens were also reset when the top of the paper was reached The paper advanced at a constant speed throughout the session and continued to advance during the timeout periods, however, responses did not operate the pens The insets show the indicated enlarged portion of the record

present maintained higher mean response rates than did saline, except at 300 µg/kg/inj for S-782, the lowest dose tested for this subject, and for S-482 at 1800 µg/kg/inj, the highest dose tested for this subject. Mean response rates with brief stimulus presentations first increased and then decreased as methohexital dose was increased. For all subjects, 1000 µg/kg/inj of methohexital maintained the highest mean response rate for conditions with brief stimulus presentations Mean response rates during conditions without brief stimulus presentations were most often lower than response rates maintained when the brief stimulus was presented. For two of the three subjects, the slopes of the dose-effect curves were less pronounced when brief stimulus presentations were omitted.

Figure 5 shows sample cumulative records for S-482 under the second-order schedule for saline and drug doses which maintained peak response rates. The left column of records are from conditions when the brief stimulus followed completion of each FR 10, while the right column shows records when the brief stimulus was omitted from all but the response unit followed by drug injection. The records shown are characteristic of this subject under similar conditions, and consistent with records of responding of the other subjects Under the second-order schedule with brief stimulus presentations, methohexital maintained patterns of responding characteristic of this schedule. Specifically, between presentations of brief stimuli, there was a short pause followed by a steady rate of responding characteristic of the FR schedule. Additionally, a pause occurred after each injection with increasing rates of responding as the interval progressed. The increases in overall rates of responding were often the result of decreases in the pauses that preceded emission of each ten-response sequence that produced a brief stimulus This pattern is highlighted in the enlarged inset at 600 µg/kg/inj in Fig. 5. With methohexital doses other than 600 µg/kg/inj, pauses at the beginning of the 10-min fixed interval and at the beginning of the FR schedule unit were generally longer than those observed at 600 µg/kg/inj of methohexital. When the brief stimulus was omitted, the pattern of responding was disrupted. Lower overall rates of responding were characterized by longer pauses interrupting sequences of greater than ten responses as seen in the inset on the right. When saline was substituted for drug there was little responding.

The lower panels of Fig. 4 show mean response rates for individual subjects under second-order schedules of cocaine injections. Higher response rates were maintained by cocaine than saline regardless of whether the brief stimulus was presented. Mean response rates of S-482 and S-984 showed inverted U-shaped dose-effect curves during sessions with brief stimulus presentations. The inverted U-shape of the dose-effect curve was less pronounced for sessions without the brief stimulus for S-782 and S-984. Peak response rates for subjects S-482 and S-984 were maintained at 100 µg/kg/inj, independently of brief stimulus presentation. For subject S-782, mean response rates under the second-order schedule with brief stimuli generally increased with increasing cocaine dose When brief stimuli were removed, only 56 µg/kg/inj maintained response rates appreciably greater than those maintained by saline.

Sample cumulative records for S-482 under the second-order schedule of cocaine injections which maintained peak response rates are shown in Fig. 5 During sessions of 100 µg/kg/inj of cocaine, the second-order response pattern was evident, as exemplified with the records shown At other cocaine doses (both higher and lower doses), pause times at the beginning of the fixed interval increased, although the response patterns were usually preserved. Pauses after brief stimulus presentations generally decreased as dose was increased. Omitting the brief stimulus generally lowered mean response rates and altered the pattern of responding, although running response rates were often similar to comparable brief stimulus conditions, as shown in the enlarged insets.

DISCUSSION

The present results demonstrate that high response rates and patterns characteristic of FR and second-order schedules can be maintained by intravenous injections of methohexital in squirrel monkeys and that those performances were similar to behavior maintained by cocaine. Under the FR 10 schedule a short pause with no responding occurred after an injection of either drug followed by a high, steady rate of responding. Even at higher drug doses where rate-decreasing drug effects might be expected (12), the integrity of the FR pattern was maintained, although the pause length tended to increase. The typical FR pattern was conspicuously absent when saline was substituted for either drug, with responding occurring at low rates and at irregular intervals. Under the second-order FI 10 (FR 10:S) schedule, consistent response patterns were maintained. The FR schedule of brief stimulus presentations maintained periods of no responding alternating with high rates of responding. Overall response rates increased as the interval progressed, primarily due to the gradually decreasing pauses which preceded each sequence of ten responses. Pauses during the FR unit of the second-order schedule were most evident at intermediate and lower drug doses. When saline was substituted for drug, these patterns of responding were disrupted

Methohexital- and cocaine-maintained responding showed marked stimulus control For both drugs, response rates were neg-

ligible during timeout periods when injections were not available. Under the second-order schedule high rates of behavior were maintained for an extended period of time in the absence of drug delivery by presenting a brief stimulus previously paired with drug delivery dependent on ten responses. Removal of this stimulus produced a decrease in responding even though drug was still available at the same intervals. When the stimulus no longer occurred after each sequence of ten responses, responding was still characterized by an alternation of high rates and pauses with high rates often being maintained for sequences of greater than ten responses. The increases in responding as the interval progressed were generally maintained with the brief stimulus removal.

Response rates under the FR and second-order schedules were dependent on drug dose and decreased markedly when saline was substituted for drug. Response rates were generally an inverted U-shaped function of drug dose. This relationship was observed for both the FR and the second-order schedule with methohexital or cocaine injections. Response patterning was also dependent on drug dose in that the length of pause times was altered with drug dose. With respect to these important qualitative aspects of schedule-maintained behavior, patterns of responding maintained by these two drugs and by stimuli associated with these two drugs were similar. Quantitatively, it may be misleading to compare overall rates of responding across either drugs or schedules since only S-482 and S-782 participated in both drug conditions and only under the second-order schedule. In addition, the variability in response rates across subjects for a particular drug makes it difficult to compare rate differences across drugs. Thus the present studies offer no significant evidence of differences in the effects of these drugs in maintaining schedule-controlled responding.

Goldberg et al. (6) suggested that pentobarbital and cocaine may not be equally effective as reinforcers when drug injections occurred at a high rate under FR schedules. Johanson (11) reduced possible rate decreasing effects by limiting the frequency of drug availability with FI schedules while maintaining identical response requirements as Goldberg et al. (i.e., either 1 response or 10 responses were required). The similarity in response rates across drugs under Johanson's conditions suggests that the higher frequency of pentobarbitial injections may be responsible for the lack of a rate increase seen by Goldberg et al. That is, the high rate of pentobarbital delivery may have decreased response rates independently of any reinforcing effects of the drug. The present study supports such an interpretation in that no differences were found in cocaine and barbiturate-maintained responding when rate-decreasing drug effects were attenuated by use of the ultrashort acting barbiturate, methohexital. Injections could occur as frequently as once every minute under the present FR 10 schedule or once every 11 minutes under the second-order schedule, yet responding was similar across drugs. An analogous interpretation was offered by Ator and Griffiths (2) when frequency of barbiturate was limited by imposing a 3-hour timeout between availability of injections of pentobarbital, amobarbital, secobarbital or cocaine under an FR 160 schedule. Thus the ability of a drug to maintain a high rate of self-administration behavior depends not only on its effectiveness as a reinforcer, but also on the duration of action of the drug and the frequency of availability.

The dependence of response patterning on the schedule of reinforcement observed here for two very different types of drugs stresses the importance of the schedule of drug availability as a powerful determinant of drug-taking behavior independently of the pharmacological action of the drug. This is evidenced in that response patterning consistently reflected type of schedule whether the available drug was methohexital or cocaine. Additionally, the ability of stimuli associated with drugs to maintain long sequences of drug-related behavior which could not be consistently maintained under comparable conditions without the stimulus reiterates that drug-related behavior is strongly dependent on environmental context.

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