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Effects of Phencyclidine and Ketamine in Pigeons on Behavior Suppressed by Brief Electrical Shocks[1,2]

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WENGER, G. R. *Effects of phencyclidine and ketamine in pigeons on behavior suppressed by brief electrical shocks.* PHARMAC. BIOCHEM. BEHAV. 12(6)865–870, 1980.—Pigeons were trained to respond under fixed-ratio 30 (FR30) schedules of grain presentation. The schedule consisted of two FR30 components. In one component, every 30th response produced access to grain; FR30. In the second component, every 30th response produced access to grain, but responding was suppressed by having every response produce a brief electrical shock; FR30 (shock). In one phase of the experiment, there were no visual stimuli associated with the separate components; mixed FR30 FR30 (shock), and in the second phase, a distinctive stimulus was associated with each of the two components; mult FR30 FR30 (shock). High rates of responding (~2.0 responses/sec) were maintained in the FR30 components, and responding was almost totally suppressed (<0.02 response/sec) in the FR30 (shock) components. The effects of phencyclidine and ketamine were compared with pentobarbital, *d*-amphetamine and morphine. Phencyclidine and ketamine, over a narrow dose range, produced small increases in responding under the FR30 (shock) component of both the mixed and multiple schedules. By comparison, pentobarbital produced very large increases in responding under the FR30 (shock) component of both schedules. Increasing doses of *d*-amphetamine and morphine either had no effect on or decreased the response rate in both components of the mixed and multiple schedules. The results suggest that phencyclidine and ketamine may have some properties qualitatively like pentobarbital and unlike *d*-amphetamine and morphine in attenuating the suppression of behavior produced by brief electrical shocks.

Pigeons Fixed-ratio Punishment Phencyclidine Ketamine Pentobarbital *d*-Amphetamine Morphine

TO date there have been no extensive reports on the effects of phencyclidine and ketamine on the responding of laboratory animals which has been suppressed by response-contingent brief electrical shocks. Two preliminary reports have suggested that these compounds may be capable of attenuating the suppression produced by such stimuli [2,31].

The presentation of a brief electrical shock upon a response can suppress the rate of responding [1], and the effect of drugs on such suppression has been widely studied. The suppression can be attenuated by meprobamate, several benzodiazepines, barbiturates, and tryptamine antagonists [5, 10, 13, 15, 16, 21, 22, 26]. The suppression of behavior by brief electrical shocks is generally not attenuated by amphetamines, phenothiazines or narcotic analgesics such as morphine [10, 11, 14, 16, 24, 26].

Phencyclidine and ketamine have previously been studied in this laboratory in mice and pigeons responding under a multiple fixed-ratio, fixed-interval (mult FR FI) schedule of food presentation [32,33]. In both species, phencyclidine and ketamine increased fixed-interval (FI) responding at low doses and decreased responding at high doses; however, responding maintained under the fixed-ratio (FR) component was decreased in a monotonic dose-dependent fashion. FR responding was decreased at lower doses than FI responding. These results are qualitatively similar to the effects of *d*-amphetamine on similar schedules in pigeons [7, 19, 20, 27, 28, 32], monkeys [4,16], rats [3], and mice [33], and qualitatively unlike the effects of barbiturates in pigeons [6, 18, 25, 27] and monkeys [29] or the general anesthetic, halothane, in pigeons [9].

Since the effects of phencyclidine and ketamine appear to be more like amphetamines than pentobarbital in pigeons and mice responding under a mult FR FI schedule of food presentation, it was of interest to determine the effects of phencyclidine and ketamine on responding suppressed by brief response-contingent electrical shocks. In addition, since the schedule of reinforcement and the degree of stimulus control maintained by the schedule are important determinants of the effects of drugs on suppressed responding [23], initially the drug effects were determined under a

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mixed schedule and then again under a multiple schedule of reinforcement.

The present results show that phencyclidine and ketamine may be similar to pentobarbital in attenuating suppressed behavior, though they are less effective than pentobarbital. *d*-Amphetamine and morphine did not attenuate the suppression of behavior under these conditions. The present results and the earlier results with a mult FR FI schedule suggest that phencyclidine and ketamine may possess an unusual spectrum of behavioral effects.

METHOD

Subjects

Four male white Carneaux pigeons (designated P120A, P123A, P124A, and P125A), weighing between 420 g and 530 g when given free access to food and water, were used. They were maintained at 70% of their free feeding weights throughout the study. Water was freely available in the home cages, but not in the test chambers. Two pigeons (P123A and P125A) died before the study was completed. For a short time before the start of the drug experiments, all four birds had been exposed to fixed-ratio schedules of food presentation in which responding had been suppressed by brief electrical shocks.

Apparatus

The experimental chamber was similar to that described previously [8]. A translucent plastic response key, 2 cm in diameter, was mounted on a false wall inside the chamber about 20 cm above the floor. A minimum force of about 15 g was required to operate the key. Opening of the key contacts defined a response. The key could be transilluminated by two 7.5 W colored bulbs. Directly below the key was a rectangular opening through which the pigeon could be given access to grain. Electric shocks (4–6 mA, 30 msec duration, 650 V AC, 60 Hz) were administered through gold wire electrodes implanted around the pubis bones. The electrodes were connected to a plug attached to a leather harness which the bird wore at all times.

During experimental sessions, a jack was attached to the plug on the harness. The jack was connected to an electrical swivel mounted on the side of the chamber, allowing the bird free movement within the chamber. The chamber was illuminated with a 25 W bulb except during magazine presentation and periods in which responding had no consequence (time-out). White noise was present at all times. Electromechanical relay programming and recording apparatus were used.

Schedule

The schedule consisted of two different fixed-ratio 30 (FR30) components. In one component, every 30th response produced 3 sec access to grain, FR30. In the second component, every 30th response produced 3 sec access to grain, but in addition, every response produced a brief electrical shock which suppressed responding, FR30 (shock). The two components occurred in an irregular order. The session always started with the following sequence: OOXOXXOXOOXXXOXO [0=FR30; X=FR30 (shock)]. This sequence repeated throughout the session until a total of 60 components had been presented; 30 presentations of the FR30 component and 30 presentations of the FR30 (shock) component. At the end of the 3 sec food presentation, the key light and house light were turned off for 5 sec during which responses had no consequence (time-out). At the end of the time-out period, the key light and house light were turned on again, signaling the beginning of the next FR component. If 30 responses were not completed within 60 sec (limited-hold), the key light and house light were turned off and the 5 sec time-out period began.

In the first phase of the experiment, the same visual stimulus (a red key light) was associated with the two different components of the schedule, mixed FR30 FR30 (shock).

In the second phase of the experiment, the programming of the schedule and the order of component presentation were identical to that in the mixed FR30 FR30 (shock) schedule, the only difference being that the key was transilluminated with a unique light during each component: a green light was associated with the FR30 component, and a white key light was associated with the FR30 (shock) component, mult FR30 FR30 (shock).

For the brief electrical shock used to suppress behavior, the amount of current administered was adjusted for each bird under the mixed FR30 FR30 (shock) schedule. The current used was the minimal intensity necessary to almost abolish responding in the FR30 (shock) component while only producing a minimal decrease in responding in the FR30 component. Thus, pigeons P124A and P125A received a current of 4 mA, and pigeons P123A and P120A received a current of 5 mA and 6 mA, respectively. These same intensities were used for the second phase of this experiment during which the schedule was mult FR30 FR30 (shock).

For both the mixed FR30 FR30 (shock) and the mult FR30 FR30 (shock) schedules, the session length on nondrug control days averaged about 35 min in duration.

Drugs

The drugs used were phencyclidine hydrochloride (Sernylan, Bio-Ceutic Laboratories), ketamine hydrochloride (Vetalar, Parke-Davis), sodium pentobarbital (Abbott Laboratories), *d*-amphetamine sulfate (Smith, Kline and French Laboratories), and morphine sulfate (Merck and Company). Phencyclidine and ketamine were used as the commercial preparations and were further diluted with saline to the appropriate concentrations. Pentobarbital, *d*-amphetamine and morphine were dissolved in saline. All drug concentrations were made so that the desired dose could be given in 1 ml/kg of body weight. All doses are expressed as μ moles of base. The dose ranges were: phencyclidine, 1.1–10.7 μ moles/kg (0.3–3 mg/kg); ketamine, 3.7–36.5 μ moles/kg (1–10 mg/kg); pentobarbital, 1.2–52.4 μ moles/kg (0.3–13 mg/kg); *d*-amphetamine, 0.54–16.3 μ moles/kg (0.1–3 mg/kg); morphine, 0.8–26.4 μ moles/kg (0.3–10 mg/kg). All drug injections were made into the breast muscle 2 min before the start of the session.

Drug injections were never more frequent than twice per week (typically Tuesday and Friday). Morphine was never administered more frequently than once per week. Doses of each drug tested were administered in a mixed non-orderly sequence. The data collected on Thursdays served as the non-injection control.

Measurement of Drug Effects

Average rates of responding were computed as responses per second from digital counters and elapsed time meters for

both FR components. The average time between the beginning of the FR component and the first response to occur in the component (latency) was computed in seconds from elapsed time meters.

The effect of a drug was considered to be different from that of the mean control value if the mean drug effect was observed to be more than 2 standard errors away from the control mean. A conservative estimate of the standard error was used in which the standard error was defined as the total standard deviation of all the control data divided by the square root of n; where n equals the smallest pool size in the study. In this experiment, the smallest pool size was the smallest number of observations at any given dose level of the drug in question.

RESULTS

In control sessions, during the FR30 component of the mixed FR30 FR30 (shock) schedule, an initial pause was followed by a high continuous rate of responding. During the FR30 (shock) component of the mixed schedule, an initial pause was typically followed by a single response, after which responding was suppressed for the duration of the component presentation.

The mult FR30 FR30 (shock) schedule maintained responding in control sessions which differed from the response pattern seen under the mixed schedule in several ways. The average rate of responding in the FR30 component of the multiple schedule was slightly higher than the rate seen under the FR30 component of the mixed schedule because the latency of the response was shorter under the multiple schedule. Under the FR30 (shock) component of the multiple schedule, there was essentially no responding in the absence of drugs. Thus, the average response latency almost equaled the 60 sec limited-hold.

Drug Effects Under the Mixed Schedule

The effects of phencyclidine and ketamine on responding under the mixed schedule can be seen in Fig. 1. Both phencyclidine and ketamine had no effect on or decreased the response rate under the FR30 component. Yet under the FR30 (shock) component, both phencyclidine and ketamine increased the rate of responding. The increases were not large, but they were significantly greater than those seen under control conditions. Phencyclidine increased the FR30 (shock) response rate 1.4 times the control rate at doses of 2.0 and 3.6 μ moles/kg. Ketamine produced slightly larger increases in FR30 (shock) responding with the maximum increase, 1.9 times control, following a dose of 20.4 μ moles/kg.

Under control conditions, the response latency under each component of the mixed schedule was about the same. Phencyclidine and ketamine had no significant effects on response latency at doses which increased response rates under the FR30 (shock) component. At 10.7 μ moles/kg phencyclidine and 36.5 μ moles/kg ketamine, the response latency was increased in both components.

Figure 2 shows the effects of pentobarbital, *d*-amphetamine and morphine on the rate of responding in the two components of the mixed FR30 FR30 (shock) schedule. The rate of responding under the FR30 component was slightly increased or unchanged by pentobarbital. The same doses of pentobarbital markedly increased responding under the FR30 (shock) component. The largest increase, 82

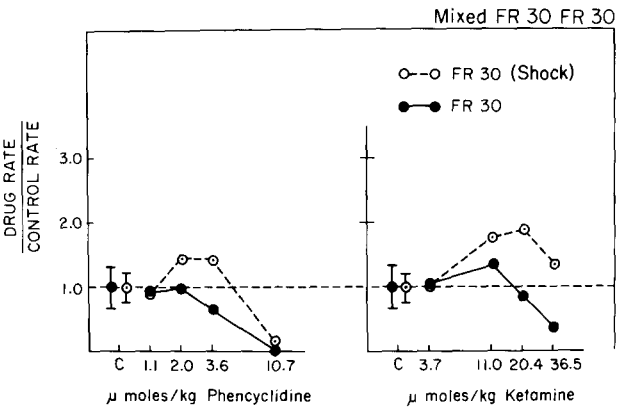

FIG. 1. Effects of phencyclidine and ketamine on the average rate of responding in each component of the mixed schedule. Abscissa: dose, μ moles/kg of body weight on a log scale; ordinate: ratio of the average rate after drug administration to the average rate on nondrug control days. Vertical lines at C represent the control mean plus or minus 2 standard errors. The broken horizontal line represents the mean control value. Mean control rates of responding for the phencyclidine and ketamine studies were 1.67 responses/sec and 0.02 response/sec for the FR30 and FR30 (shock) components, respectively. Each point represents the mean of duplicate determinations in each of 4 pigeons.

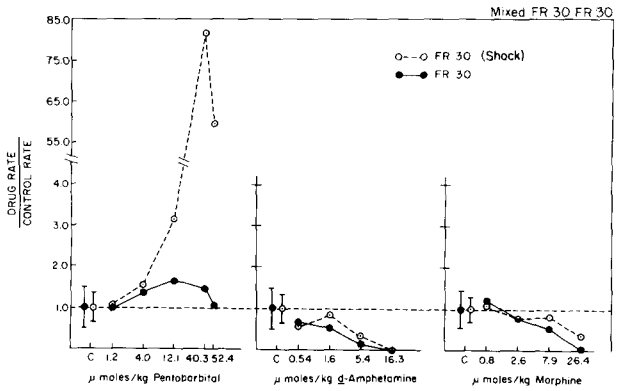

FIG. 2. Effects of pentobarbital, *d*-amphetamine and morphine on the average rate of responding in each component of the mixed schedule. Abscissa: dose, μ moles/kg of body weight on a log scale; ordinate: ratio of the average rate after drug administration to the average rate on nondrug control days. Vertical lines at C represent the control mean plus or minus 2 standard errors. The broken horizontal line represents the mean control value. Mean control rates of responding for the pentobarbital and *d*-amphetamine studies were 1.92 responses/sec and 0.02 response/sec for the FR30 and FR30 (shock) components, respectively. Mean control rates for the morphine study were 1.67 responses/sec and 0.02 response/sec for the FR30 and FR30 (shock) components, respectively. Each point represents the mean of single determinations in each of 3 pigeons for pentobarbital and *d*-amphetamine, and in each of 4 pigeons for morphine.

times the control rate, occurred at 40.3 μ moles/kg. By contrast, *d*-amphetamine or morphine decreased or had no effect on responding under each component of the mixed schedule.

Pentobarbital had no significant effect on response latency under either component of the mixed schedule. In contrast, *d*-amphetamine and morphine increased the response

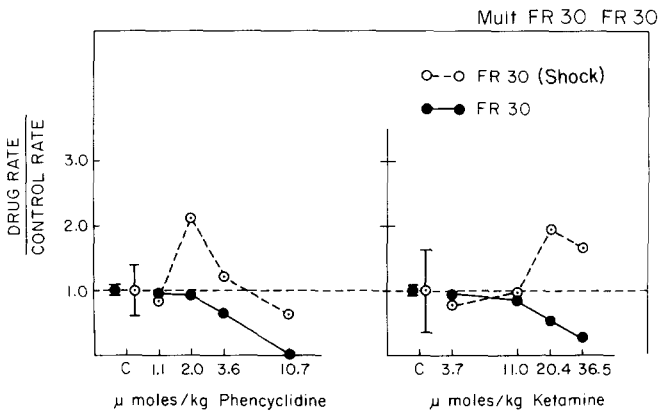

FIG. 3. Effects of phencyclidine and ketamine on the average rate of responding in each component of the multiple schedule. Abscissa: dose, μ moles/kg of body weight on a log scale; ordinate: ratio of the average rate after drug administration to the average rate on nondrug control days. Vertical lines at C represent the control mean plus or minus 2 standard errors. The broken horizontal line represents the mean control value. Mean control rates of responding for FR30 and FR30 (shock) components are: phencyclidine, 3.33 responses/sec and 0.003 response/sec; ketamine, 3.35 responses/sec and 0.002 response/sec. Each point represents the mean of duplicate determinations in each of 3 pigeons.

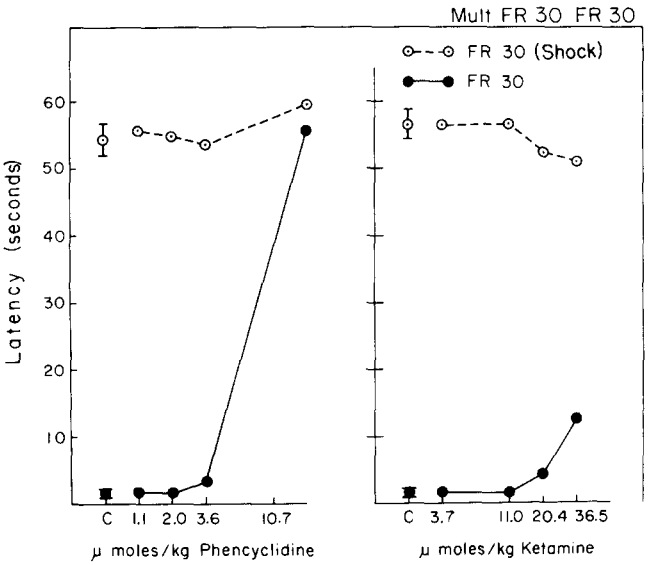

FIG. 4. Effects of phencyclidine and ketamine on the average response latency. Abscissa: dose, μ moles/kg of body weight on a log scale; ordinate: average response latency in seconds. Vertical lines at C represent the control mean plus or minus 2 standard errors. Each point represents the mean of duplicate determinations in each of 3 pigeons.

latency under both components. Doses of *d*-amphetamine (5.4 and 16.3 μ moles/kg) which clearly reduced responding (Fig. 2) significantly increased response latency. Morphine, however, increased the response latency at 7.9 μ moles/kg, a dose which had no significant effect on response rates under the FR30 (shock) component and only marginal effects on response rates under the FR30 component.

Drug Effects Under the Multiple Schedule

In the second phase of the experiment, the schedule was changed to mult FR30 FR30 (shock). The effects of phencyclidine and ketamine on the rate of responding under the mult FR30 FR30 (shock) schedule (Fig. 3) were qualitatively similar to those observed under the mixed schedule. However, the dose range over which increases occurred was narrower. Only 2 μ moles/kg phencyclidine and 20.5 and 36.5 μ moles/kg ketamine increased responding under the FR30 (shock) component of the multiple schedule. Under the FR30 component, low doses of phencyclidine and ketamine were ineffective, and doses greater than or equal to 3.6 μ moles/kg phencyclidine and 20.4 μ moles/kg ketamine decreased responding.

The highest dose of phencyclidine, 10.7 μ moles/kg, increased the response latency under both components of the multiple schedule (Fig. 4). Lower doses of phencyclidine were without effect. Ketamine also increased the response latency under the FR30 component following high doses (20.4 and 36.5 μ moles/kg), but the same doses decreased the response latency under the FR30 (shock) component of the multiple schedule (Fig. 4).

The effects of pentobarbital, *d*-amphetamine and morphine on the rate of responding in both components are shown in Fig. 5. Under the multiple schedule there were several differences in the effects of these drugs on responding under the two components of the schedule compared to

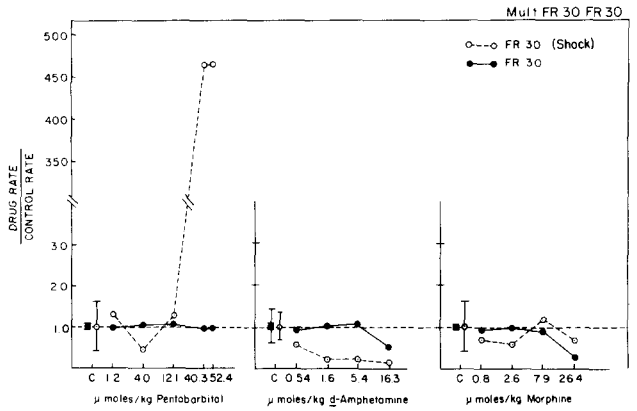

FIG. 5. Effects of pentobarbital, *d*-amphetamine and morphine on the average rate of responding in each component of the multiple schedule. Abscissa: dose, μ moles/kg of body weight on a log scale; ordinate: ratio of the average rate after drug administration to the average rate on non-drug control days. Vertical lines at C represent the control mean plus or minus 2 standard errors. The broken horizontal line represents the mean control value. Mean control rates of responding for the FR30 and FR30 (shock) components are: pentobarbital, 3.18 responses/sec and 0.002 response/sec; *d*-amphetamine, 2.38 responses/sec and 0.002 response/sec; morphine, 3.39 responses/sec and 0.002 response/sec. Each point represents the mean of duplicate determinations in each of 3 pigeons for pentobarbital, and in each of 2 pigeons for *d*-amphetamine and morphine.

the results obtained under the mixed schedule. Pentobarbital had no effect on the rate of responding under the FR30 component of the multiple schedule. However, the rate of responding under the FR30 (shock) component was markedly increased at 40.3 and 52.4 μ moles/kg.

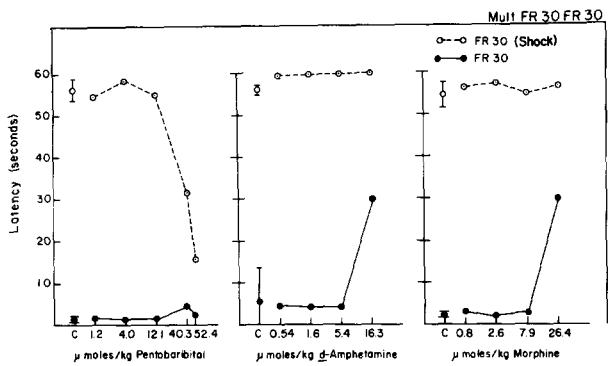

FIG. 6. Effects of pentobarbital, *d*-amphetamine and morphine on the average response latency. Abscissa: dose, μ moles/kg of body weight on a log scale; ordinate: average response latency in seconds. Vertical lines at C represent the control mean plus or minus 2 standard errors. Each point represents the mean of duplicate determinations in each of 3 pigeons for pentobarbital, and in each of 2 pigeons for *d*-amphetamine and morphine.

In contrast, *d*-amphetamine decreased the rate of responding under the FR30 (shock) component at all doses studied, and only the highest dose of *d*-amphetamine (16.3 μ moles/kg) decreased responding under the FR30 component of the multiple schedule. Morphine had no effect on responding under the FR30 (shock) component over a dose range of 0.8–26.4 μ moles/kg. At the highest dose of morphine tested, the rate of responding in the FR30 component was significantly decreased.

The response latency in the FR30 component of the multiple schedule was unaffected at doses below 40.3 μ moles/kg pentobarbital, 16.3 μ moles/kg *d*-amphetamine, and 26.4 μ moles/kg morphine (Fig. 6). Following these high doses, the response latency was increased. Under the FR30 (shock) component, pentobarbital decreased the response latency at doses of 40.3 and 52.4 μ moles/kg. Lower doses of pentobarbital were ineffective. All doses of *d*-amphetamine increased the response latency under the FR30 (shock) component. Morphine did not affect the response latency in the FR30 (shock) component over the dose range examined.

DISCUSSION

In this study, phencyclidine and ketamine produced a small but consistent attenuation of the suppression of responding by brief electrical shocks. Quantitatively, this effect was much less marked than that of barbiturates as seen in this study or in the existing literature on barbiturates [16, 17, 21, 22, 23, 26]. The increases in suppressed responding following phencyclidine in the present study are of the same magnitude as those reported earlier in pigeons responding under a mult FI FI (shock) schedule [2]. The increases observed under the mult FI FI (shock) schedule occurred at slightly lower doses than those reported in the present study, but this probably is a function of the schedule of reinforcement used to maintain the behavior. Phencyclidine and pentobarbital produced greater relative increases in FR30 (shock) responding under the multiple schedule than under the mixed schedule. Ketamine produced approximately equivalent increases in FR30 (shock) responding under both schedules. However, the range of doses of all three drugs which produced increases in suppressed responding was larger under the mixed schedule.

Two factors which have been shown to be important determinates of the behavioral effect of a drug are the rate of responding and the degree of stimulus control. The larger relative increases in suppressed responding under the multiple schedule may in part be due to a 10-fold lower response rate in the FR30 (shock) component of the multiple schedule compared to the mixed schedule. The observed difference in the range of doses producing increases in suppressed responding under the mixed and multiple schedules in this study may be due to differences in stimulus control. As indicated by the response rate in this study, the degree of suppression is greater under the multiple schedule than the mixed schedule even though the shock intensity was the same. Thus, increasing the degree of stimulus control in this situation produces the same expected effect as increasing the intensity of the shock. It has been shown [22] that as responding is increasingly suppressed by increasing intensities of brief electrical shocks, the range of doses of pentobarbital which attenuate the suppression becomes narrower.

d-Amphetamine and morphine, unlike pentobarbital, phencyclidine and ketamine, produced only decreases in response rates under the FR30 (shock) components of both schedules. Even at relatively low doses of *d*-amphetamine, 5.4 μ moles/kg, the rate of responding under both components of the mixed schedule is decreased to less than half of the respective control values. This dose of *d*-amphetamine is generally lower than the doses reported in the literature which decrease FR rates of responding in pigeons in the absence of a suppressing stimulus [18, 19, 20, 28, 30, 32]. That response rate under the FR30 component of the mixed schedule is also decreased a proportional amount, even though brief electrical shocks are not presented in this component, is presumably a function of the lack of stimulus control under the mixed schedule. Under the multiple schedule, the rate of responding in the FR30 component is not decreased by *d*-amphetamine until a dose level of 16.3 μ moles/kg is reached. Thus, when stimulus control is strong and responding has not been suppressed by response-contingent shocks, higher doses of *d*-amphetamine are needed to decrease responding. However, when stimulus control is strong, the rate-decreasing effect of *d*-amphetamine on responding suppressed by brief electrical shocks is greater. Under the multiple schedule, *d*-amphetamine decreased the rate of responding in the FR30 (shock) component at a 10-fold lower dose than that observed under the mixed schedule. This would suggest that *d*-amphetamine may actually enhance the suppression of responding produced by brief electrical shocks. A similar observation was made previously [10,11] following amphetamine administration to rats. There is no suggestion of a similar effect of morphine in this study.

In summary, phencyclidine and ketamine have been shown to possibly possess an unusual profile of behavioral effects. Under a multiple FR FI schedule, phencyclidine and ketamine had previously been shown to have effects similar to amphetamine and unlike pentobarbital [32,33], but in the present study, phencyclidine and ketamine have been shown to have effects unlike amphetamine and possibly like pentobarbital on responding suppressed by brief electrical shocks.

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