Comparison of the Behavioral Effects of Phencyclidine, Ketamine, d-Amphetamine and Morphine in the Squirrel Monkey

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ABSTRACT

The behavioral effects of phencyclidine, ketamine, d-amphetamine and morphine were studied and compared in squirrel monkeys trained to press a response key under an 8-mm fixed-interval (FI) schedule of electric shock presentation with a 30-sec timeout after shock presentation. Under nondrug conditions, a pattern of positively accelerated responding was maintained under the FI schedule and mean response rates were 0.39 and 0.25 response/sec for each of two monkeys. Overall mean rate of responding increased after 0.03 to 0.17 mg/kg of phencyclidine and after 0.01 to 0.1 mg/kg of d-amphetamine and rate decreased after higher doses of either drug. In contrast, ketamine had little effect on responding after 0.3 mg/kg and caused only brief, transient decreases in responding after 1.0 or 3.0 mg/kg. When morphine was administered, mean rate of responding changed little after 0.03 to 0.1 mg/kg and decreased after higher doses. Increases in mean response rate after phencyclidine and d-amphetamine were due primarily to increased responding during the first 5 to 6 min of each FI. Responding either changed little or increased slightly during the last 2 to 3 min of each FI. Whereas the effects of phencyclidine and d-amphetamine were similar, the effect of ketamine was more like morphine in that the latter two drugs decreased responding during the last several minutes of each FI and neither drug reliably increased mean response rate. None of the effects of phencyclidine was shared with morphine. The results extend the response-rate enhancing effects of phencyclidine to shock-maintained behavior and provide additional evidence that phencyclidine can have stimulant-like effects on behavior.

Phencyclidine and ketamine are arylocyclohexylamines that have been used extensively in veterinary medicine as dissociative anesthetics in a variety of species (Chen et al., 1959; Domino et al., 1965; Melby and Baker, 1965). During recent years, however, this class of compounds has been increasingly used by humans as recreational drugs (Petersen and Stillman, 1978). With increased human use have come increased reports of violent behavior, referrals for emergency room treatment and psychiatric hospitalization (Burns and Lerner, 1976; Fauman and Fauman, 1979; Goldstein et al., 1979). The need to understand the dissociative anesthetics and their effects on behavior, including the characterization of changes in learned behavior after drug administration, has precipitated renewed research activity in animal and human subjects.

Recent reports of studies with phencyclidine and ketamine have described effects of subanesthetic doses on conditioned behavior in the mouse (Balster and Baird, 1979; Wenger and Dews, 1976), the pigeon (Wenger, 1976), the rhesus monkey (Balster et al., 1976; Brady et al., 1980; Downs et al., 1980) and the squirrel monkey (Chait and Balster, 1978a, b). In these experiments, subjects were deprived of food and conditioned responding was maintained under various schedules of food presentation. Phencyclidine and ketamine increased responding under FI schedules of food presentation in the mouse and pigeon and phencyclidine had behavioral effects that were described as qualitatively similar to the amphetamines (Balster and Baird, 1979; Wenger, 1976; Wenger and Dews, 1976). Phencyclidine also increased responding during the FI component of a chained schedule of food presentation in the rhesus monkey (Chait and Balster, 1978a), an FI schedule of food presentation in the rhesus monkey (Brady et al., 1980) and a variable-interval schedule of food presentation in the squirrel monkey (Chait and Balster, 1978b). In the experiments with monkeys, at least one dose of phencyclidine increased responding in each subject, although the rate-increasing doses differed among the monkeys.

The present experiment was undertaken to determine and describe the effects of phencyclidine and ketamine on responding under FI schedules of shock presentation in the squirrel monkey and to determine whether the behavioral effects of the two drugs are similar to those reported under schedules of food presentation.

ABBREVIATION: FI, fixed-interval.
presentation. A second objective was to determine whether the effects of phencyclidine and ketamine resemble the behavioral effects of d-amphetamine in the squirrel monkey. Balster and Baird (1979), Wenger (1976) and Wenger and Dews (1976) have reported that amphetamine, phencyclidine and ketamine have similar behavioral effects in the mouse and the pigeon, but a comparison has not been made in monkeys. Subsequently, morphine, an opiate agonist, was added to the study when the behavioral effects of ketamine appeared to be qualitatively similar to effects obtained with morphine in an earlier study with squirrel monkeys (Byrd, 1976).

**Methods**

**Subjects.** Two mature male squirrel monkeys (*Saimiri sciureus*) were housed between daily sessions in individual wire-mesh cages where food and water were available. The monkeys (SM-145 and SM-146) were fitted with leather collars and handled in a manner similar to that described by Kelleher et al. (1963). Each monkey had extensive behavioral training involving schedules of shock presentation, but each was drug-naive at the beginning of the present experiment.

**Apparatus.** Experimental sessions were conducted daily in a ventilated, sound-attenuating chamber containing a Plexiglas restraining chair of the type described previously (Byrd, 1979). When seated in the restraint chair, the monkey faced a wall supporting a response key (Coulbourn Instruments, no. E21-03) and 7.5-watt (a.c.) colored bulbs. Each downward depression of the key with a force of approximately 20 g (0.19 n) registered a response and produced a click of a feedback relay. A small stock held the monkey's tail motionless so that electric current could pass through two brass plates resting on a shaved area 6 to 12 cm from the tip of the tail. Electrode paste (EKG Sol) was applied to the shaved area minimized changes in resistance between the monkey and a 650-V (a.c.), 60 Hz shock source. Continuous white noise and an exhaust fan masked extraneous sounds. Electronic switching circuitry controlled the experiment and recorded data.

**Procedure.** Key-press responding was initially engendered under a schedule of shock postponement and then maintained under a schedule of shock presentation as described previously (Byrd, 1972, 1979). Numerous studies now have shown that schedule-appropriate responding can be maintained in the squirrel monkey (Barrett, 1978; Byrd, 1972, 1976, 1979; McKeearney, 1968, 1969) and the cat (Byrd, 1969) by the response-dependent presentation of electric shock after a history of training under shock postponement.

For the present experiment, responding was maintained under an 8-min FI schedule of shock presentation, i.e., the first response to occur after 8 min had elapsed in the presence of red light was followed by the delivery of a 200 msec, 8 mA electric shock through the brass electrodes resting on the tail. A 30-sec timeout, during which the experimental chamber was darkened and key pressing had no consequences, followed completion of the interval and presentation of electric shock. Experimental sessions were conducted daily, Monday through Friday. Each session terminated after the completion of 10 FIs or 100 min, whichever occurred first.

Phencyclidine hydrochloride, ketamine hydrochloride, d-amphetamine sulfate and morphine sulfate were dissolved in distilled water for injection. Doses were determined in terms of the salt and were injected i.m. into the thigh in a volume of approximately 0.5 ml. Doses of a given drug were studied in a mixed sequence with at least 3 days intervening between successive administrations of the drug. The order in which the four drugs were studied and the number of administrations of each dose per animal were: ketamine, 1; phencyclidine, 3; d-amphetamine, 2; and morphine, 2. Sodium chloride (0.9%) was used for control (placebo) injections. Ketamine and phencyclidine were administered immediately before the session and d-amphetamine and morphine were injected approximately 10 min before the session.

**Results**

**Control performance.** Responding under the 8-min FI schedule of shock presentation during sessions without drugs was similar to the performance typically maintained in the squirrel monkey under FI schedules of food presentation (Goldberg et al., 1976), stimulus shock termination (Kelleher and Morse, 1964) or shock presentation (Byrd, 1972, 1976; McKeearney, 1974). The pattern of responding under the FI schedule comprised an initial period of little or no responding followed by a gradual increase in rate of responding during the

![Fig. 1. Effect of phencyclidine, d-amphetamine and morphine dose on overall mean response rate maintained under an 8-min FI schedule in two squirrel monkeys. The horizontal broken line at 100% represents the mean rate obtained when saline was injected (control) and the response rate after each dose is expressed as percentage of control rate. Vertical lines through the symbols indicate the S.E.M.](image-url)
remainder of the interval, i.e., a pattern of positively accelerated responding. Mean response rates for the two monkeys were 0.39 (SM-145) and 0.25 (SM-146) response/sec during the period encompassed by the study.

Effects of phencyclidine. The relation between phencyclidine dose and overall mean response rate conformed to an inverted U-shaped function (fig. 1). Intermediate doses increased response rate and a dose of 0.3 mg/kg decreased responding. Cumulative response records revealed that the higher mean rate of responding after phencyclidine was due to increased responding during the first 5 to 6 min of the interval, with little or no change in responding during the remainder of the interval (fig. 2). As a result, the pattern of positively accelerated responding became more linear as dose increased. Also, the effect of phencyclidine persisted for the duration of the session. At a dose of 0.17 mg/kg, for example, phencyclidine produced relatively constant responding at an enhanced rate in SM-146 during each of the 10 intervals comprising the session, and there was little evidence of recovery of the base-line performance during the session.

Effects of ketamine. In contrast to phencyclidine, doses of 0.3 to 3.0 mg/kg of ketamine had only transient effects on performance. When injected immediately before the session, 0.3 mg/kg of ketamine decreased responding slightly during the first interval of the session, but had no effect on responding during the remainder of the session (fig. 3). A dose of 1.0 mg/kg decreased responding during the first two intervals and 3.0 mg/kg decreased responding during the first 3 to 4 intervals of the session. Even at 3.0 mg/kg, however, responding during the last half of the session was similar to control performance. The brevity of the effect of ketamine was confirmed when 0.3 mg/kg was injected during the timeout after the second FI of the session. Response rate decreased slightly during the third interval of the session, but otherwise, responding was relatively unaffected by the injection. The transient nature of the suppressant effect of ketamine and the absence of enhancement of responding were confirmed when the intervals with decreased responding were ignored and mean rate was computed based on the remaining intervals of the session. When 0.3, 1.0 or 3.0 mg/kg was injected and mean rate was determined during the last 9, 8 or 6 intervals of the session, respectively, the rates obtained fell within the range of rates observed after saline injection. Therefore, at none of the doses studied was there evidence of enhanced responding after ketamine administration.

Effects of d-amphetamine. The relation between d-amphetamine dose and overall mean response rate followed an inverted U-shaped function (fig. 1). The magnitude of the enhancing effect of d-amphetamine on mean response rate was greater than the enhancing effect observed with phencyclidine. Doses of 0.01 to 0.1 mg/kg of d-amphetamine increased overall mean response rate under the FI schedule as much as 2.5 times the control rate in SM-146 and doses of 0.3 to 1.0 mg/kg decreased mean rate. Cumulative records indicated that the increase in overall mean rate of responding was due to increased responding during the first 5 to 6 min of each FI and lesser increases during the last 2 to 3 min of each FI (fig. 4). As a consequence, the pattern of positively accelerated responding
became more linear and rate became more constant throughout each FI as dose increased.

**Effects of morphine.** In contrast to the response-rate enhancing effects of phencyclidine and d-amphetamine, morphine did not reliably increase mean response rate in either monkey at doses of 0.03 to 1.0 mg/kg. Responding was relatively unaffected at the lower doses (0.03–0.1 mg/kg) and mean response rate either changed little or decreased at doses above 0.1 mg/kg (fig. 1). The cumulative records showed further that the primary effect of morphine at the higher doses was to decrease responding during the last 3 to 4 min of each FI (fig. 5). Although there was occasionally some slight increase in responding during the first half of the FI, as after 0.3 mg/kg in monkey SM-146 (fig. 5), overall mean response rate did not reflect an increase because responding during the last several minutes of the FI decreased at the same time and offset the earlier increase. Consequently, the pattern of responding became more linear as dose increased due primarily to a decrease in rate during the last half of the FI. At 1.0 mg/kg, responding occurred at a relatively constant, uniform rate throughout each interval and the session.

**Discussion**

This study shows that phencyclidine can enhance shock-maintained responding in the squirrel monkey in a manner similar to that observed with food-maintained responding. Responding maintained under an 8-min FI schedule of shock presentation in the squirrel monkey increased to nearly 1.5 times the nondrug rate after the administration of 0.03 to 0.17 mg/kg of phencyclidine. Lower doses had little or no effect and higher doses decreased responding, resulting in an inverted U-shaped function. Phencyclidine produced comparable increases in response rate and a similar inverted U-shaped function in the mouse (Balster and Baird, 1979; Wenger and Dews, 1976), the pigeon (Wenger, 1976), the squirrel monkey (Chait and Balster, 1978a,b) and the rhesus monkey (Brady et al., 1980). Therefore, the present results confirm earlier reports of the enhancing effect of phencyclidine on schedule-controlled responding and extend this effect to responding maintained under a schedule of response-produced electric shock.

In contrast with the phencyclidine data, there was no evidence that ketamine enhanced response rate under the FI schedule in the squirrel monkey. Doses as high as 3.0 mg/kg decreased responding for relatively brief periods, but none of the doses increased responding. The absence of an enhancing effect after ketamine contrasts with earlier reports describing increased responding in the mouse (Wenger and Dews, 1976), the rat (Meliska and Trevor, 1978), the pigeon (Wenger, 1976) and the rhesus monkey (Brady et al., 1980). In those species, ketamine reportedly increased responding under FI schedules of food presentation. The basis for the difference in effect is not apparent inasmuch as the present experiment shared many features in common with the earlier studies. For example, the duration of the FI schedule and the range of doses were similar to those used in the study by Brady et al. (1980) in the rhesus

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**Fig. 4.** Effect of d-amphetamine dose on pattern of responding under an 8-min FI schedule in a squirrel monkey. Otherwise, as in figure 2.

**Fig. 5.** Effect of morphine dose on pattern of responding under an 8-min FI schedule in a squirrel monkey. Otherwise, as in figure 2.
monkey, yet responding reportedly increased in the rhesus monkey but did not increase in the squirrel monkey. It is possible that the difference in effect between the rhesus and squirrel monkeys could be due to 1) the previous experience of the rhesus monkeys with cannabinoids because the squirrel monkeys were drug naive at the beginning of the experiment, 2) the use of food-maintained responding with the rhesus monkeys and shock-maintained responding with the squirrel monkeys or 3) differences in the metabolic fate of ketamine in the two species. None of these possibilities can be rejected on the basis of available data.

In addition to the absence of increased responding, the effect of ketamine was extremely brief when compared with phencyclidine, and even after 3.0 mg/kg, responding was decreased for less than half a session. In contrast, the effects of phencyclidine in squirrel monkeys could be due to 1) the previous experience of the rhesus monkey with cannabinoids because the squirrel monkeys were drug naive at the beginning of the experiment, 2) the use of food-maintained responding with the rhesus monkeys and shock-maintained responding with the squirrel monkeys or 3) differences in the metabolic fate of ketamine in the two species. None of these possibilities can be rejected on the basis of available data.

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To test the hypothesis that phencyclidine has "amphetamine-like" effects in the squirrel monkey, a wide range of doses of d-amphetamine was administered and the effects of the two drugs were compared. The effects obtained with d-amphetamine were characteristic of this drug when responding in the squirrel monkey is maintained under FI schedules of food presentation (Kelleher and Morse, 1968; Goldberg et al., 1976), shock termination (Kelleher and Morse, 1964) or shock presentation (Barrett, 1977; Byrd, 1976; McKearney, 1974). Mean response rate under the FI schedule increased after doses of 0.01 to 0.1 mg/kg and higher doses decreased response rate. Although the magnitude of the increase in rate was greater after d-amphetamine, the dose-effect functions for d-amphetamine and phencyclidine were similar, approximating inverted U-shaped curves. Both drugs increased responding under schedules of shock presentation and both drugs increased responding under FI schedules of food presentation in the monkey (Brady et al., 1980; Chait and Balster, 1978a; McKearney, 1974). Moreover, with both drugs, the pattern of positively accelerated responding engendered under the FI schedule became more linear, i.e., response rate became more uniform and constant, as dose increased. This effect was due largely to the action of d-amphetamine and phencyclidine in increasing responding during the first several minutes of each FI.

In the present experiment, ketamine, unlike phencyclidine, decreased responding during the last half of each FI with little effect on responding during the first part of the FI. This result was sufficiently similar to the effect of morphine reported previously in squirrel monkeys (Byrd, 1976) that morphine was administered and compared directly with ketamine and phencyclidine. In contrast with d-amphetamine, morphine decreased mean rate of responding after doses greater than 0.1 mg/kg and had little or no effect otherwise. These results provide additional evidence that morphine decreases responding monotonically in the squirrel monkey when responding is maintained under FI schedules of food presentation (Goldberg et al., 1976) or FI schedules of shock presentation (Byrd, 1976). In a comparison of morphine with ketamine, both drugs had qualitatively similar effects on shock-maintained responding, but the effect of ketamine was briefer in duration. Neither drug reliably increased mean response rate; both drugs increased responding during the last several minutes of each FI with little or no increase in rate during the first part of the FI. Comparison of the effects of morphine with those of phencyclidine revealed little similarity in the behavioral effects of those two drugs. Phencyclidine had enhancing effects on responding in the squirrel monkey, as described above, whereas morphine decreased mean response rates in the same subjects.

The similarity between the effects of phencyclidine and d-amphetamine in the present experiment contributes to the growing evidence that phencyclidine has some amphetamine-like properties. In addition to studies showing that phencyclidine and amphetamines have similar effects on schedule-controlled behavior (Balster and Baird, 1978; Wenger, 1976; Wenger and Dew, 1976), experiments have shown that phencyclidine can also enhance amphetamine-induced behavior (Balster and Chait, 1978). Moreover, phencyclidine can block dopamine uptake in the rat brain and can result in rotational movements in the rat that are blocked by dopamine antagonists (Finnegan et al., 1976; Smith et al., 1975). These effects of phencyclidine are characteristic of amphetamine and other substances that can act as indirect dopaminergic agonists, thus supporting the speculation that phencyclidine and amphetamine may share a common mode of action.

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References


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