JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 1983, 40, 313-320 NUMBER 3 (NOVEMBER)

EFFECTS OF d-*AMPHETAMINE ON SELF-AGGRESSION AND POSTURING IN STUMPTAIL MACAQUES*

P. G. PEFFER-SMITH, E. O. SMITH, AND L. D. BYRD

YERKES REGIONAL PRIMATE RESEARCH CENTER
EMORY UNIVERSITY

The behavioral effects of *d*-amphetamine sulfate were studied in adult male stumptail macaques living within a large heterogeneous group in an outdoor enclosure. Among five subjects that received a range of doses (.01 to .3 mg/kg), *d*-amphetamine increased self-aggressive behavior and abnormal posturing in subjects that exhibited these types of behavior prior to drug administration, but it had no effect in subjects not exhibiting those activities in the absence of the drug. For the former subjects, the dose-effect curves for self-aggression were of an inverted U-shape analogous to the effect of *d*-amphetamine on schedule-controlled behavior. Over the range of doses studied, the curve for abnormal posturing was monotonic. The data indicate that *d*-amphetamine can have effects on untrained behavior in individual animals in a quasinatural environment that are qualitatively and quantitatively similar to the behavioral effects observed in other laboratory environments, and that *d*-amphetamine does not evoke or increase a behavioral response in individual subjects that do not exhibit the response in the absence of the drug.

Key words: *d*-amphetamine, self-aggression, posturing, *Macaca arctoides*

Amphetamine has been studied extensively for its effects on behavior in human and nonhuman subjects. A pronounced rate-enhancing effect of amphetamine on nonpunished, schedule-controlled responding has been demonstrated in a number of species under a variety of conditions (Dews & Wenger, 1977; Kelleher & Morse, 1968). Moreover, amphetamine typically has little tendency to increase responding that is suppressed or punished by the presentation of a noxious stimulus even though response rate can be increased by other drugs, such as sedative-hypnotics (Geller & Seifter, 1960; Kelleher & Morse, 1964; Wuttke & Kelleher, 1970). Also, for certain types of performances, amphetamine can increase low rates of responding and decrease high rates, with the result that there is a transition toward a relatively constant or uniform rate of responding (Byrd, 1981; Dews, 1958; Gonzalez & Byrd, 1977).

In addition to the above, there is another, less well established behavioral phenomenon that is associated with the administration of amphetamine. It has its origins in data reported by Dews (1955) and Verhave (1958) and involves the significance of predrug responding as a determinant of the behavioral effect of the drug. In the study reported by Verhave (1958), the behavioral effect of methamphetamine was studied in rats trained to press a response key and in untrained rats that did not respond or press the key. The administration of methamphetamine did not result in key pressing in the untrained rats but did increase responding substantially in trained rats. When the untrained rats were given training, methamphetamine increased their responding also. Dews (1955) reported related results in an experiment on the effect of methamphetamine on discriminative performance in pigeons. Under nondrug conditions, little or no responding occurred in the presence of a stimulus (S^{Δ}) associated with nonreinforcement, and doses that would typically produce marked increases in response rate failed to induce or increase responding during the S^{Δ} stimulus. A subsequent study by Clark and Steele (1966) showed, however, that response rate during an S^{Δ} stimulus could be increased by amphetamine even though the rate prior to drug administration was quite low.

This work was supported by U. S. Public Health Service Grants DA-01161, DA-02128, RR-00165, and RR-00167 (Division of Research Resources, National Institutes of Health). S. Martin, F. Haman, P. Plant, and F. Kiernan assisted in preparing the manuscript and illustrations. Send reprint requests to: P. G. Peffer-Smith, Yerkes Regional Primate Research Center Field Station, Emory University, 2409 Collins Hill Rd., Lawrenceville, Georgia 30245.

Unfortunately, the data from these experiments do not allow one to determine whether (a) some minimum rate of responding is necessary for amphetamine to have an enhancing effect on responding or (b) a specific history of training, conditioning, or experience with the contingencies controlling the availability of reinforcement is necessary. In an effort to clarify this issue and to determine more definitively whether the occurrence of the behavior prior to the administration of amphetamine is a determinant of the effect of the drug, we conducted a study in monkeys using two classes of behavior that occurred spontaneously or naturally—that is, they occurred without explicit training or conditioning—and we compared the effect of *d*-amphetamine in monkeys exhibiting the behavior with those not exhibiting the behavior. *d*-Amphetamine was chosen because it is one of the more behaviorally active of the amphetamines and because there is a relatively extensive literature describing the behavioral effects of the compound in various animal subjects.

METHOD

Subjects

The subjects were five adult male stumptail macaques (*Macaca arctoides*) ranging in age from 5 to 11.5 years that were members of a large group. The 37 members of the group were of both sexes and varied in age from newborn to aged adult. The group was confined within a 28.4 by 32.7 m outdoor enclosure or compound with environmentally controlled indoor quarters adjacent to and accessible via two metal tunnels (Smith & Peffer-Smith, in press).

Procedure

Animals were restricted to the outdoor compound by locking them out of the indoor quarters on a strict daily schedule, weather permitting. Observations of the subjects and acquisition of data were made from a tower located 4.3 m above one side of the compound. All animals were readily visible from the tower. Data were obtained using the focal-animal observation technique described by Altmann (1974). The focal-animal sampling technique allows the recording of all occurrences of behavioral action of a specific monkey and its interactions with other monkeys during a given time period. The technique documents when the focal animal initiated or received any type of behavior, with which animal, and in what sequence. Data were collected by experienced observers during 15-min time periods at 0 to 15, 15 to 30, 30 to 45, 45 to 60, 90 to 105, 150 to 165, 210 to 225, and 330 to 345 minutes postinjection. Observational periods were distributed in this manner in order to obtain data characterizing the effects over time without continuous observation and to document behavioral changes we thought might occur during the first hour postinjection as the drug effect developed. The data were entered in a digital format into a portable microprocessor-based data collection device, the Datamyte 900, as the behavior was occurring. Briefly, each monkey was assigned a two-digit numerical code, and each activity was assigned a three-digit numerical code so that a behavioral occurrence would require the entrance of a seven-digit sequence into the Datamyte, as described by Smith and Begeman (1980). Later in the day, the data stored in the Datamyte were transferred via direct hook-up to a Digital Equipment Corporation PDP 11/23 minicomputer for permanent storage and for data processing and analysis. To assure reliability among observers, tests for levels of agreement were conducted intermittently, as described by Smith (1981a). Agreement was consistently high.

In order to administer drugs without using physical restraint and without exciting the animals, each of the five subjects in the experiment was trained to enter a small, isolated area along one side of the outdoor compound (Smith, 1981b), extend an arm through an opening, and accept an intramuscular injection according to procedures described previously (Byrd, 1973, 1977). On a given day, each of the five monkeys received either a drug injection, a saline (placebo) injection, or no injection. Only the experimental animal for that day received the drug, however. The drug was administered two days per week, but a given animal was the experimental or drug subject no more than once per week. *d*-Amphetamine sulfate was dissolved in sterile normal saline and all injections were intramuscular in a volume of .4 to 1.0 ml. Normal saline served as a control or placebo injection. Each of four doses (.01 to .3 mg/kg) was studied three times in each subject in an

unsystematic order, with saline administrations interspersed irregularly among the drug administrations. The observers responsible for data collection did not know whether saline or drug was administered to the focal animal on a given day.

Two types of behavior were studied. Self-aggression was defined as any self-directed facial or vocal threat or any self-directed activity that had the potential for physical damage. A self-aggressive bout was scored as one occurrence regardless of duration; self-aggression was scored again if the animal interrupted or changed the pattern of behavior—for example, bit its hand after pulling the hair on its chin. A second class of behavior, posturing, was characterized by the unusual placement or positioning of a part of the body (e.g., a limb) and was scored in a manner similar to that described for self-aggression (i.e., an unusual placement was scored as one occurrence regardless of duration and was scored as another occurrence if the monkey interrupted or changed the unusual posture). Frequency counts of each class of behavior were used to derive mean rate of occurrence of each activity per hour for individual subjects under drug and nondrug conditions. Dose-effect functions were determined based on the rate of occurrence of the behavior during the period 45 to 165 minutes postinjection, a time period during which maximum effects were typically obtained with the various doses studied and a time period that has frequently served as a basis for quantifying the effects of *d*-amphetamine with other behavioral paradigms.

RESULTS

During the course of the experiment, three of the monkeys (M-13, M-18, and M-24) never exhibited any type of self-aggressive behavior or abnormal posturing in the control or nondrug condition. The other two subjects, however, did exhibit self-aggression in the absence of the drug. The mean rate of occurrence of self-aggressive behavior during the period 45 to 165 min postinjection was 10.67 per hour in Monkey M-06 and .67 per hour in Monkey M-10 on days when saline was administered. Monkey M-10 typically was very intense and almost frantic in its self-aggression. It would repeatedly bite its arms, legs, fingers, or toes, firmly grip its arms or legs, and emit facial and vocal threats to parts of its own body. Monkey M-06 was less intense in its self-aggression, and it would hit or pull its brow or arms, pull hair on its chin, and bite its arms, often while slowly jumping up and down bipedally. The factors that precipitated this behavior were not always apparent. Self-aggression was preceded occasionally by abrupt termination by another monkey of mounting or grooming attempts by the subject, aggression to or from other group members, self-grooming, or disturbances from infants. In addition to self-aggression, Monkey M-10 also occasionally exhibited unusual or abnormal posturing. The rate of occurrence of this behavior was very low and typically did not exceed once or twice per day under nondrug conditions. Abnormal posturing in Monkey M-10 was characterized by the movement of a hind limb to the top of the head where it rested motionless or moved slowly across the top of the head. Posturing typically occurred while the monkey sat quietly and appeared inattentive to its surroundings. During the course of the experiment, there was no evidence of change in the baseline or nondrug rate of occurrence of self-aggression or posturing in either monkey.

Over a range of doses encompassing 1.5 log units (.01 to .3 mg/kg), *d*-amphetamine increased markedly the rate of self-aggressive behavior in Monkey M-06 and M-10 (Figure 1). Both monkeys displayed dose-dependent effects of *d*-amphetamine on self-aggression and the dose-effect curves were of an inverted-U shape. No change in rate was observed after .01 mg/kg, and maximum increases in self-aggression were observed after a dose of .1 mg/kg. The highest dose (.3 mg/kg) yielded increases of lesser magnitude for both monkeys. The rate of self-aggression after .1 mg/kg was significantly greater ($p < .05$) than the rate observed after saline administration (*t* test for samples with unequal variances; Sokal & Rohlf, 1981). Self-aggressive behavior was never observed in Monkeys M-13, M-18, and M-24 when *d*-amphetamine or saline was administered and, consequently, data for those monkeys are not shown.

A time-course analysis of the effects of *d*-amphetamine on self-aggression revealed comparable functions for Monkeys M-06 and M-10, even though the former monkey displayed a much larger increase in self-aggressive behavior than the latter. Individual time-

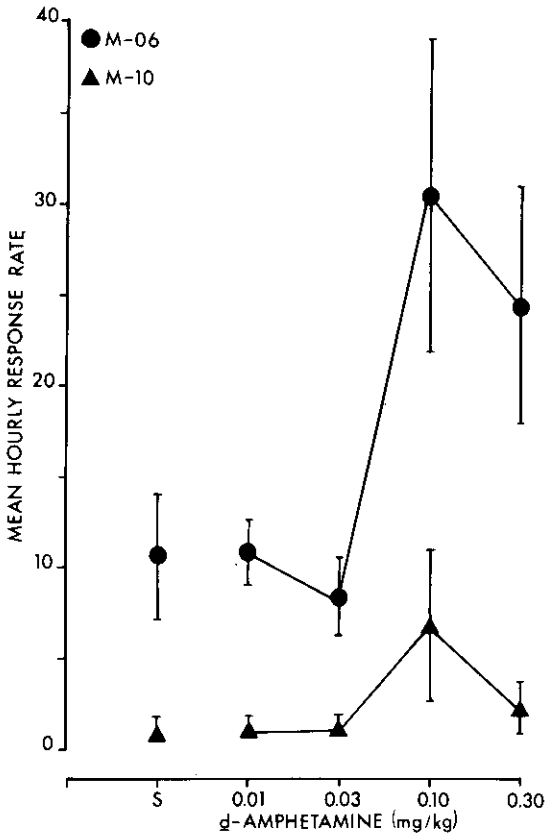

Fig. 1. Effect of *d*-amphetamine on rate of self-aggression in two stumptail macaques. Each data point is the mean rate ± SEM during the period 45 to 165 min postinjection based on three administrations of each dose. Data points (*S*) to the left of the dose-effect curves were obtained when saline was administered as a control.

course functions for .1 mg/kg *d*-amphetamine, the dose that produced the maximum increase in self-aggressive behavior, are displayed in Figure 2. For both monkeys, the maximum increase in self-aggressive behavior after .1 mg/kg occurred during the period 45 to 105 min postinjection; self-aggressive activity then decreased as postinjection time increased. The rate of occurrence of self-aggressive behavior returned to baseline values within 6 hours postinjection.

Analysis of the effects of *d*-amphetamine on posturing revealed that the drug had a similar rate-enhancing effect on this behavior in Monkey M-10, the only animal in which posturing was ever observed to occur under nondrug conditions. As dose increased from .01 to .3 mg/kg, the rate of occurrence of posturing increased, and the maximum rate was observed at the highest dose studied (Figure 3). At .3 mg/kg, the rate of occurrence of posturing was approximately 17 times the rate observed in the absence of the drug. This rate was significantly greater ($p < .05$) than the rate observed after saline administration (*t* test for samples with unequal variances; Sokal & Rohlf, 1981). In none of the other four subjects was there ever an occurrence of any behavior resembling the posturing behavior observed in Monkey M-10.

When the time-course effect of the drug on posturing was determined, *d*-amphetamine was found to have its maximum enhancing effect on posturing during a period 90 to 105 min postinjection (Figure 4). The increased rate then diminished toward the original baseline value as postinjection time increased. The time of maximum increase in posturing in Monkey M-10 coincided with the postinjection time of maximum increase in self-aggression in Monkey M-06. A saline curve is not shown in Figure 4 because posturing behavior did not occur on the days when saline was administered. The behavior was observed, however, on days when neither saline nor drug was administered and, therefore, it was known that the behavior had an average rate of 1 to 2 times per day under nondrug conditions.

DISCUSSION

The results presented in this report show that *d*-amphetamine can have effects on the behavior of individual animals in a semifree ranging or quasinatural environment that are qualitatively and quantitatively similar to the behavioral effects observed in an isolated and highly controlled laboratory environment. *d*-Amphetamine produced dose-dependent increases in the rate of occurrence of activities that were emitted under nondrug conditions in the group setting. For self-aggressive behavior, the dose-effect curves that resulted described an inverted U-shape. These results are consistent with and indicative of the effects *d*-amphetamine has been found to have on conditioned or learned behavior in individual subjects of various species (Dews & Wenger, 1977; Kelleher & Morse, 1968). Moreover, there is a close correlation between the time-course functions described by the present data and those reported previously. In the present study, the enhancing effect of *d*-amphetamine

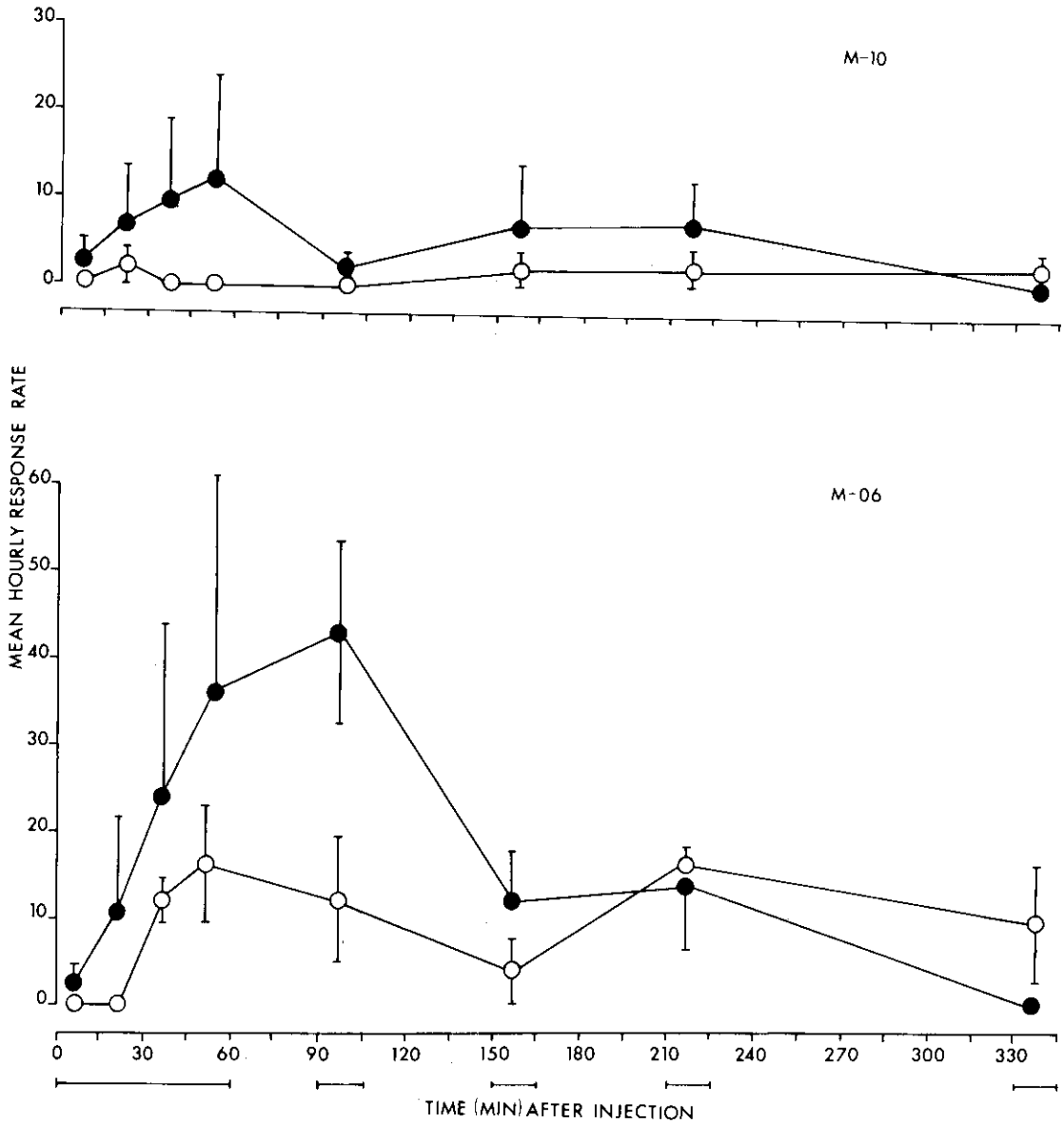

Fig. 2. Time-course effects of .1 mg/kg *d*-amphetamine on self-aggressive behavior in Monkeys M-10 (top) and M-06 (bottom). Each data point is the mean ± SEM based on three administrations of the drug (filled circles) or saline (unfilled circles). Line segments beneath the *x* axis indicate time periods during which subjects were observed and data were obtained.

on self-aggression reached a maximum 45 to 105 min after injection, and then responding decreased gradually. Others have reported comparable time-course functions showing that the maximum plasma level and behavioral effect are obtained during the first two to three hours postinjection (Costa & Garattini, 1970; Gonzalez & Goldberg, 1977). Therefore, the present experiment extends the generality of the rate-enhancing effect of *d*-amphetamine to include behavior emitted by members of a group in a quasinatural environment and, more specifically, behavior for which there is no known history of conditioning.

The present experiment also emphasizes the importance of the occurrence of behavior under nondrug conditions as a determinant of the behavioral effect of the drug. *d*-Ampheta-

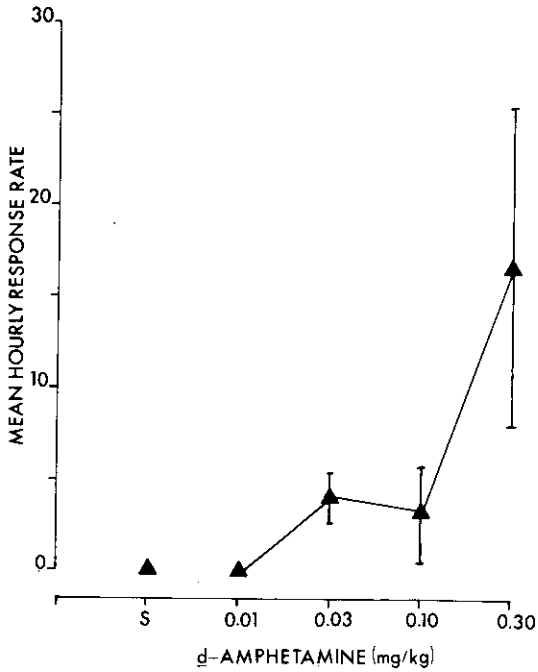

Fig. 3. Effect of *d*-amphetamine on rate of abnormal posturing in Monkey M-10. Each data point is the mean rate ± SEM during the period 45 to 165 min postinjection based on three administrations of each dose. The data point (*S*) to the left of the dose-effect curve was obtained when saline was administered as a control.

mine increased the rate of self-aggression in the two monkeys that exhibited self-aggression prior to drug administration, but self-aggression was not observed to occur prior to or following drug administration in the other three subjects. Moreover, *d*-amphetamine increased abnormal posturing in the monkey (M-10) that exhibited posturing under nondrug conditions, but the drug did not cause posturing in the other four subjects. Therefore, *d*-amphetamine produced dose-dependent increases in the rate of occurrence of self-aggression and of abnormal posturing when those types of behavior were emitted prior to drug administration, but *d*-amphetamine did not result in the occurrence of those activities when they were not emitted in the absence of the drug.

The failure of *d*-amphetamine to evoke or increase self-aggression or posturing in subjects that did not exhibit the behavior under nondrug conditions contributes to a better understanding of the studies reported previously by Dews (1955), Verhave (1958), and Clark and Steele (1966). In those experiments, the effects of amphetamine on conditioned key pecking in the pigeon and key pressing in the rat were studied. Verhave reported that methamphetamine did not affect key pressing in rats not trained to make the response, but it did enhance responding once training began and the subjects were emitting the behavior prior to drug administration. In Dews' experiment, methamphetamine did not evoke or increase key pecking during a stimulus (S^{Δ}) in the presence of which reinforcement was not scheduled and responding did not occur, but responding did increase in the presence of the

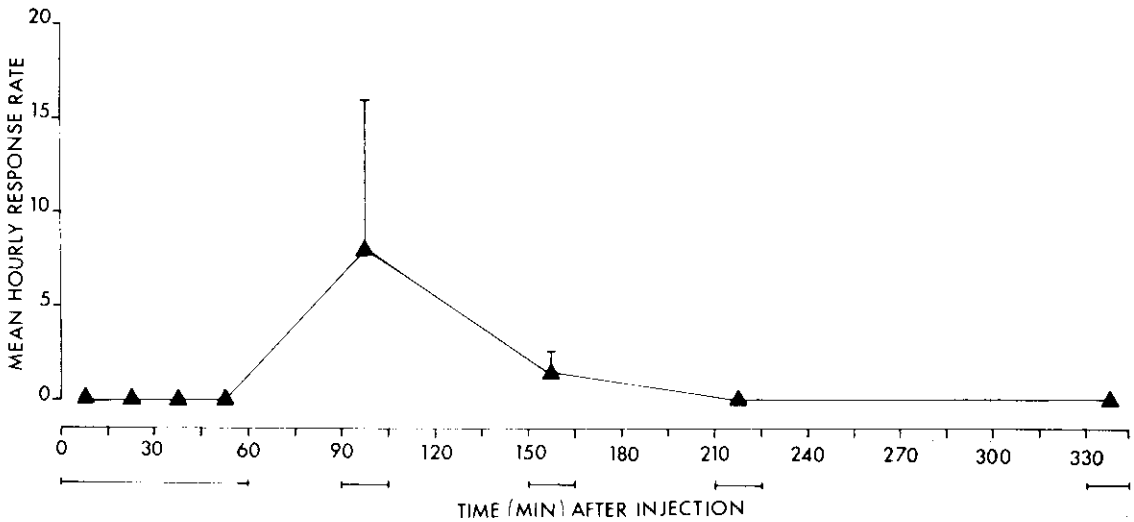

Fig. 4. Time-course effects of .1 mg/kg *d*-amphetamine on abnormal posturing in Monkey M-10. Each data point is the mean ± SEM based on three administrations of the drug. Line segments beneath the *x* axis indicate time periods during which subjects were observed and data were obtained.

stimulus associated with food presentation. In the Clark and Steele (1966) experiment, responding occurred at a low rate during an S^{Δ} stimulus and responding increased after the administration of *d*-amphetamine. Unfortunately, these three studies did not allow one to determine unambiguously whether the effects of amphetamine were dependent upon prior occurrence of the behavior per se or upon control of the behavior via a reinforcement contingency. The present experiment eliminated the latter possibility from consideration by focusing on behavior that occurred without the imposition of a reinforcement contingency, and it was possible to demonstrate that the effects of amphetamine were dependent upon the occurrence of the behavior prior to drug administration. The present data cannot be attributed to a specific history of training or conditioning or to the presence of a reinforcement contingency because there were no known contingencies controlling self-aggression for any of the five subjects studied.

In view of the studies by Verhave, Dews, and Clark and Steele, Kelleher and Morse (1968) concluded that "amphetamines have less tendency to enhance responding in individuals that have no history of responding than in individuals that have responded" (p. 33). The present data are consistent with the Kelleher and Morse statement and they provide additional confirmation of the validity of the statement. *d*-Amphetamine can increase the occurrence of behavior such as self-aggression only in subjects that exhibit the behavior in the absence of the drug. Sollmann characterized the phenomenon more eloquently in his book when he stated that "pharmacologic agents do not create new functions . . . they can only modify existing functions" (Sollmann, 1934, p. 87).

The effects of drugs on the behavior of individual subjects in a relatively natural group setting have not received extensive investigation in the experimental analysis of behavior. Yet, the understanding of behavior and its pharmacological modification in a natural environment are of ultimate concern, especially as they apply to human health and welfare. The present study provides additional evidence that the behavioral effects of drugs observed in the laboratory do generalize to the natural environment and that the study of behaviorally active substances in a relatively natural social group of nonhuman primates can provide orderly and meaningful data.

REFERENCES

Altmann, J. Observational study of behavior: Sampling methods. *Behaviour*, 1974, **49**, 227-265.

Byrd, L. D. Effects of *d*-amphetamine on schedule-controlled key pressing and drinking in the chimpanzee. *Journal of Pharmacology and Experimental Therapeutics*, 1973, **185**, 633-641.

Byrd, L. D. Introduction: Chimpanzees as biomedical models. In G. H. Bourne (Ed.), *Progress in ape research*. New York: Academic Press, 1977.

Byrd, L. D. Quantitation in behavioral pharmacology. In T. Thompson, P. B. Dews, & W. A. McKim (Eds.), *Advances in behavioral pharmacology* (Vol. 3). New York: Academic Press, 1981.

Clark, F. C., & Steele, B. J. Effects of *d*-amphetamine on performance under a multiple schedule in the rat. *Psychopharmacologia*, 1966, **9**, 157-169.

Costa, E., & Garattini, S. (Eds.). *International symposium on amphetamines and related compounds* (Proceedings of the Mario Negri Institute for Pharmacological Research, Milan, Italy). New York: Raven Press, 1970.

Dews, P. B. Studies on behavior: II. The effects of pentobarbital, methamphetamine and scopolamine on performances in pigeons involving discriminations. *Journal of Pharmacology and Experimental Therapeutics*, 1955, **115**, 380-389.

Dews, P. B. Studies on behavior: IV. Stimulant actions of methamphetamine. *Journal of Pharmacology and Experimental Therapeutics*, 1958, **122**, 137-147.

Dews, P. B., & Wenger, G. R. Rate-dependency of the behavioral effects of amphetamine. In T. Thompson & P. B. Dews (Eds.), *Advances in behavioral pharmacology* (Vol. 1). New York: Academic Press, 1977.

Geller, I., & Seifter, J. The effects of meprobamate, barbiturates, *d*-amphetamine and promazine on experimentally induced conflict in the rat. *Psychopharmacologia*, 1960, **1**, 482-492.

Gonzalez, F. A., & Byrd, L. D. Physiological effects of cocaine in the squirrel monkey. *Life Sciences*, 1977, **21**, 1417-1423.

Gonzalez, F. A., & Goldberg, S. R. Effects of cocaine and *d*-amphetamine on behavior maintained under various schedules of food presentation in squirrel monkeys. *Journal of Pharmacology and Experimental Therapeutics*, 1977, **201**, 33-43.

Kelleher, R. T., & Morse, W. H. Escape behavior and punished behavior. *Federation Proceedings*, 1964, **23**, 808-817.

Kelleher, R. T., & Morse, W. H. Determinants of the specificity of behavioral effects of drugs. *Ergebnisse der Physiologie, Biologischen Chemie und Experimentellen Pharmakologie*, 1968, **60**, 1-56.

Smith, E. O. Assessment of interobserver reliability in observational research. *American Journal of Primatology*, 1981, **1**, 357-358. (a)

Smith, E. O. Device for capture and restraint of monkeys. *Laboratory Animal Science*, 1981, **31**, 305-306. (b)

Smith, E. O., & Begeman, M. L. BORES: Behavior observation recording and editing system. *Behavior Research Methods & Instrumentation,* 1980, **12,** 1-7.

Smith, E. O., & Peffer-Smith, P. G. Adult male-immature interactions in captive stumptail macaques (*Macaca arctoides*). In D. M. Taub (Ed.), *Primate paternalism: An evolutionary and comparative view of male investment.* New York: Van Nostrand Reinhold, in press.

Sokal, R. R., & Rohlf, F. J. *Biometry: The principles and practice of statistics in biological research* (2nd ed.). San Francisco: W. H. Freeman, 1981.

Sollmann, T. H. *A manual of pharmacology* (4th ed.). Philadelphia: Saunders, 1934.

Verhave, T. The effect of methamphetamine on operant level and avoidance behavior. *Journal of the Experimental Analysis of Behavior,* 1958, **1,** 207-219.

Wuttke, W., & Kelleher, R. T. Effects of some benzodiazepines on punished and unpunished behavior in the pigeon. *Journal of Pharmacology and Experimental Therapeutics,* 1970, **172,** 397-405.

Received February 23, 1983
Final acceptance July 6, 1983