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Effects of Phencyclidine, *d*-Amphetamine and Pentobarbital on Schedule-Controlled Behavior in Rats[1]

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SEGAL, S. A., J. M. MOERSCHBAECHER AND D. M. THOMPSON. *Effects of phencyclidine, d-amphetamine and pentobarbital on schedule-controlled behavior in rats.* PHARMAC. BIOCHEM. BEHAV. **15**(5) 807–812, 1981.—The effects of phencyclidine, *d*-amphetamine, and pentobarbital on responding maintained under a multiple fixed-interval (FI) 3-min fixed-ratio (FR) 30 schedule of food presentation were studied in rats. Phencyclidine (0.32–7.5 mg/kg) had a biphasic effect on overall response rate in both components; response rate increased and then decreased as the dose was increased. The FR was slightly more sensitive to the rate-decreasing effects of phencyclidine than the FI. The effects of *d*-amphetamine (0.1–7.5 mg/kg) on overall response rate were qualitatively similar to those of phencyclidine. The FI tended to be slightly more sensitive than the FR to the rate-increasing effects of *d*-amphetamine. Pentobarbital (1–18 mg/kg) produced little or no rate-increasing effects in the FR at low doses and decreased FR response rate at higher doses. In the FI, pentobarbital produced small increases in overall rate at intermediate doses while decreasing response rate at higher doses. The FR tended to be more sensitive than the FI to the rate-decreasing effects of pentobarbital. Unlike *d*-amphetamine and pentobarbital, phencyclidine produced smaller rate-increasing effects when the dose-effect curves were redetermined. Within the FI, the effects of phencyclidine and *d*-amphetamine on response rate were generally independent of the control rate of responding.

Multiple schedule Fixed ratio Fixed interval Phencyclidine *d*-Amphetamine Pentobarbital
Rate-dependency analyses Lever press Rats

PHENCYCLIDINE has been reported to produce both increases and decreases in schedule-controlled responding in rodents. For example, in mice responding under a multiple fixed-interval (FI) 300-sec fixed-ratio (FR) 30 schedule of milk presentation, Wenger and Dews [17] found that phencyclidine had a biphasic effect on the overall response rate in the FI component. Low doses (1 and 3 mg/kg) increased while high doses (10, 18 and 30 mg/kg) decreased the rate of responding. Wenger and Dews [17] also found that phencyclidine produced rate-dependent effects on local response rates within the FI component. Low rates occurring early in the interval were increased while high terminal rates were decreased. In the FR component of the multiple schedule, phencyclidine was reported to decrease the overall rate of responding in a monotonic dose-related manner. The decrease in FR responding occurred at doses lower than those that decreased FI responding. Woolverton and Balster [18] found phencyclidine to have similar effects in rats responding under an FI 1-min schedule of water presentation. Low doses (1, 2 and 4 mg/kg) increased and a high dose (8 mg/kg) decreased the overall rate of responding. They also reported that phencyclidine produced rate-dependent effects on local response rates within the FI.

The effects of *d*-amphetamine and pentobarbital as compared to phencyclidine on multiple-schedule responding were also studied by Wenger and Dews [17]. They reported that "at some dose range, *d*-amphetamine, ketamine and phencyclidine produced dose-related increases in FI response rates but only decreases in FR response rates" (p. 616). Pentobarbital, however, increased both the FR and FI response rates at low doses. Higher doses of pentobarbital progressively decreased both the FR and FI response rate in a parallel manner.

The purpose of the present study was to characterize the effects of phencyclidine on responding maintained under a multiple FR FI schedule of food presentation in rats. The effects of *d*-amphetamine and pentobarbital were also studied in order to permit a direct comparison of phencyclidine to these reference drugs, and to compare these effects with those observed in mice [17].

METHOD

Subjects

Three experimentally naive adult male Sprague-Dawley rats were maintained at 80% (±10 g) of their free-feeding

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body weights by food presented during the sessions and by supplemental postsession feeding (Purina Rat Chow) throughout the experiment. Water was continuously available in the individual home cages. The home cages were kept in a temperature controlled room under an approximately 10 hr light–14 hr dark cycle.

Apparatus

The experimental chamber (Lehigh Valley Electronics model #132-04) measured 23.5 cm × 30 cm × 26.5 cm. A lever was mounted on the side wall 5 cm above the grid floor. A downward force of 25 g was required to activate the lever. A food cup was located 9 cm to the left of the lever. Three pilot lamps (#1820) were located 5 cm above the lever. The lamps were spaced 2 cm apart (center-to-center). The middle lamp had a white glass lens and the two side lamps had green glass lenses. A houselight was located 23 cm above the food cup. The chamber was housed in a larger insulated shell equipped with a blower for ventilation. Events were programmed with solid-state circuitry and were recorded on counters, running-time meters, and a cumulative recorder.

Procedure

The rats were first trained to respond under an FR 30 schedule of food reinforcement. After stabilization under the FR 30 baseline, they were switched to a multiple FR 30 FI 3-min schedule of food presentation, where the components changed after reinforcement or 5 min, whichever occurred first. The white center lamp was on during the FR component, and the green lamps were on during the FI component. A 45-mg food pellet (Bioserve Biomix #T101) served as the reinforcer. The reinforced response began a 3-sec feeder cycle during which the stimuli over the levers were off and the houselight was on; responses during the feeder cycle had no programmed consequences. A session was 2 hr in duration. Sessions were conducted Monday through Friday.

Drugs

Drug testing began when responding under the multiple schedule stabilized (25–30 sessions). Drug sessions were generally conducted on Tuesdays and Fridays with saline control sessions on Thursdays. Phencyclidine hydrochloride (Research Technical Branch, NIDA), *d*-amphetamine sulfate (Sigma Chemical Co.), and pentobarbital sodium (Abbott Laboratories) were tested in that order. All drugs were dissolved in saline. Injections were given intraperitoneally, 5 min presession. The volume of each injection was 2 ml/kg body weight.

Data Analysis

The data were analyzed in terms of the overall response rate (responses/sec, excluding the feeder cycle) in each component. The data for each subject were analyzed by comparing a given drug session with the control range of variability (saline sessions). A drug was considered to have an effect on overall response rate to the extent that the drug data fell outside of the control range. Within-session changes in responding were monitored by a cumulative recorder. The FI data were also analyzed for rate-dependent effects by two methods. In the first method, the rate of responding during drug sessions (drug rate), expressed as percent of the control rate, was plotted against the control rate of responding (responses/sec) in ten bins within the FI. The first nine were 18-sec bins and the tenth bin was greater than or equal to 18-sec and included the reinforced response. In the second method, drug rate (responses/sec) was simply plotted against the control rate (responses/sec) for each of the 10 bins. In both cases, rather than fitting a regression line through the points, the individual points were connected to form a line (cf. [13]).

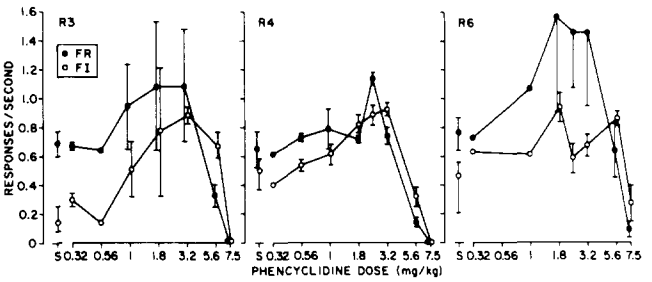

FIG. 1. Effects of varying doses of phencyclidine on the overall response rate in each component of the multiple schedule for each subject. The points and brackets at S indicate the mean and range for 12 saline sessions. The points with brackets in the dose-effect curves represent the mean and range for 2 to 4 determinations; the points without brackets indicate either a single determination or, occasionally, an instance in which the range is encompassed by the point.

RESULTS

Phencyclidine dose-effect curves for each subject are shown in Fig. 1. The control rate of responding in the FR component was higher than the control rate of responding in the FI component in each subject. Phencyclidine had a biphasic effect on overall response rate in both components; response rate increased and then decreased as the dose was increased. Peak rate-increasing effects in both components were seen at the intermediate doses (1.8–3.2 mg/kg). The FR tended to be slightly more sensitive than the FI to the rate-decreasing effects of phencyclidine. The large amount of variability is related to the fact that when the dose-effect curves were redetermined, the rate-increasing effects of phencyclidine were generally attenuated in both components.

The effects of selected doses of phencyclidine on the within-session responding of subject R4 are shown in the cumulative records in Fig. 2. The control pattern of responding (saline session) is characterized by a "break and run" pattern in both components. The rate-increasing effects of phencyclidine in the FI component can be seen in the first part of the session at the 1.8 mg/kg dose, but are most pronounced in both components at the 2.4 mg/kg dose during the first half of the session. At this dose, the pre-run pause in the FR component was attenuated. The response rate tended to be constant throughout the FI component. At the 5.6 mg/kg dose, after an initial run, responding was virtually abolished during the first half of the session. When responding resumed the rate was low and erratic in both components.

d-Amphetamine dose-effect curves are shown for each subject in Fig. 3. The effects of *d*-amphetamine on overall response rate were qualitatively similar to those of phencyclidine. Overall response rate in each component increased and then decreased with increasing doses. The peak rate-increasing effects of *d*-amphetamine in the FR component

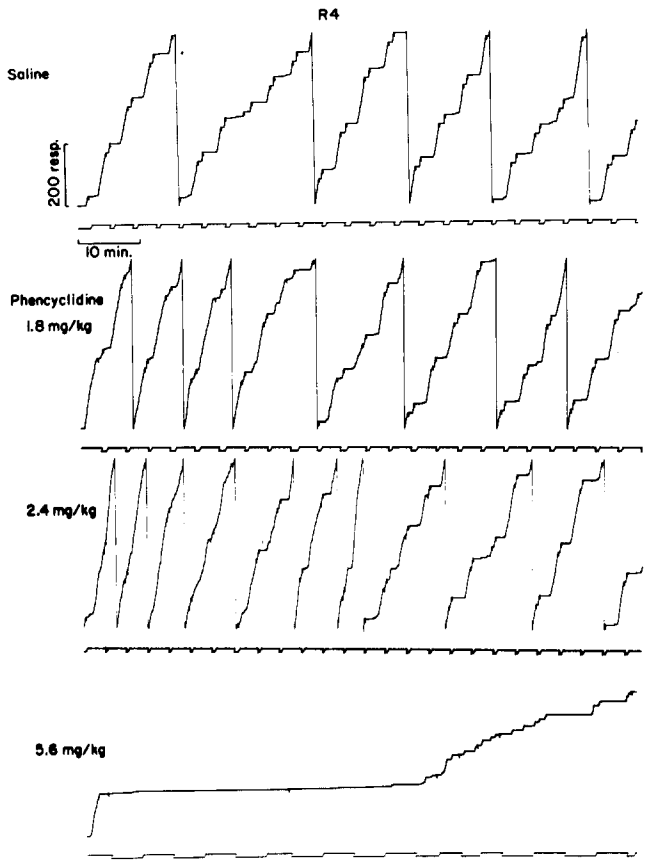

FIG. 2. Cumulative records for subject R4 showing the effects of three doses of phencyclidine on responding under the multiple schedule for the first 90 min of each session. The response pen stepped with each response and was deflected downward each time food was presented. The event pen was down during the FR component and was up during the FI component.

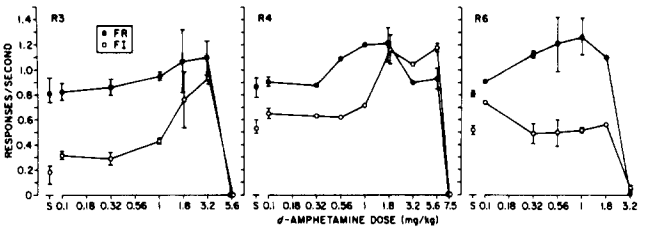

FIG. 3. Effects of varying doses of *d*-amphetamine on the overall response rate in each component of the multiple schedule for each subject. The points and brackets at S indicate the mean and range for 7 saline sessions. The points with brackets in the dose-effect curves represent the mean and range for two determinations; the points without brackets indicate either a single determination or, occasionally, an instance in which the range is encompassed by the point.

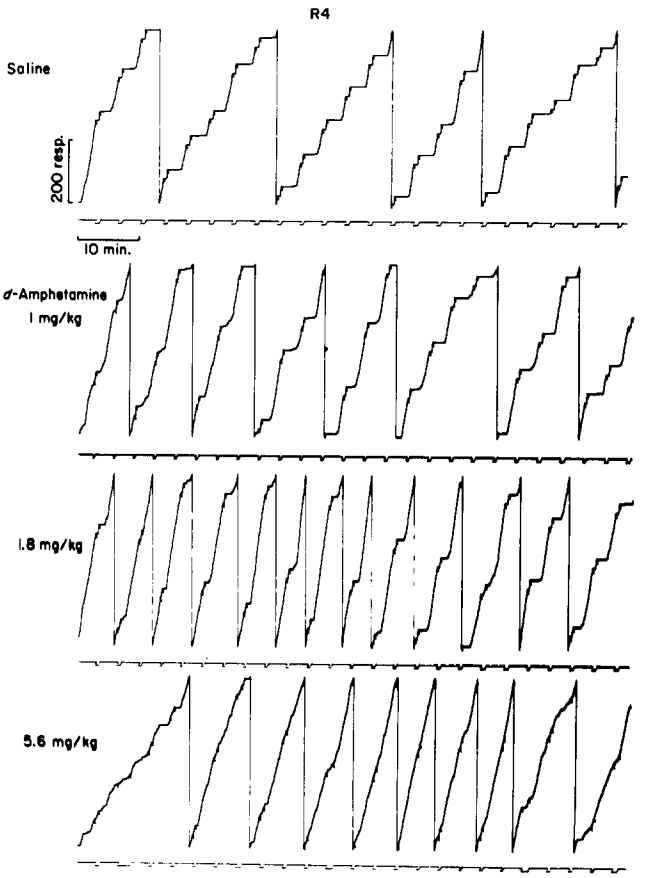

FIG. 4. Cumulative records for subject R4 showing the effects of three doses of *d*-amphetamine on responding under the multiple schedule for the first 90 min of each session. The recording details are the same as in Fig. 2.

occurred at doses of 3.2, 1.8 and 1 mg/kg for subjects R3, R4 and R6, respectively. For subjects R3 and R4 the peak rate-increasing effects in the FI component occurred at 3.2 and 5.6 mg/kg. The FI tended to be slightly more sensitive than the FR to the rate-increasing effects of *d*-amphetamine.

The effects of *d*-amphetamine on the within-session pattern of responding of subject R4 are shown in the cumulative records in Fig. 4. The rate-increasing effects of *d*-amphetamine in the FR component can be seen at both the 1 and 1.8 mg/kg doses. Though it is not readily apparent, the increase in overall rate of responding in the FR at the 1.8 mg/kg dose was due primarily to a decrease in the pre-run pause rather than an increase in the local rate of responding. In the FI component, the largest increases in the local rate of responding occurred at the 1.8 mg/kg dose, while the 5.6 mg/kg dose tended to produce a more constant rate of responding with very little pausing.

Pentobarbital dose-effect curves are shown for each subject in Fig. 5. In the FR component, pentobarbital produced little or no rate-increasing effects at low doses and decreased response rate at higher doses. In the FI component, pentobarbital produced small increases in overall rate at the intermediate doses (e.g., 5.6 mg/kg in R6 and 7.5 mg/kg in R3 and R4) while decreasing response rate at higher doses. As was seen with phencyclidine, the FR tended to be more sensitive than the FI to the rate-decreasing effects of pentobarbital.

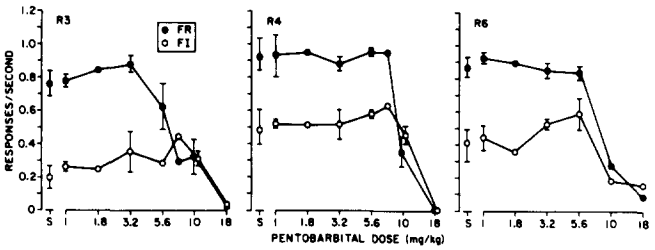

FIG. 5. Effects of varying doses of pentobarbital on the overall response rate in each component of the multiple schedule for each subject. The points and brackets at S indicate the mean and range for 9 saline sessions. The points with brackets in the dose-effect curves represent the mean and range for two or three determinations; the points without brackets indicate either a single determination or, occasionally, an instance in which the range is encompassed by the point.

The effects of pentobarbital on the within-session responding of subject R4 are shown in Fig. 6. Slight rate-increasing effects in the FI component can be seen at the 5.6 and 7.5 mg/kg doses. After an initial run, responding was virtually abolished during most of the first half of the session at the 10 mg/kg dose. When responding resumed, it was erratic. FR responding returned to control rates first, while FI response rate was higher than control.

In general, the within-session effects of the three drugs in subject R4 (Figs. 2, 4 and 6) were replicated with the other two subjects, although the particular doses and the magnitude of the effects varied. At doses that produced the peak rate-increasing effects, both phencyclidine and *d*-amphetamine, unlike pentobarbital, produced relatively constant local rates of responding with little pausing.

Rate-dependency analyses for phencyclidine, *d*-amphetamine, and pentobarbital are presented for subject R4 in Fig. 7. In the traditional method of analysis [5] rate-dependency is assumed if the distribution of points approximates a straight line having a slope other than zero [1]. The data are plotted in this manner for each drug in the top row of Fig. 7. With this method of analysis, the traditional interpretation of the data would be that all three drugs produced rate-dependent effects on responding. For both phencyclidine and pentobarbital there are no clear differences in the slopes of the lines at each dose; this would imply the absence of dose-dependency. However, the rate-dependent effects of *d*-amphetamine appear to be dose-dependent. That is, the slope of the line tends to increase with increasing doses of drug. On the other hand, when the drug rate is plotted against the control rate (shown in the bottom row of Fig. 7), a different conclusion is reached. For all three doses of phencyclidine the lines approach a slope of zero, indicating that the drug rate of responding is independent of the control rate of responding [1,7]. Therefore, by this method of analysis, it would be concluded that phencyclidine tended to produce rate constancy rather than rate-dependent effects on FI responding. The effects of *d*-amphetamine also approach rate-constancy, but unlike phencyclidine, this seemed to occur in a dose-dependent manner. Generally, the slope of the line approaches zero with increasing doses. Unlike phencyclidine and *d*-amphetamine, pentobarbital produced rate-dependent effects by this method of analysis. The slope of the line for each dose is close to the diagonal, and did not approach zero at any of the doses tested.

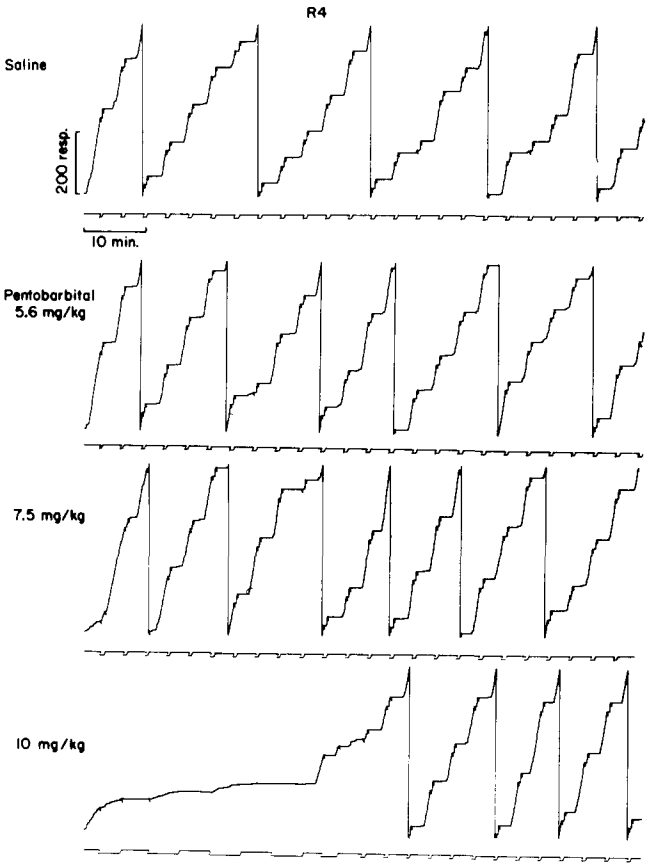

FIG. 6. Cumulative records for subject R4 showing the effects of three doses of pentobarbital on responding under the multiple schedule for the first 90 min of each session. The recording details are the same as in Fig. 2.

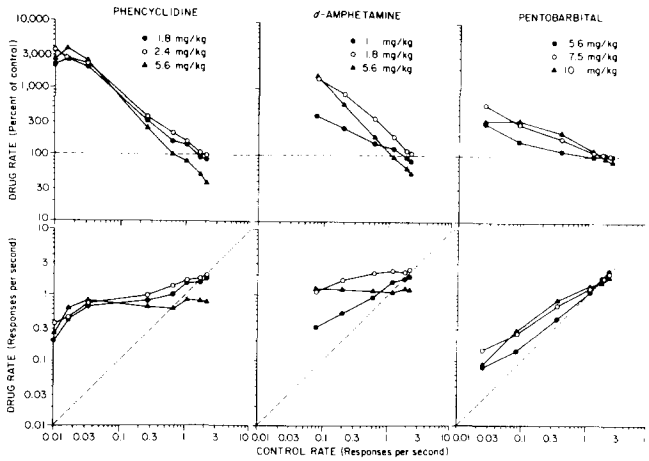

FIG. 7. Rate-dependency analyses for phencyclidine, *d*-amphetamine, and pentobarbital in subject R4. The data are from the sessions shown in Figs. 2, 4, and 6. Abscissa: control rate of responding on a log scale in successive 18-sec bins of the FI 3-min component. Bins with response rates less than 0.01 responses/sec are not plotted. Ordinate (top row): drug rate of responding on a log scale in successive 18-sec bins of the FI 3-min component expressed as percent of control rate. Ordinate (bottom row): drug rate of responding on a log scale in successive 18-sec bins of the FI 3-min component.

DISCUSSION

The present finding that overall response rate in the FI component of the multiple schedule increased and then decreased with increasing doses of phencyclidine is consistent with reports of its effects on responding under FI schedules (e.g., [2, 16, 17]). However, the present finding that phencyclidine also produced a biphasic effect on overall response rate in the FR component is in contrast to the monotonic rate-decreasing effects previously reported (e.g., [2, 16, 17]). One possible explanation for this discrepancy is that the control rates of responding under the FR schedules differed between the studies. Under the FR schedule the control rate reported by Wenger and Dews [17] was almost twice that observed in the present study (approximately 1.43 responses/sec vs 0.7 responses/sec). The peak rate-increasing effect of phencyclidine obtained in the present study (Fig. 1) approximates this control rate observed in the mouse. High control rates of responding were also found in the pigeon (2.91 responses/sec) and the squirrel monkey (2–3 responses/sec) [2,16]. It is possible, therefore, that phencyclidine did not increase FR response rate in these previous studies because of the relatively high control rates of responding. These differences in control rates of responding may be related to the different operants (e.g., pressing a lever, as in the present study vs breaking a light beam onto a photocell, as in [17]) or to other procedural differences. The attenuation of the rate-increasing effects of phencyclidine upon redetermination of the dose-effect curves (Fig. 1) may indicate either the development of tolerance (e.g., [2]) or simply a large degree of variability in terms of the behavioral response to this drug.

The biphasic effects of *d*-amphetamine on overall FI responding (Fig. 3) were qualitatively similar to those observed with phencyclidine (Fig. 1). This similarity has previously been reported in the mouse [17] and the pigeon [16]. Monotonic rate-decreasing effects on overall FR responding have previously been reported for *d*-amphetamine in rats (e.g., [3, 8, 9, 10, 11, 15]) and pigeons (e.g., [16]). However, in the present study, like phencyclidine, *d*-amphetamine produced biphasic effects on the overall response rate in the FR component. In previous studies of rodents responding under FR schedules, low doses of *d*-amphetamine (0.1–0.2 mg/kg) increased the overall rate of responding [6,17]. In those studies which reported that *d*-amphetamine produced only decreases in FR response rate in rats, doses less than 0.3 mg/kg were not tested (e.g., [3, 8, 9, 10, 11, 15]). It might seem that the rate-increasing effects of *d*-amphetamine on FR responding in rodents occur primarily at doses lower than 0.3 mg/kg. This would appear unlikely, however, given the present data.

Pentobarbital has been reported to increase and then decrease FI responding as a function of increasing doses in pigeons (e.g., [4, 12, 14]) and mice [17]. Similar results were obtained in the present study with rats, though the rate-increasing effects of pentobarbital were smaller than those produced by phencyclidine or *d*-amphetamine. Reports of the effects of pentobarbital on FR responding are, however, less consistent. While rate-increasing effects have been reported at low to moderate doses (e.g., [4, 14, 17]), this effect is not always observed (e.g., [12]). Similarly, in the present study, only small rate-increasing effects in the FR were found (subject R3 at 3.2 mg/kg). More generally, pentobarbital produced only monotonic rate decreases in the FR.

Wenger and Dews [17] reported that phencyclidine, *d*-amphetamine and pentobarbital all produced rate-dependent effects in mice. Consistent with these findings, the present data (Fig. 7) showed that by the traditional method of analysis and interpretation, phencyclidine, *d*-amphetamine, and pentobarbital all produced rate-dependent effects on FI responding. However, when the same data were analyzed according to the method described by Gonzalez and Byrd [7], both phencyclidine and *d*-amphetamine tended to produce rate constancy rather than rate-dependent effects on FI responding, whereas pentobarbital produced rate-dependent effects. The present study has demonstrated the utility of analyzing the effects of drugs by both methods. At the doses tested, there is a difference in interpretation when absolute rather than relative rates are plotted against control rates for phencyclidine and *d*-amphetamine. In addition, Byrd's method of analysis [1,7] of the present data has demonstrated a difference between phencyclidine, *d*-amphetamine and pentobarbital that has not previously been reported.

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