FIXED-INTERVAL SCHEDULES OF INTRAVENOUS COCAINE PRESENTATION IN RATS¹

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Fixed-interval schedules of intravenous cocaine presentation were examined as a function of injection dose (0.32 to 0.64 mg/kg) and interval duration (200 to 400 sec) in two rats. Cocaine was found to exert a dose-related temporal control over the initiation of responding that was unaffected by the fixed-interval contingency. Fixed-interval pause duration was linearly related to injection dose and was the same duration as the interresponse time found on continuous reinforcement schedules of cocaine presentation. The fixed-interval pause remained constant with changes in interval duration. Characteristic fixed-interval patterns of responding were observed. However, overall response rates were inversely related to injection dose and directly related to interval duration. Running response rates varied unsystematically with both variables. These findings are at variance with results typically found in studies of fixed-interval food and electric shock presentation.

On fixed-interval (FI) schedules of food and electric shock presentation, running rate and overall response rate are directly related to reinforcement magnitude and frequency (Skinner, 1938; Wilson, 1954; Stebbins, Mead, and Martin, 1959; McKearney, 1969; Catania and Reynolds, 1968; Schneider, 1969). The characteristic pause early in the fixed interval also increases with increases in interval duration (Shull, 1971; Innis and Staddon, 1971).

A recent investigation of FI schedules of intravenous cocaine presentation in the rhesus monkey found overall response rate directly related to reinforcement frequency, but inversely related to the magnitude of the drug injection dose (Pickens and Thompson, 1972). The present investigation further analyzed the controlling relationship between response rate and injection dose on FI schedules of cocaine presentation in the rat.

METHOD

Subjects

Two male Sprague-Dawley (Holtzman) albino rats, approximately 150 days old at the beginning of the experiment, were maintained in constant illumination at 24° Centigrade, and had continuous access to Purina Lab Chow and water.

Apparatus

The subjects were surgically prepared with chronic intravenous cannulas, placed in individual Gerbrands Model C rat chambers, and connected to a remote infusion pump via a flexible harness and tubing system (Pickens and Dougherty, 1972). Two Gerbrands rat levers were mounted on one wall of each chamber, with a small stimulus light located above and between the levers. Responses on one lever activated the infusion pump and delivered an intravenous injection of a predetermined volume of drug solution. The stimulus light was illuminated for the duration of the injection. Responses on the other lever had no scheduled consequence, but were recorded along with drug-lever responses on cumulative recorders and digital counters.

The rat chambers and flexible harness systems were located within ventilated, sound-attenuating enclosures. All experimental

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events were controlled by electromechanical programming equipment located in an adjoining room. White noise (65 dB) was present in the experimental room at all times.

Procedure

After cannulation, the subjects were housed in the rat chambers for the duration of the study. At least three days were allowed for recovery from surgery. Except during periods of cocaine availability, hourly non-contingent injections of 0.5 ml saline were given to prevent blood clotting in the cannula. To allow the rats to recover body weight lost during drug sessions, cocaine access in all cases was limited to sessions of approximately 12 hr in duration, scheduled three to four days apart. Initially, cocaine hydrochloride (0.32 to 1.28 mg/kg/injection, as the salt) was available on a continuous reinforcement (CRF) schedule for three sessions. During this time, the characteristic pattern of cocaine responding developed, consisting of single drug responses separated by relatively long, uniform intervals of time (Pickens and Thompson, 1968). Both animals were then trained for two sessions on response-initiated FI schedules (Mechner, Guevrekian, and Mechner, 1963), with FI values of 40 to 240 sec at injection doses of 0.32 to 1.28 mg/kg, before the start of the present experiment. Because of the short life of the cannula (4 to 6 weeks), the experiment was carried out in six drug sessions over 20 to 25 days.

In determining the effects of interval duration on drug-maintained behavior, cocaine was available on a CRF schedule, at 0.64 mg/kg/injection, during the first hour of each session and on a fixed-interval schedule thereafter. The lowest FI duration was selected to equal the mean IRT (interresponse time) of CRF cocaine presentation during the first hour of each session. During this time, the mean IRT for Rat T-21 was approximately 200 sec, and for Rat T-22 approximately 240 sec. The FI durations selected for each animal were 200, 300, and 400 sec, and 240, 360, and 480 sec, respectively. Each interval duration was tested for approximately 20 reinforcements, with two sessions in ascending (low, middle, high) and two sessions in descending order (see Table I).

The effect of injection dose on FI cocaine presentation (0.32, 0.48, 0.64 mg/kg) was studied during two experimental sessions. Fixed-

Table 1
Summary of Procedures

Session No.	Rat T-21	Rat T-22
1	FI 200-400	FI 240-480
2	FI 400-200	FI 480-240
3	Dose 0.32-0.64	Dose 0.64-0.32
4	Dose 0.64-0.32	Dose 0.32-0.64
5	FI 400-200	FI 480-240
6	FI 200-400	FI 240-480

interval durations were 300 sec for Rat T-21, and 360 sec for Rat T-22. Blocks of 20 reinforcements were allowed at each injection dose during each session, with the session beginning and ending with a 1-hr period of CRF cocaine presentation. Doses were studied in ascending order in one session, and in descending order in the other. The injection dose was manipulated by changing the volume and the duration of the injection, holding the concentration of the drug solution constant. The injection dose of 0.32 mg/kg was delivered in 12.5 sec (0.25 ml); 0.48 mg/kg in 18.75 sec (0.38 ml); and 0.64 mg/kg in 25 sec (0.5 ml). The interval was timed from the end of the previous injection. The injection time was excluded from all data analyses, as were any responses that occurred during the injection. After each drug session, the response levers were immobilized.

Four measures of FI performance were used: mean post-reinforcement pause, mean overall response rate, mean running response rate, and index of curvature. The post-reinforcement pause was the interval between the end of the drug injection and the first response of the next interval. The mean overall response rate was computed by dividing the mean number of responses per interval (including the reinforced response) at each dose level by the interval duration. The mean running rate was the rate of responding between the first response in the interval and the onset of the drug injection. It was calculated by dividing the mean number of responses per interval by the difference between the interval duration and the mean post-reinforcement pause. The index of curvature is a measure of the temporal distribution of responses within the interval and is relatively independent of response rate (Fry, Kelleher, and Cook, 1960). In computing the index, the fixed-interval was divided into four quarters and the number of responses

Fig. 1. Cumulative records of fixed-interval responding in Rats T-21 and T-22, at each injection dose and FI duration. Offset of event pen indicates drug injections. Drug-lever responses are on stepper pen, which resets at the beginning and end of the drug injection. The fixed-interval is timed from the end of the injection.

recorded separately for each quarter. The responses in each quarter were then cumulated over each block of 20 fixed-intervals allowed at each dose and interval duration. The computation was performed on these summed quarterly response totals, giving an averaged index of curvature. If responses were equally distributed throughout the four quarters of the interval, the index would be zero. If all responses occurred during the last quarter, the index would be 0.75, the highest possible value when an interval has been divided into quarters.

RESULTS

Figure 1 shows representative cumulative records of FI cocaine responding for both rats at each interval duration and injection dose. The performance was similar to FI responding maintained by other reinforcers, except that the overall response rate was lower. The pattern of responding included a long pause after each injection. This was immediately apparent when both rats were first shifted from the CRF to the FI contingency, and was present across abrupt changes in interval duration. The pause was followed by a low to moderate response rate until the next drug presentation. A high response rate often occurred during the injection, but responding usually stopped before the end of the injection. At times, responding was relatively consistent, and at other times contained breaks and knees.

The total number of drug and control lever responses across all sessions was 2817 and 30, respectively for Rat T-21, and 4026 and 758, respectively, for Rat T-22. Control lever responding occurred just before onset of the injection.

Figure 2 shows the relationship between injection dose and four measures of performance: mean post-reinforcement pause, mean overall response rate, mean running response rate, and index of curvature. The duration of the post-reinforcement pause was a direct, linear function of injection dose, regardless of whether the doses were presented in ascending or descending order. At the beginning of each session, cocaine was presented on a CRF schedule for 1 hr before the FI contingency was imposed. The mean IRT from the first hour is indicated by "C" on the horizontal axis of the graph. The filled circle is the 0.32

mg/kg CRF IRT, and the open circle is the 0.64 mg/kg CRF IRT. After the shift to the interval schedule, the 0.32 and 0.64 mg/kg post-reinforcement pause durations closely approximated the corresponding CRF IRTs.

As the injection dose was increased, overall response rate decreased for both rats, despite no change in the running rate for Rat T-21 and an increase in running rate for Rat T-22. The index of curvature was found to increase with increases in injection dose, indicating that at higher doses the bulk of responding shifted to later quarters of the interval.

Figure 3 summarizes the effects of fixed-interval duration on mean post-reinforcement pause, mean overall and running rates, and index of curvature. With increases in interval duration, the post-reinforcement pause remained constant for Rat T-21 and increased moderately for Rat T-22. For Rat T-21, the post-reinforcement pause time closely approximated the 0.64 mg/kg/injection CRF IRT (indicated by "C" on the horizontal axis) for each individual session. The intersession variability of the post-reinforcement pause appeared to result from session-to-session shifts in the intake rate of cocaine as indicated by changes in the CRF IRT baseline. For Rat T-22, the relationship between the post-reinforcement pause and the CRF IRT was less clear.

Overall response rate increased with increases in interval duration. The change in overall rate was smaller for Rat T-22 than for Rat T-21. The running rate showed no consistent relationship to interval duration or to overall response rate. The overall response rate increased in at least three of the sessions for both rats, despite a decreasing or stable running rate. The running rate could not be computed where the mean post-reinforcement pause time equalled or exceeded the mean interval duration, *i.e.*, where many intervals contained only one response. The index of curvature was inversely related to interval duration, with changes for Rat T-22 again being smaller than for Rat T-21.

DISCUSSION

The post-reinforcement pause in fixed-interval schedules of cocaine presentation was relatively insensitive to changes in interval duration, but varied directly with injection dose.

Fig. 2. Effects of injection dose on post-reinforcement pause, overall response rate, running rate, and index of curvature for both rats. Solid line is for session in which doses were given in ascending order; dashed line is for descending session. In the post-reinforcement pause graphs, the unattached points (indicated by C on horizontal axis) are the mean CRF IRTs determined during the first hour for each session. The filled point is for the first hour of ascending session, and the open point for the first hour of descending session.

Fig. 3. Effects of fixed-interval duration on post-reinforcement pause, overall response rate, running rate, and index of curvature for both rats. Solid lines are for sessions in which blocks of FI durations were given in ascending order; dashed lines are for descending sessions. Sequence of sessions was: filled points, solid line; filled points, dashed line; open points, dashed line; open points, solid line. In the post-reinforcement pause graphs, the unattached points (indicated by C on the horizontal axis) are the mean CRF IRTs determined during the first hour of each session. The mean running rates could not be computed in some instances when the mean post-reinforcement pause exceeded the nominal FI duration. See text for further explanation.

As a result, overall response rates were inversely related to injection dose and directly related to interval duration.

When injection dose was increased, responding occurred over a smaller portion of the fixed interval, therefore reducing overall response rate even when running rate increased. Because responding began in later quarters of the interval, the index of curvature increased with increases in injection dose.

When interval duration was increased, however, the post-reinforcement pause remained relatively stable. This resulted in higher overall response rates in longer intervals, despite the decreased reinforcement frequency. Because the post-reinforcement pause tended to remain the same, responses were distributed over a relatively greater portion of the longer intervals, thereby increasing the overall number of responses per minute, even though running rates decreased or remained unchanged. Since responding also began in earlier quarters of the longer intervals, the index of curvature was decreased.

The post-reinforcement pause on the FI cocaine schedule (Figure 2) was almost identical to the CRF IRT for the two comparison injection doses. In addition, the post-reinforcement pause did not vary with interval duration (Figure 3), but tended to remain constant at a value approximating the CRF IRT determined at the beginning of each session. These results indicate that the control by drug dose over pausing remained intact and was not modified by the interval contingency. This contrasts with previous studies of FI schedules of food presentation in which pause time has been found to increase linearly with interval duration, ranging from one-third to two-thirds of the interval duration (Innis and Staddon, 1971; Shull, 1971; Schneider, 1969). That overall cocaine response rate increased with interval duration also contrasts with FI food and electric shock studies, which have generally found overall response rate to vary inversely with interval duration (McKearney, 1969; Schneider, 1969; Skinner, 1938; Wilson, 1954), although one study found no systematic relationship between the two variables (Catania and Reynolds, 1968).

While consistent results were found with both animals in the present study, individual differences were also noted. The change in overall rate and index of curvature with

changes in FI duration for Rat T-22 was smaller than for Rat T-21 (Figure 3). This was because the post-reinforcement pause increased slightly with increases in FI duration, therefore tending to attenuate increases in overall response rate and decreases in the index of curvature. Running rate varied unsystematically with interval duration for both rats. While running rate increased with injection dose for Rat T-22, there was no apparent change for Rat T-21.

Pickens and Thompson (1972) found that overall response rate on FI 30-min and FI 60-min schedules of cocaine presentation in monkeys decreased when injection dose was increased over a 0.5 to 1.5 mg/kg range. The present finding of an inverse relationship between overall response rate and injection dose in rats at smaller FI durations therefore extends the generality of this cocaine effect.

Although overall response rate in FI schedules of food, sucrose, or electric shock presentation has generally been directly related to the amount presented (Hutt, 1954; Stebbins, Mead, and Martin, 1959; McKearney, 1969), inverse relationships similar to that found with cocaine have also been observed. Collier and Willis (1961) demonstrated that under some conditions, overall FI response rate in rats varied inversely with sucrose concentration and volume. Staddon (1970) found overall and running rates of key pecking to decrease with increases in duration of access to grain. Pickens, Bloom, and Thompson (1969) also found that response rate and frequency of reinforcement were inversely related to the number of 1-g banana pellets delivered per reinforcement on a continuous access CRF schedule in rhesus monkeys. Similar relationships have also been found with electrical brain stimulation and heat used as reinforcers (Reynolds, 1958; Weiss and Laties, 1960).

The dose-related control over FI post-injection pause was responsible for the inverse relationship between response rate and injection dose of cocaine in the present study. Staddon (1970) has also implicated increases in FI post-reinforcement pause duration resulting from increases in duration of access to grain as contributing to declining overall response rates. Hatten and Shull (1972) have also observed direct correlations between feeder duration and FI post-reinforcement pause under some conditions.

The inverse relationship between response rate and injection dose indicates that simple response rate measures that neglect the temporal pattern of responding may be inappropriate for assessing the degree to which a given drug dose will support behavior. Using large fixed-intervals (30, 60, and 90 min) in monkeys, however, Pickens and Thompson (1972) found the typical direct relationship between overall response rate and reinforcement frequency. Balster and Schuster (personal communication) used an FI 9-min schedule with a 3-min limited hold contingency and a long timeout (15 min) after each cocaine injection in monkeys. They found overall response rate to increase with increases in injection dose. Both findings suggest that if drug effects on pausing are controlled, or if pausing is short relative to the duration of the behavior maintained by each injection, then overall rate may be a valid measure of the response-strengthening properties of the drug. By the use of non-rate measures, such as choice (Catania, 1970; Johanson, 1971), however, the difficulty may be avoided entirely.

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