

# A Comparison of the Effects of d-Amphetamine, Cocaine, Imipramine and Pentobarbital on Local and Overall Rates of Responding Maintained Under a Four-Component Multiple Fixed-Interval Schedule<sup>1</sup>

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ZUCCARELLI, R. R. AND J. E. BARRETT. *A comparison of the effects of d-amphetamine, cocaine, imipramine and pentobarbital on local and overall rates of responding maintained under a four-component multiple fixed-interval schedule.* PHARMAC. BIOCHEM. BEHAV. 12(6) 899-907, 1980.—Key pecking of pigeons was maintained under a four-component multiple fixed-interval schedule with values of 1-min, 3-min, 5-min and 10-min. Each schedule value was correlated with a different key color, each of which controlled distinctively different performances. This schedule generated a range of response rates both within and across the different interval components that permitted a direct comparison of drug effects on local and overall rates of responding. d-Amphetamine, cocaine, imipramine and pentobarbital all increased low local response rates at doses that did not affect or decreased higher rates within each fixed interval. Similar effects were obtained when different overall rates of responding were analyzed except that imipramine and pentobarbital also increased the highest overall rates occurring under the 1-min schedule.

d-Amphetamine	Cocaine	Imipramine	Pentobarbital	Schedules of reinforcement
Operant behavior	Rate-dependency	Pigeons		

THE rate or frequency with which a particular behavior normally occurs in the absence of a drug is known to play an important role in determining the effects of a wide variety of drugs on behavior (for reviews see [6, 13, 18, 20]). Analyses of the relationship between response rate and drug effects have generally consisted of relative comparisons of different response rates either under diverse schedules or under the same schedule when that schedule engenders different response rates. For example, the first of these procedures involves a comparison of drug effects on different overall rates of responding occurring during two or more schedules of reinforcement (e.g., under a fixed-interval (FI) or fixed-ratio (FR) schedule). Frequently, when such schedules are used, it has been shown that the relatively lower overall rates of responding during the FI schedule are substantially increased by certain doses of drugs such as the amphetamines

that have no effect on or slightly decrease the higher rates occurring during the FR schedule.

A second approach to studying the influence that different control rates of responding can have on the behavioral effects of drugs has involved an analysis of local rates of responding within different portions of FI schedules. The rate of responding during an FI schedule can be characterized typically as being low early in the FI, followed by a gradually increasing rate of responding throughout the interval until a response produces a reinforcer [7]. Analysis of responding during successive temporal segments of FI schedules has been shown repeatedly to be an effective procedure for evaluating the influence that different control response rates can have in determining the effects of a variety of drugs [4, 5, 6, 16, 18, 19]. When the effects of amphetamines have been analyzed in terms of the mean local rate of response during

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successive segments of the FI, it has been found that the relatively low response rates occurring during the early segments of the interval are markedly increased at doses that either increase less or decrease the higher response rates in later segments.

Generally then, there is rather good correspondence between the two dominant methods of analysis of rate-dependent drug effects. Whether derived from within different portions of the same schedule or from different schedules altogether, relatively higher response rates are generally unaffected or are decreased by appropriate doses of drugs such as the amphetamines that increase lower rates of responding. There are, however, certain instances where differences are obtained in the effects of certain drugs on high overall response rates under FR schedules and the highest local rates under FI schedules (e.g., [14]). The present experiment was designed to examine the effects of a variety of drugs on a wide range of *both* local and overall rates of responding all of which were derived from four different FI schedule values. This schedule, which is similar to that used previously by Dews [3], permitted a direct analysis of the correspondence between local and overall response rates as factors determining the effects of drugs.

#### METHOD

##### Subjects

Three male White Carneaux pigeons were maintained at 80% ( $\pm 15$  g) of their unrestricted body weights. Water and grit were continuously available in separate living cages. All pigeons had a history of exposure to a variety of reinforcement schedules.

##### Apparatus

A standard pigeon chamber [7] was enclosed in a sound-attenuated, ventilated enclosure that was supplied with white noise. A response key (R. Gerbrands Co., Arlington, MA) was mounted 22 cm above the floor behind a 1.9 cm circular opening on the front wall of the chamber. The key could be transilluminated by pairs of 7-W lamps. Key pecks exceeding approximately 15 g (0.15 N) were recorded as responses and also produced a feedback relay closure behind the front panel. An opening directly below the response key provided access to mixed grain. When food was delivered, the grain magazine will illuminate and the key light was extinguished.

##### Procedure

Pigeons initially responded under an FI 1-min schedule of food delivery where the first response after 1 min had elapsed produced 4-sec access to mixed grain. Over a period of several weeks three additional FI components were added to yield the terminal schedule which was a multiple FI 1-min FI 3-min FI 5-min FI 10-min schedule of food presentation. Food was delivered after each component; the schedule always progressed in this sequence. Each individual FI component was separated by a 1-min period during which all lights were extinguished and responding had no scheduled consequences (timeout). The response key was transilluminated with either white (FI 1-min), green (FI 3-min), blue (FI 5-min) or red (FI 10-min) lights. Sessions were conducted five days per week and lasted for four cycles of the schedule sequence.

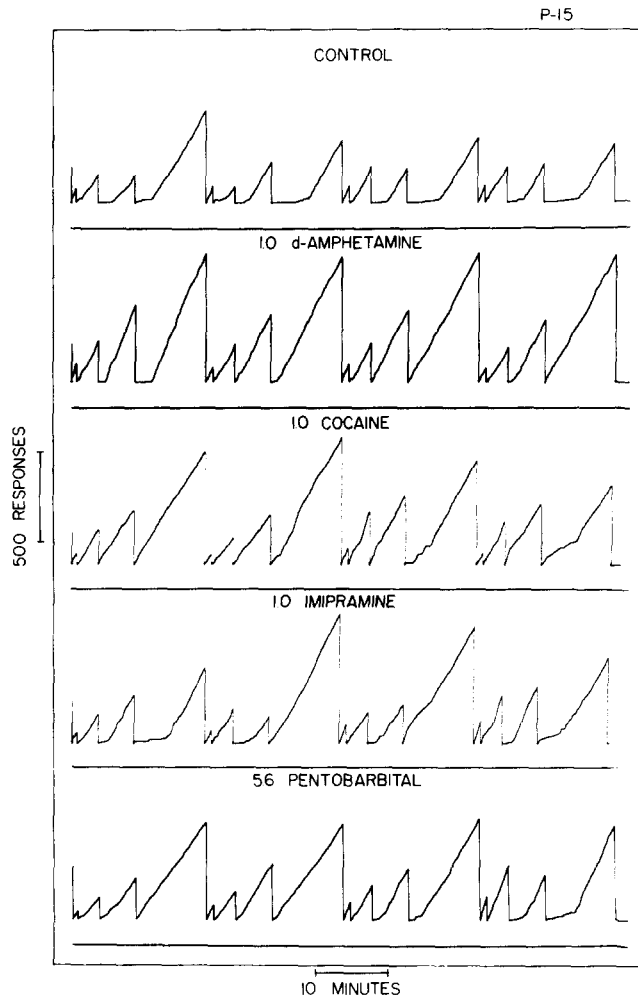


FIG. 1. Cumulative response records for P-15 showing a control session (non-drug) and selected doses of d-amphetamine, cocaine, imipramine and pentobarbital under the multiple FI 1-min FI 3-min FI 5-min and FI 10-min schedule of food presentation. Ordinates: cumulative responses; Abscissae: time. The multiple schedule sequence was repeated four times throughout the session. Each component was separated by a 1-min timeout period during which the cumulative recorder did not run. At the end of the timeout period the response pen reset to the baseline.

##### Drug Procedure

d-Amphetamine sulfate, cocaine hydrochloride, pentobarbital sodium and imipramine hydrochloride were dissolved in 0.9% sodium chloride. Solutions were injected into the breast muscle in a volume of 1.0 ml/kg of body weight immediately before the session with the exception of imipramine which was injected 30 min before the start of the session. Given that responding was stable, drugs were administered on Tuesdays and Fridays, with Thursdays serving as non-injection control. Saline was also administered occasionally on a Tuesday or Friday. Control performances were based on at least seven saline and non-injection sessions. The pigeons received the injections in an irregular dose series. All doses were given at least twice and are expressed in terms of the total salt.

TABLE 1  
OVERALL CONTROL RATE OF RESPONDING FOR ALL SUBJECTS DURING  
EACH COMPONENT SCHEDULE FOR EACH DRUG SEQUENCE

	FI 1	FI 3	FI 5	FI 10
<b>d-Amphetamine</b>				
P-329	1.45 ( $\pm 0.10$ )	1.16 ( $\pm 0.18$ )	0.87 ( $\pm 0.16$ )	0.62 ( $\pm 0.18$ )
P-15	1.25 ( $\pm 0.14$ )	0.82 ( $\pm 0.19$ )	0.72 ( $\pm 0.12$ )	0.65 ( $\pm 0.12$ )
P-8	0.48 ( $\pm 0.06$ )	0.39 ( $\pm 0.17$ )	0.15 ( $\pm 0.02$ )	0.20 ( $\pm 0.07$ )
<b>Cocaine</b>				
P-329	1.42 ( $\pm 0.13$ )	1.00 ( $\pm 0.24$ )	0.76 ( $\pm 0.09$ )	0.44 ( $\pm 0.06$ )
P-15	1.03 ( $\pm 0.13$ )	0.63 ( $\pm 0.16$ )	0.54 ( $\pm 0.18$ )	0.50 ( $\pm 0.09$ )
P-8	0.56 ( $\pm 0.19$ )	0.36 ( $\pm 0.16$ )	0.26 ( $\pm 0.08$ )	0.23 ( $\pm 0.07$ )
<b>Imipramine</b>				
P-329	1.25 ( $\pm 0.11$ )	1.17 ( $\pm 0.11$ )	0.88 ( $\pm 0.11$ )	0.51 ( $\pm 0.13$ )
P-15	1.42 ( $\pm 0.14$ )	0.67 ( $\pm 0.07$ )	0.76 ( $\pm 0.35$ )	0.69 ( $\pm 0.15$ )
P-8	0.60 ( $\pm 0.08$ )	0.48 ( $\pm 0.12$ )	0.35 ( $\pm 0.05$ )	0.23 ( $\pm 0.01$ )
<b>Pentobarbital</b>				
P-329	1.38 ( $\pm 0.01$ )	1.22 ( $\pm 0.07$ )	0.96 ( $\pm 0.05$ )	0.45 ( $\pm 0.06$ )
P-15	1.32 ( $\pm 0.11$ )	0.73 ( $\pm 0.14$ )	0.63 ( $\pm 0.15$ )	0.54 ( $\pm 0.08$ )
P-8	0.78 ( $\pm 0.17$ )	0.54 ( $\pm 0.11$ )	0.38 ( $\pm 0.08$ )	0.22 ( $\pm 0.03$ )

Numbers in parentheses are  $\pm 1$  SD.

## RESULTS

### Data Analysis

Response rates were calculated in responses per second. Each FI was divided into successive fifths and responses were separately cumulated during each fifth for the entire session. This measure provided a means of analyzing local response rates within each FI and permitted a direct comparison of comparable local rates from the four different FI schedules. In addition, comparisons were made of drug effects on the overall different rates during each FI. Regression lines were fit to local rates under each FI schedule and to the overall rates taken from the four different FIs.

### Control Performances

Patterns of responding during the FI 3-, FI 5- and FI 10-min schedules under control conditions (Fig. 1) were characteristic of those reported previously [7]. At the beginning of the interval responding did not occur or was low and increased gradually throughout the interval to a high terminal rate until a response produced food. Responding during the FI 1-min schedule was less positively accelerated throughout the interval and little or no pausing occurred at the beginning of the interval. Pause duration preceding the initiation of responding was directly related to interval length.

Control overall response rates during each drug regimen are shown in Table 1. Under all conditions and for all pigeons, as the FI value increased from 1 to 10 min, control response rates generally decreased. Table 1 also shows that control response rates for individual pigeons were generally unchanged throughout the course of the study.

### Effects of d-Amphetamine

The effects of d-amphetamine on overall rates of responding are shown in Fig. 2. The relatively high rates of responding maintained under the FI 1-min schedule were generally

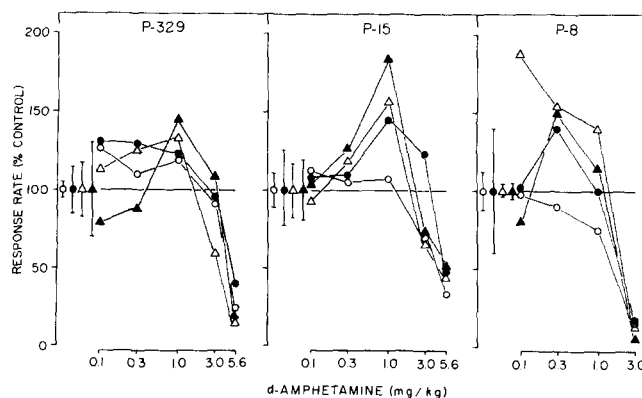


FIG. 2. Effects of d-amphetamine on overall rates of responding under the four-component multiple FI schedule. Open circles represent the FI 1-min schedule, filled circles the FI 3-min schedule. The open triangles represent the FI 5-min schedule, filled triangles the FI 10-min schedule. Points on the extreme left represent control values  $\pm 1$  SD.

unaffected or decreased by d-amphetamine. Intermediate to low rates of responding during the FI 3-, 5-, and 10-min schedules, however, were increased substantially with intermediate doses (0.3–1.0 mg/kg), while the highest dose (3.0–5.6 mg/kg) decreased responding during all schedules. In general, the highest percentage increases in overall rates of responding were inversely related to the control rates engendered by the different schedules. Figure 1 shows that d-amphetamine shortened pause duration and reduced the curvature during the longer FI values.

The effects of d-amphetamine on local as well as on overall rates of responding show that, except at the lowest dose (0.1 mg/kg), where all rates of responding were generally unaffected, d-amphetamine increased low local rates of

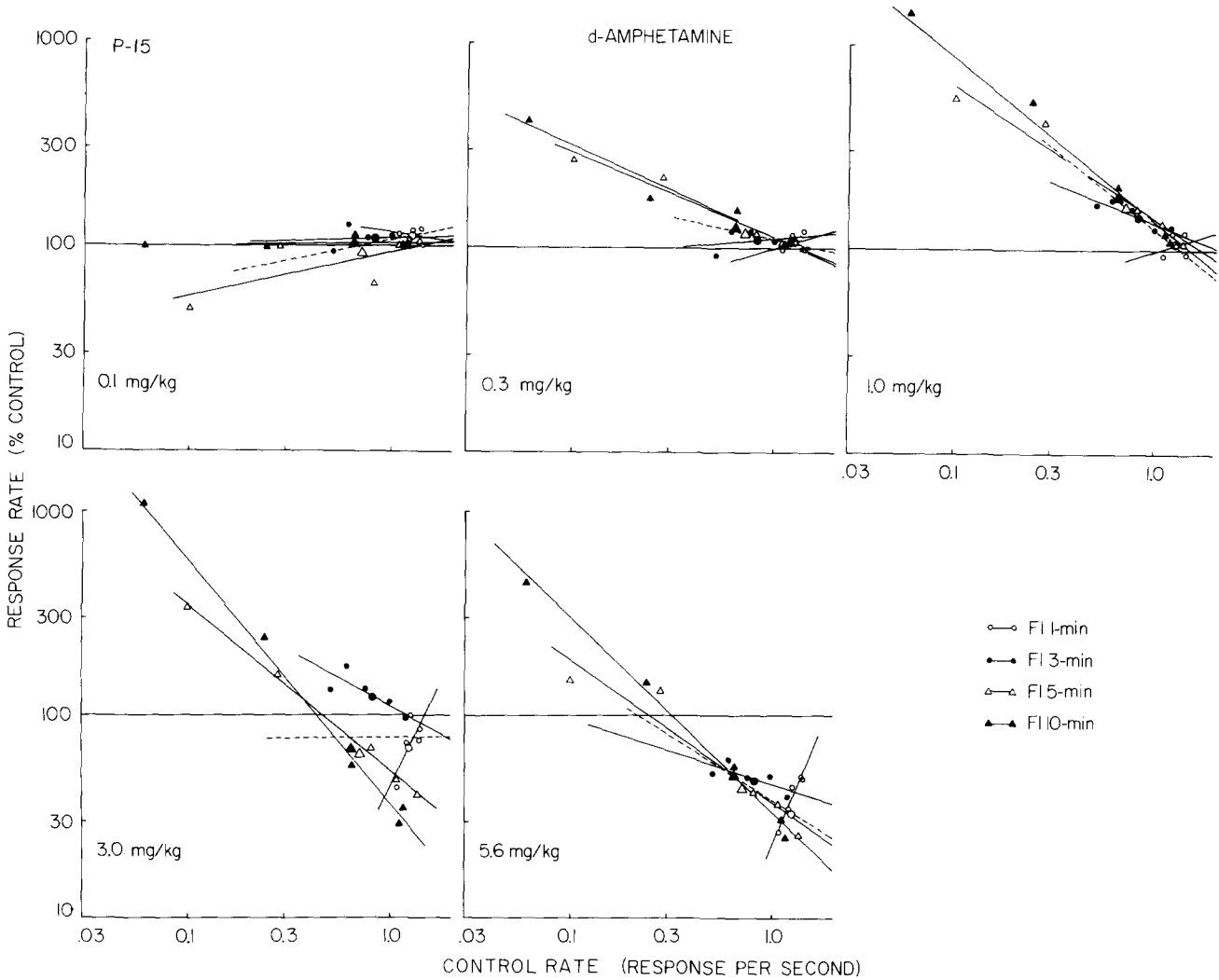


FIG. 3. Effects of d-amphetamine for P-15 on local and overall rates of responding under the four-component FI schedule. Both abscissae and ordinates are log scales. Abscissae: average control rate of responding during successive fifths of each FI schedule; Ordinates: response rate after drug as a percentage of control rate. Large symbols and dashed lines represent overall rates of responding under the four-component multiple schedule; smaller symbols and solid lines denote points taken from local response rates during successive fifths of each FI. Lines were fitted by the method of least squares.

responding while the higher local response rates were unaffected or decreased. These effects are shown for P-15 in Fig. 3 and are similar to those obtained with other pigeons. Increasing doses generally increased the slopes of the regression lines during the FI 3-, 5- and 10-min schedules indicating that the lower local control rates were increased more at the higher doses, while higher local control rates of responding were unaffected or decreased even further. Effects of the 1.0-5.6 mg/kg doses of d-amphetamine on local rates under the FI 1-min schedule differed from that found with rates drawn from other components. As shown in Fig. 1 response rates under this schedule were more uniform than those under the other schedules. Under the 1-min FI, relatively lower local response rates were decreased more than slightly higher rates.

Generally the regression lines for the different overall response rates under each of the four FI schedules (shown in Fig. 3 by the dashed line and larger symbols) were similar to those obtained when local response rates were analyzed.

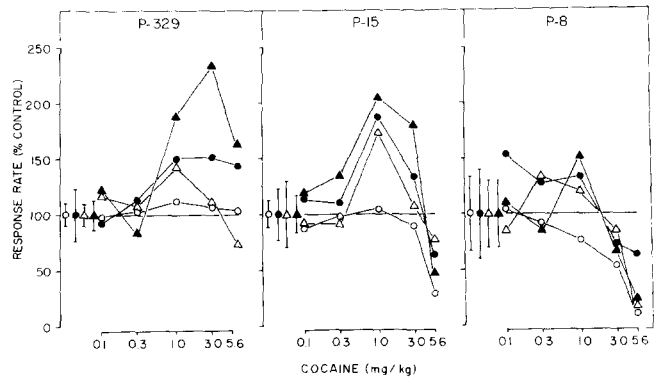


FIG. 4. Effects of cocaine on overall rates of responding under the four-component multiple FI schedule. Open circles represent the FI 1-min schedule, filled circles the FI 3-min schedule. The open triangles represent the FI 5-min schedule, filled triangles the FI 10-min schedule. Points on the extreme left represent control values  $\pm 1$  SD.

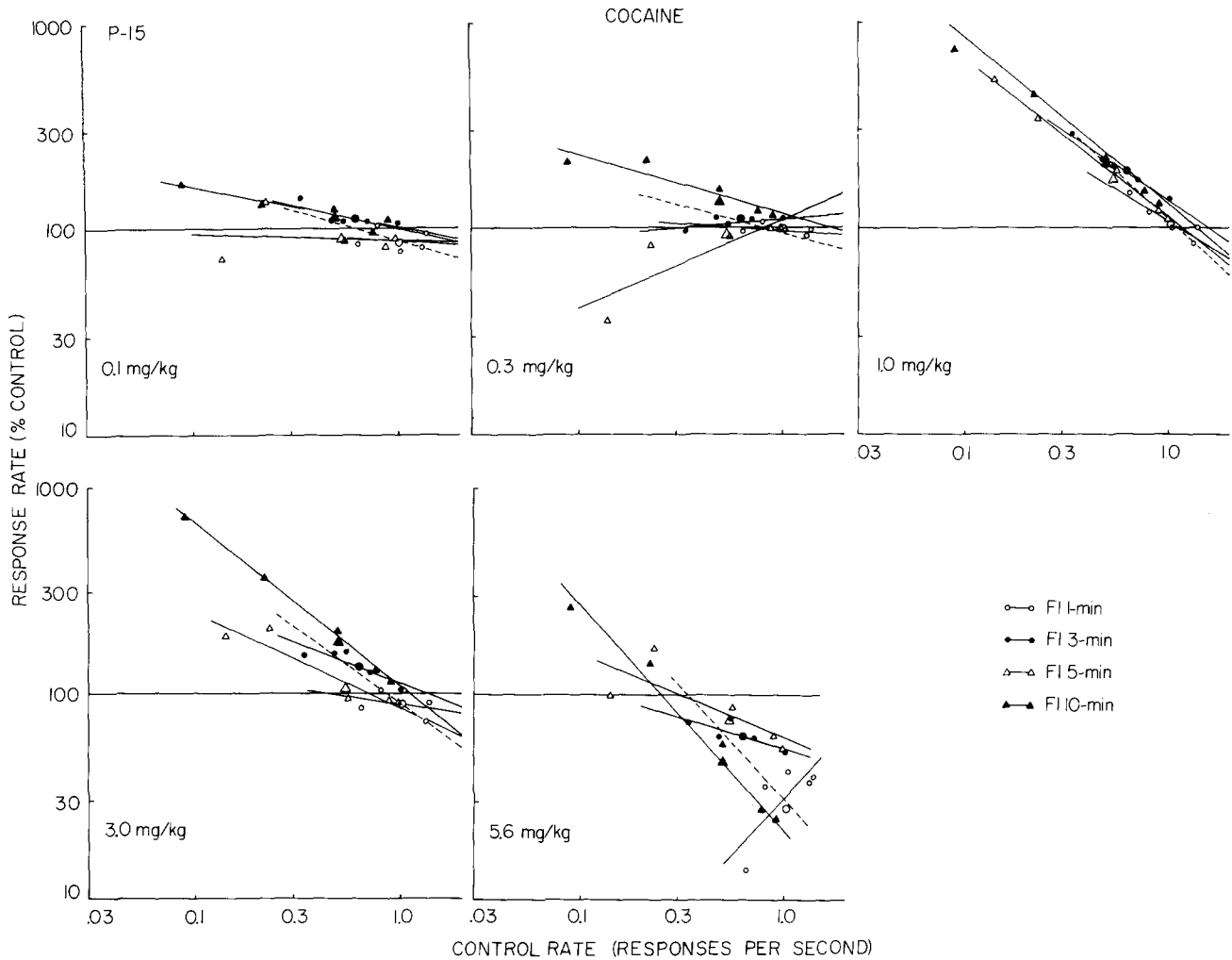


FIG. 5. Effects of cocaine for P-15 on local and overall rates of responding under the four-component FI schedule. Both abscissae and ordinates are log scales. Abscissae: average control rate of responding during successive fifths of each FI schedule; Ordinates: response rate after drug as a percentage of control rate. Large symbols and dashed lines represent overall rates of responding under the four-component multiple schedule; smaller symbols and solid lines denote points taken from local response rates during successive fifths of each FI. Lines were fitted by the method of least squares.

*Effects of Cocaine*

The effects of cocaine on overall rates (Fig. 4) and patterns (Fig. 1) of responding were similar to those of d-amphetamine. Low to intermediate doses of cocaine (0.1–1.0 mg/kg) had no effect on or decreased the relatively higher rate of responding during the FI 1-min schedule while, in general, intermediate to low rates of responding during the FI 3-, 5-, and 10-min schedules were substantially increased. The highest dose of cocaine (5.6 mg/kg) decreased responding during all schedules with P-8 and P-15, while responding during the FI 3- and 10-min schedules was still increased above control rates with P-329.

Generally low local rates of responding were markedly increased at the low to intermediate doses of cocaine (0.1–1.0 mg/kg); these same doses had no effect on or decreased slightly the high local rates of responding (Fig. 5). At the highest dose of cocaine (5.6 mg/kg) moderate and high local rates of responding were decreased while the lowest local rates of responding continued to show increases. As with

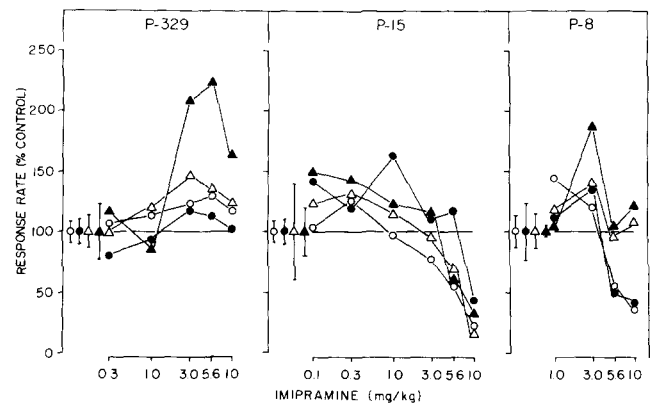


FIG. 6. Effects of imipramine on overall rates of responding under the four-component multiple FI schedule. Open circles represent the FI 1-min schedule, filled circles the FI 3-min schedule. The open triangles represent the FI 5-min schedule, filled triangles the FI 10-min schedule. Points on the extreme left represent control values  $\pm 1$  SD.

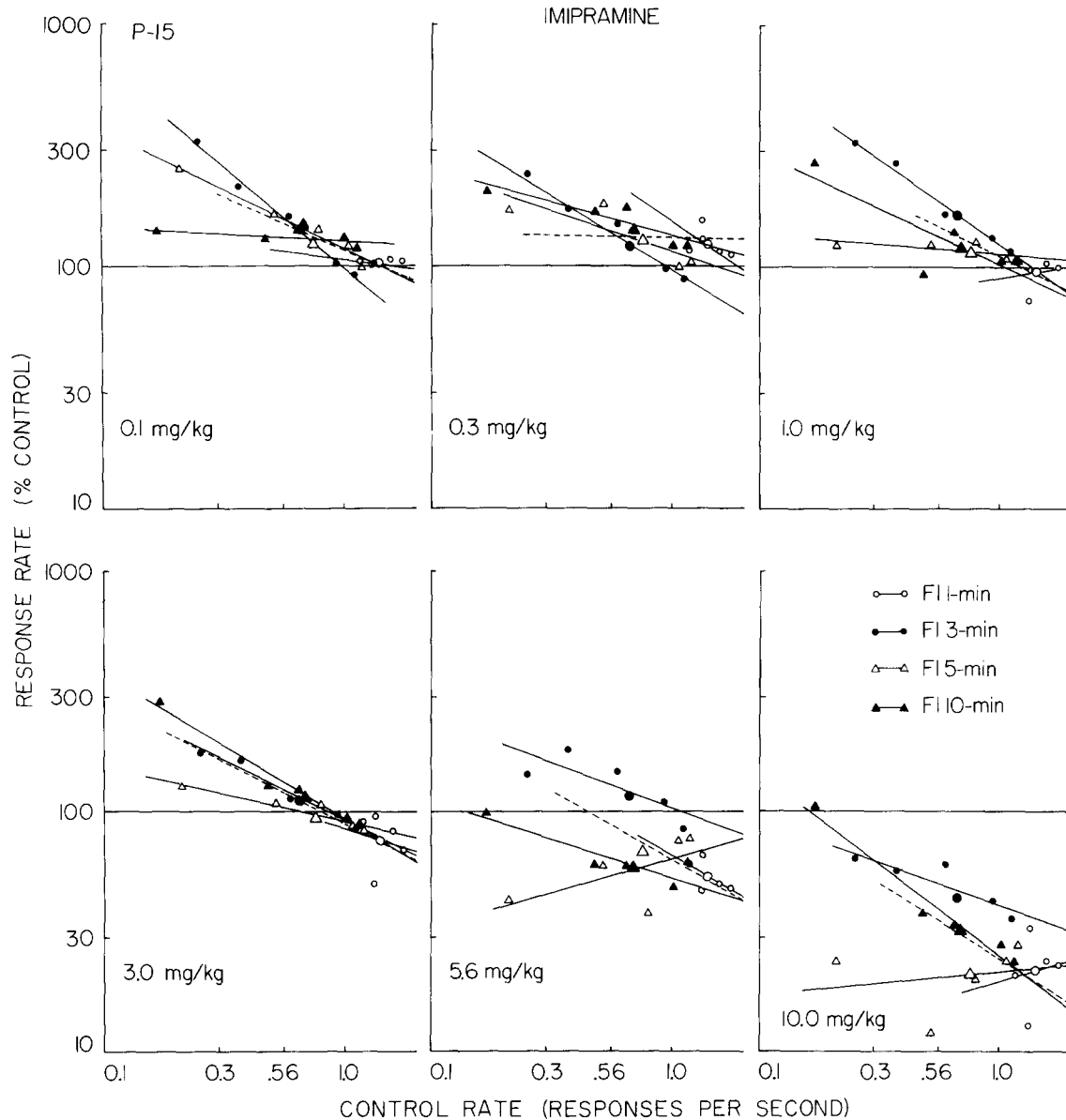


FIG. 7. Effects of imipramine for P-15 on local and overall rates of responding under the four-component FI schedule. Both abscissae and ordinates are log scales. Abscissae: average control rate of responding during successive fifths of each FI schedule; Ordinates: response rate after drug as a percentage of control rate. Large symbols and dashed lines represent overall rates of responding under the four-component multiple schedule; smaller symbols and solid lines denote points taken from local response rates during successive fifths of each FI. Lines were fitted by the method of least squares.

d-amphetamine, the slopes of the regression lines coincided for both overall response rate and local response rate and increased with increasing doses of cocaine. The highest dose of cocaine also produced the atypical effects on high uniform rates under the FI 1-min schedule seen with d-amphetamine (Fig. 3).

#### Effects of Imipramine

Increases in overall response rate at certain low to intermediate doses of imipramine occurred during all schedules (Fig. 6). These doses substantially increased low local rates of responding while having no effect on or slightly decreasing

the high local rates of responding (Fig. 7). At the 3.0 mg/kg dose of imipramine high local rates of responding were decreased (Fig. 7) while the low local rates continued to show increases. As with cocaine and d-amphetamine, changes in different overall response rates generally paralleled those derived from different segments of the FI. The cumulative response records in Fig. 1 show that unlike d-amphetamine and cocaine some degree of patterning was still evident during many cycles with imipramine.

#### Effects of Pentobarbital

Low to intermediate doses of pentobarbital (1.0–3.0

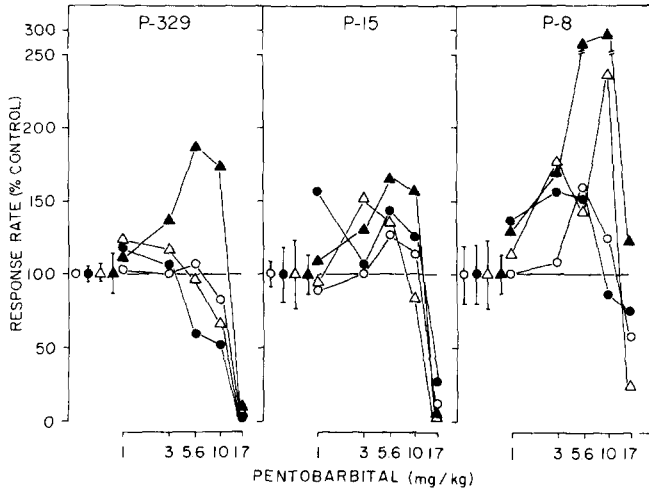


FIG. 8. Effects of pentobarbital on overall rates of responding under the four-component multiple FI schedule. Open circles represent the FI 1-min schedule, filled circles the FI 3-min schedule. The open triangles represent the FI 5-min schedule, filled triangles the FI 10-min schedule. Points on the extreme left represent control values  $\pm 1$  SD.

mg/kg) had no effect on the high overall rates of responding during the FI 1-min schedule (Fig. 8). However, these same doses substantially increased the lower rates of responding during the longer 3-, 5- and 10-min FI schedules. In contrast to the effects of d-amphetamine and cocaine and, as found with imipramine, certain doses of pentobarbital (5.6 and 10.0 mg/kg) did increase the higher response rates occurring during the FI 1-min schedule (Figs. 1 and 8). The greatest increases with pentobarbital occurred in the lower rates under the FI 10-min schedule.

In general, low to intermediate doses of pentobarbital (1.0–5.6 mg/kg) increased low local rates of responding while these same doses either had no effect on or decreased slightly the high local response rates (Fig. 9). Higher doses produced steeper slopes. At the 10.0 mg/kg dose of pentobarbital high local rates of responding under the FI 3-, 5- and 10-min schedules were decreased while the lower local response rates under these schedules were still markedly increased. The higher local response rates during the FI 1-min schedule were either increased or decreased to a lesser extent than comparable rates occurring under the other schedule values at 5.6 and 10.0 mg/kg pentobarbital. This displaced the 1-min regression line to the right of the other functions. Except for the 10.0 mg/kg dose, the effects of pentobarbital on local and overall rates were generally comparable.

#### DISCUSSION

The effects of d-amphetamine and cocaine on overall rates of responding during the different FI schedules were relatively consistent. Low to intermediate rates of responding during the FI 3-, FI 5- and FI 10-min schedules were substantially increased with these drugs, whereas the relatively higher overall rates of responding maintained under the FI 1-min schedule were generally unaffected or decreased. Similarly, pentobarbital and imipramine markedly

increased the low to intermediate overall response rates maintained under the FI 3-, FI 5- and FI 10-min schedules. In contrast to the other drugs, however, certain doses of pentobarbital and imipramine also increased the high overall rates of responding during the FI 1-min schedule. Under all drug conditions, the highest percentage increases in overall response rate were inversely related to the control rate of responding.

These findings with d-amphetamine, cocaine, imipramine and pentobarbital are consistent with results previously reported when responding was maintained under FI schedules [1, 3, 11, 13, 17, 21]. Increases in high response rates under the FI 1-min schedule with pentobarbital are similar to those frequently reported with this drug as well as with ethanol when high rates are maintained under FR schedules [2, 12, 22]. These drugs share the distinctive characteristic of increasing high response rates at doses that do not affect or even decrease lower response rates.

Imipramine has been shown to produce rate-dependent effects under FI schedules [3,21] and to decrease high response rates under FR schedules [21]. The increases with imipramine in high response rates under the 1-min FI schedule reported in the present study may be based partly on the fact that overall rates under the FI 1-min schedule (Table 1), though relatively high, were still lower than those (approximately 1.5–2.6 responses per second) under the FR 33 schedule studied by Smith [21]. Despite this possibility, the generally similar effects of pentobarbital and imipramine under the conditions studied here may warrant further study.

Analysis of drug effects on local rates of responding showed that low rates of responding were generally increased, while higher rates of responding were unaffected or decreased. Generally, the effects of these drugs on local response rates within the different FI values were similar to those reported with pharmacologically similar drugs by other investigators (see review [6] and reports [8, 9, 10]). Certain doses of most drugs studied (e.g., 1.0 mg/kg cocaine and d-amphetamine, and 3.0 mg/kg imipramine) increased comparable local rates drawn from the different schedule components to a similar extent. Other, usually higher, doses of these same drugs produced effects that differed depending on the particular component in which these rates were maintained (cf., [15]). With pentobarbital, the effects on generally high local rates under the FI 1-min schedule clearly differed from comparably high local rates occurring under the other schedules.

The direct comparisons reported here of changes in overall and local rates of responding generally revealed similar effects; the regression line for overall rates occurring under the different components was typically quite comparable in both slope and y-intercept to the regression lines for local rates under the four different schedules. Notable exceptions to this general finding occurred typically only with the highest rates maintained under the FI 1-min schedule and then only at certain drug doses (e.g., 5.6 and 10.0 mg/kg pentobarbital and 3.0 and 5.6 mg/kg d-amphetamine). Thus, even though there were occasional dose-dependent differences between overall and local response rates, rate-dependent drug effects occurred both when different local response rates were maintained within a single FI schedule, and also when different overall rates were maintained under different FI schedules.

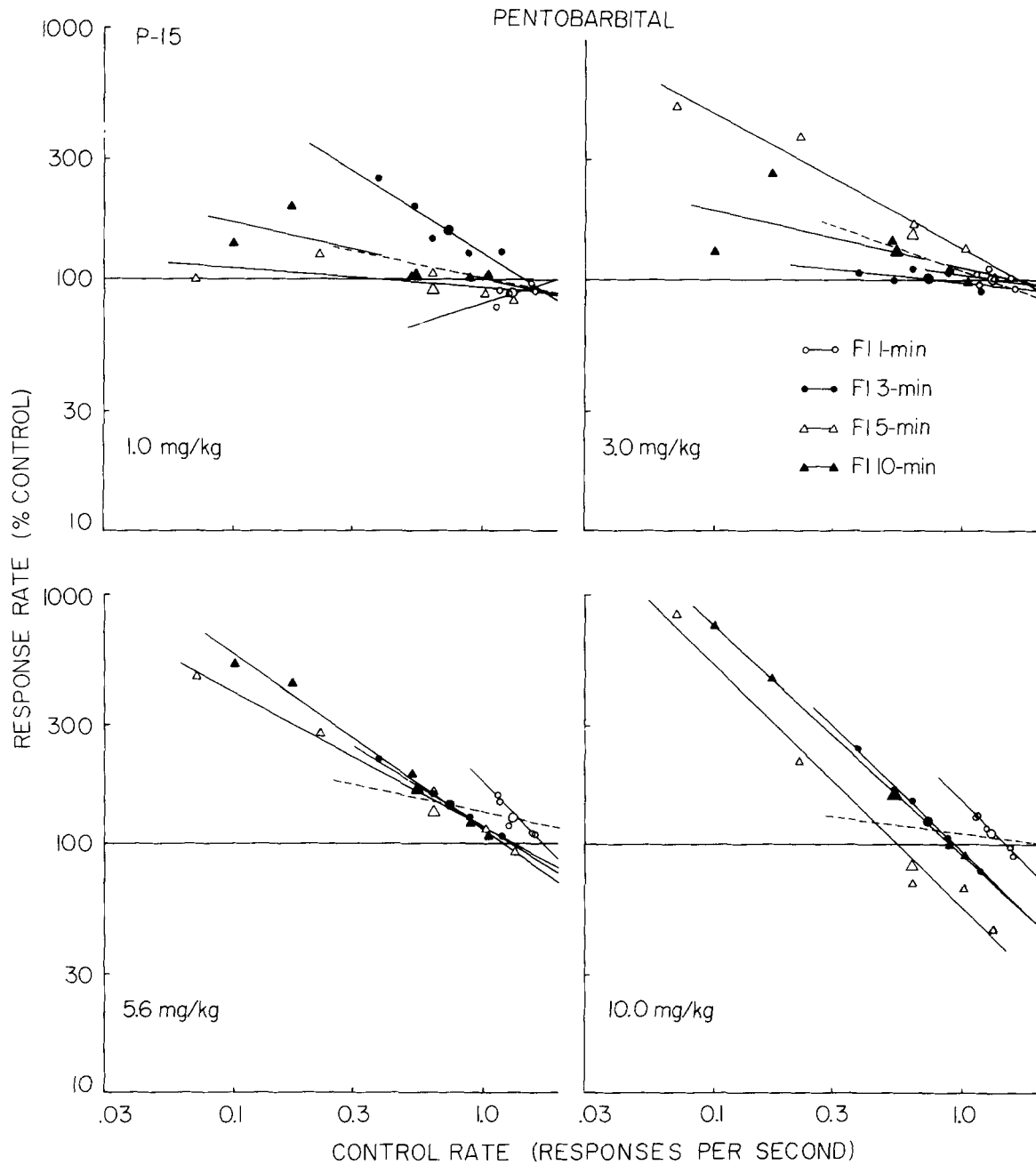


FIG. 9. Effects of pentobarbital for P-15 on local and overall rates of responding under the four-component FI schedule. Both abscissae and ordinates are log scales. Abscissae: average control rate of responding during successive fifths of each FI schedule; Ordinates: response rate after drug as a percentage of control rate. Large symbols and dashed lines represent overall rates of responding under the four-component multiple schedule; smaller symbols and solid lines denote points taken from local response rates during successive fifths of each FI. Lines were fitted by the method of least squares.

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