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Differential Effects of d-Amphetamine on Fixed Ratio 30 Performance Maintained by Food versus Brain Stimulation Reinforcement

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CAREY, R. J., E. B. GOODALL AND G. F. PROCOPIO. *Differential effects of d-amphetamine on fixed ratio 30 performance maintained by food versus brain stimulation reinforcement.* PHARMAC. BIOCHEM. BEHAV. 2(2) 193–198, 1974. – Four rats with implanted unilateral hypothalamic bipolar electrodes were trained to bar press for both intracranial self-stimulation (ICSS) and food on a fixed ratio 30 schedule of reinforcement. The animals were tested at 90% and 100% body weight. d-Amphetamine (0.1, 0.5, 1.0, 1.5, 2.0 mg/kg) always decreased responding for food reinforcement but increased responding up through the 1.0 mg/kg dose level for ICSS. An analysis of error responses emitted for ICSS reinforcement showed that perseverative responding did not occur up through the 1.0 mg/kg level.

d-Amphetamine Fixed ratio Food Brain stimulation

IT IS well-established that the schedule of reinforcement under which a behavior is maintained is an important determinant of the behavioral effect of amphetamine [2]. In addition to the reinforcement schedule, it has recently been suggested that the type of reinforcer which is delivered on a particular schedule is also important [1]. Specifically, it has been reported that responding generated by a fixed interval (FI) schedule using intracranial self-stimulation (ICSS) of the brain as the reinforcer is markedly increased by amphetamine at dose levels which sharply decrease responding on the same FI schedule when food reinforcement is used.

The present study was undertaken to extend this comparison of ICSS vs. food reinforcement to a fixed ratio (FR) schedule. This particular schedule was selected because it has been repeatedly demonstrated that the high rates of responding generated by FR schedules using appetitive reinforcers are decreased by amphetamine [3]. The present study evaluates whether this general finding applies also to FR responding when ICSS is used as the reinforcer. In addition to varying the reinforcer, food vs. ICSS, response rate was also manipulated by modifications in the level of food deprivation.

METHOD

Animals

Four male Sprague-Dawley rats, weighing 450–500 g at the start of the experiment, were used. Three rats completed all phases of testing but one rat because its electrode loosened could only be tested at the 2 lowest dose levels of amphetamine. Throughout the experiment the rats were housed individually in a temperature- (72° ± 2°), humidity- (60% ± 5%), and illumination- (12-hr light, 12-hr dark)

controlled room. Water was available ad lib, but food availability depended upon experimental conditions.

Surgery

A bipolar stainless-steel electrode (Plastic Products Co., Roanoke, Va.) 0.01 in. in dia. and insulated except for the cross-sectional area at the tip was implanted in each rat. Each electrode was positioned in the lateral hypothalamus with the aid of a Kopf stereotaxic instrument. Surgery was aseptic and performed with the rat under deep ether anesthesia. The stereotaxic coordinates used were: 1.2 mm posterior to bregma, 1.5 mm lateral to the midline sinus, and 8.9 mm ventral to the surface of the skull with the incisor bar fixed 3.2 mm above the interaural line. Each rat received 200,000 units of procaine penicillin following surgery. Upon completion of testing, the rats were sacrificed by ether anesthesia and intracardially perfused with 0.9% saline followed by 10% Formalin. Electrodes were removed with the skull held in the stereotaxic instrument. After fixation in 10% Formalin, 3 mm thick blocks of brain tissue containing the area of electrode implants were embedded in paraffin and from this block 6 μ thick sections were cut, mounted and stained with cresyl violet. All electrode tip placements were histologically verified to be located in the lateral hypothalamus.

Apparatus

All testing was done in two 10 1/2 × 12 × 9 1/2 in. operant chambers housed individually in sound-attenuating enclosures (LVE No. 1417). One chamber was used for ICSS reinforcement and was equipped with two 1 1/8 × 3/8 in. levers mounted 5 1/2 in. apart on one panel. The levers projected 1 1/4 in. into the chamber and required a force of 15 g to activate an attached microswitch. The second chamber contained a single lever and food cup mounted on one panel. A pellet feeder which dispensed 45 mg P. J. Noyes lab rat pellets provided reinforcement in this chamber. Each chamber was illuminated by a 15 V lamp mounted at the top center of the side panel.

For the ICSS, each lever press triggered a Grass Brief Pulse Stimulator (Model BPS1) to deliver intracranially a 0.2 sec train of 0.1 msec bidirectional pulse pairs at 100 pulses/sec. Current was monitored continuously on a Tektronix Type 502A oscilloscope by determining the voltage drop across a 1K resistor in series with the animal. The rat was connected to the stimulator through a mercury-swivel commutator mounted above each chamber.

Two large photoactivity cages (LVE No. 1497) were used to record activity changes. These were cylindrical cages, 24 in. in dia., and 21 in. high, with a wire mesh floor. Six infra-red photocells were placed 1 in. above the floor and equally spaced around the perimeter of the cage to detect movement. Two digital counters recorded beam interruptions. Each counter recorded from a set of 3 photocell units.

Procedure

ICSS training was started 2 weeks postoperatively. During this phase only one lever was present in the chamber and each response was reinforced. After ICSS was well-established, a second lever was introduced into the chamber. Using a procedure adapted from Pliskoff, Wright and Hawkins [4], ICSS was made available on the left lever only after the required number of responses were made on the right lever. Throughout testing 15 ICSS reinforcements were delivered on a CRF schedule on the left lever. The response requirements on the right lever were gradually increased over sessions from 1 to 30 for all animals. During this FR segment of the schedule the house light was off and any responses made on the left ICSS lever were not reinforced. After the 30th response was made on the right FR lever, the house light went on and 15 ICSS reinforcements were available on the left lever. After the 15th ICSS reinforcement was obtained on the left lever, the house light again went off and the FR segment of the schedule was reinstated.

Concurrent with ICSS training, a food deprivation regimen was established and animals were maintained at 90% of their ad lib body weight. In a separate operant chamber the animals were trained to lever press for food (45 mg pellets, P. J. Noyes Co., Lancaster, N. H.). Response requirements were gradually increased from 1 to 30 and then maintained at FR 30 until a reliable FR 30 performance was established for each animal. During the FR segment, the house light was off and the 30th response turned on the house light and the next response produced delivery of a food pellet. After delivery of the food pellet the house light went off and the FR 30 schedule was reinstated.

Testing for food and ICSS on the FR 30 schedule was conducted daily in successive sessions separated by a 5 min interval spent in the home cage. The test order of food vs. ICSS was always counterbalanced and all animals were tested until stable response rates were achieved.

Amphetamine test sequence. Over-all, the test procedure was to compare the effects at five dose levels of d-amphetamine HCl (K and K Laboratories, Jamaica, N.Y.) on FR responding for food vs. ICSS reinforcement under deprived (90% body weight) and nondeprived (100% body weight) conditions. After stable response rates were established for ICSS and food under the deprived conditions all animals were placed on ad lib feeding and tested first at the 2 lowest dose levels (0.1 and 0.5 mg/kg) under the nondeprived condition. Next, the animals were returned to the deprived condition and tested under the 5 dose levels of amphetamine in ascending order. Finally, animals were again returned to the nondeprived condition and tested at the three highest dose levels of amphetamine. This test sequence was used in order to counterbalance to some extent the possible order effects of amphetamine treatments for the deprived and nondeprived conditions.

The test procedures were the same under all conditions. Initially the animals were placed in the activity cages for 30 min to obtain a measure of general activity. Immediately after the activity measurement, the animals were tested in the operant chambers for food or ICSS reinforcement in two successive 30 min sessions separated by a 5 min interval spent in the home cage. Throughout the experiment the order of testing, ICSS vs. food, was counterbalanced. On amphetamine test days the animals were given the IP amphetamine injection and immediately placed in the activity cages and run through the entire sequence which required approximately 95 min. At least 3 days intervened between amphetamine injections and a nondrug test day always preceded an amphetamine test day. Under the deprived and nondeprived conditions the amphetamine doses were administered in an ascending order.

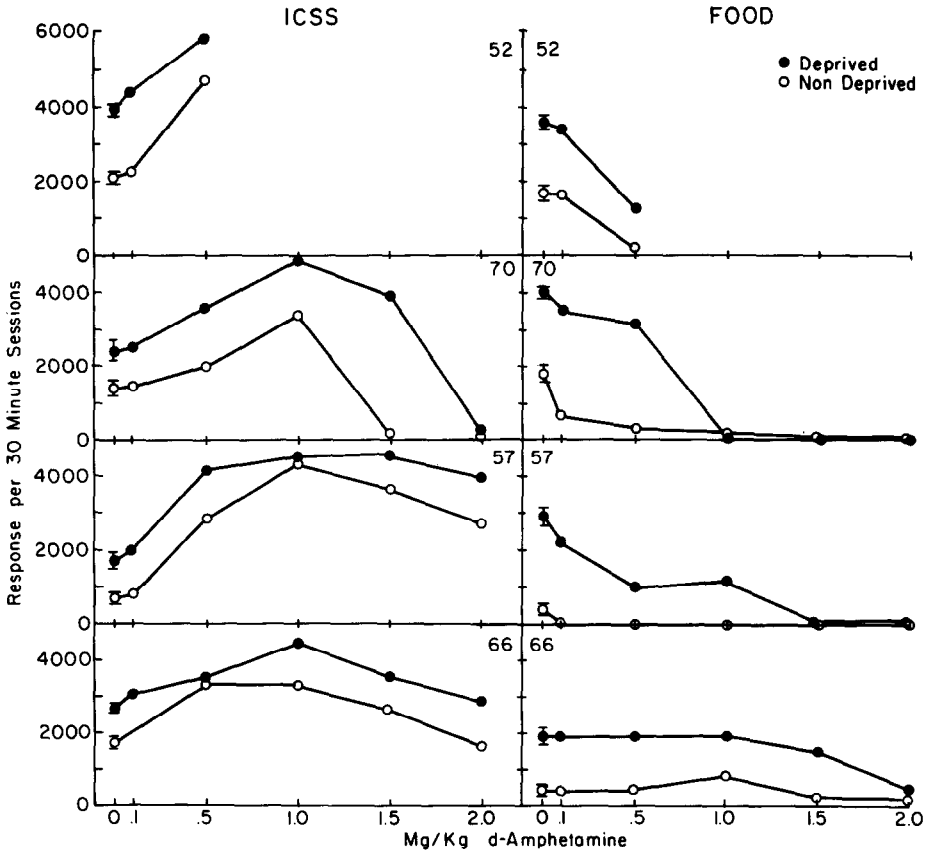

FIG. 1. Individual data showing the responses emitted for food vs. ICSS reinforcement delivered on a FR 30 session under 5 dose levels of d-amphetamine. Vertical bars indicate standard errors of the means on the non-drug sessions.

RESULTS

Figure 1 presents the responses emitted per session by individual animals for food and ICSS reinforcement delivered on an FR 30 schedule under food-deprived and nonfood-deprived conditions. The zero drug level in this and all other figures indicates the mean and standard error for the 5 nondrug or baseline tests. As expected, food deprivation resulted in a large increase in food-reinforced responding and also reliably increased responding for ICSS. Surprisingly, 2 animals (No. 52 and No. 70), when tested nondeprived, maintained substantial response rates for food and always consumed the food pellets. Possibly these 2 animals preferred the food pellets delivered in the operant chamber to the food provided in the home cage. Amphetamine, however, differentially affected food vs. ICSS-reinforced FR 30 responding.

For food-reinforced FR 30 performance amphetamine only decreased responding from baseline levels, whereas for ICSS amphetamine facilitated responding in 3 animals up through the 1.0 mg/kg dose levels. Animal No. 52 was similarly affected by amphetamine, but could only be tested at the two lowest dose levels because its electrode loosened. Thus, the reinforcer which maintained the FR responding rather than the baseline response rate was the important determinant of the effect of amphetamine. Also, large differences in baseline response rates produced by alterations in deprivation level did not modify the observed effect of amphetamine on responding for food or ICSS.

In order to provide a further analysis of the effect of amphetamine on responding for ICSS reinforcement, Fig. 2 presents the percentage of perseverative or error responses emitted on the FR and CRF levers, respectively. The percentage of error responses on the FR lever was calculated by dividing the total number of responses on the FR lever into the number of responses which exceeded the FR 30 requirement. As can be seen in Fig. 2, under baseline conditions the error-response level on the FR lever was very low and remained low for all animals up through the 1.0 mg/kg dose level. For 2 animals (No. 57 and No. 66), error responses did increase at the 2 highest dose levels (1.5 and 2.0 mg/kg) suggesting a response perseveration effect. The missing data points for No. 70 occur at dose levels where no responses were emitted. Again, No. 52 could only be tested at the two lowest dose levels of amphetamine. For the CRF lever, the error responses were computed by dividing the total number of CRF responses emitted on the CRF lever into the number of nonreinforced responses made on this lever. Although the baseline error responses were somewhat higher for the CRF lever compared to the FR lever, the over-all effect of amphetamine was similar. In general, the

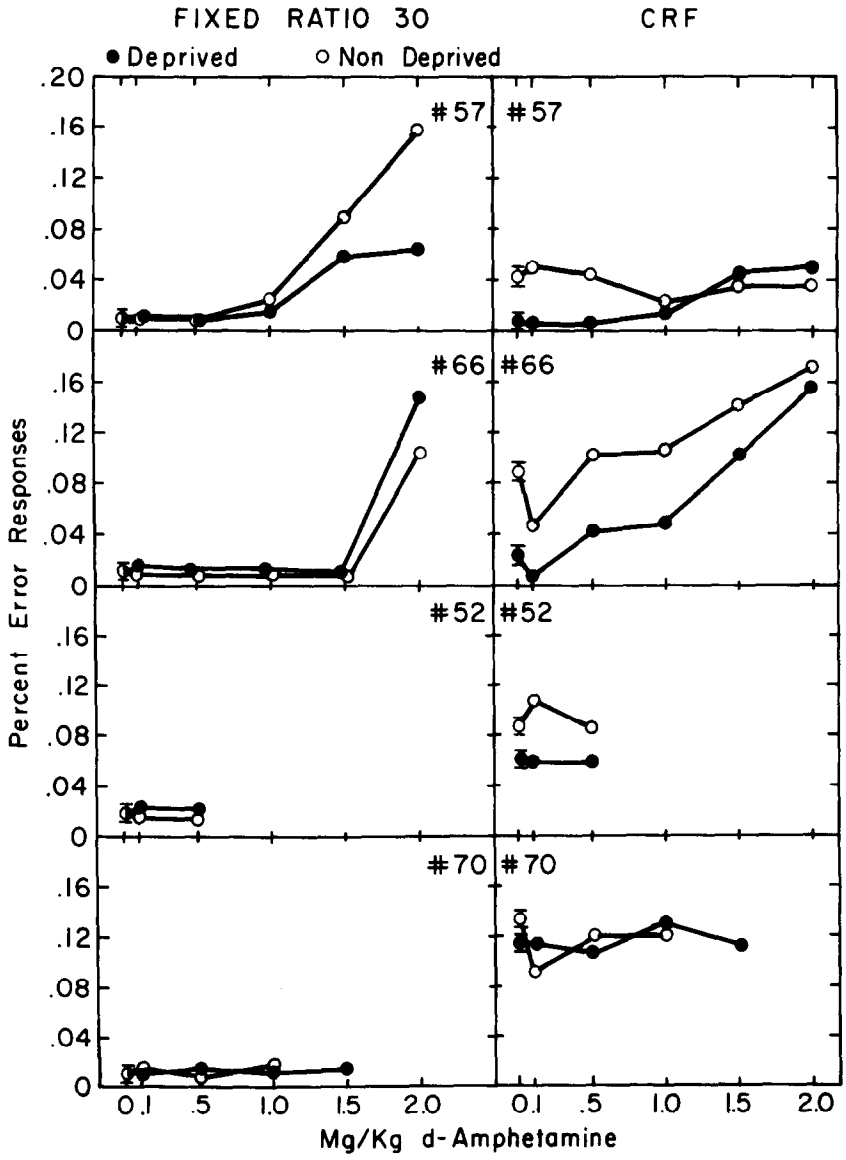

FIG. 2. Individual data showing the percentage of total responses per ICSS session which were error responses under the 5 dose levels of d-amphetamine. Error responses emitted on both the FR and ICSS levers are indicated. Vertical bars indicate the standard errors of the means on the nondrug sessions.

results presented in Fig. 2 indicate that perseverative responding accounted for but a small percentage of the FR responding for ICSS and at only the highest dose levels of amphetamine was perseverative responding increased.

Figure 3 presents the photobeam activity measures obtained for each animal. For the 3 rats which received all dose levels of amphetamine activity level was a monotonic increasing function of amphetamine up to the 1.0 mg/kg dose and then became asymptotic. A comparison of Figs. 1 and 3 indicates that the facilitative effects of amphetamine on activity and ICSS performance were comparable in magnitude and direction up to the 1.0 mg/kg dose level, but at higher dose levels the dose effect functions for these two behavioral measures were dissimilar. While it might be construed that the effects of the higher doses of amphetamine on ICSS performance were independent of effects on activity, it is also possible that important but undetected changes occurred in the topography but not the frequency of activity behavior at the higher dose levels. Finally, the virtual identity of the effects of amphetamine on activity

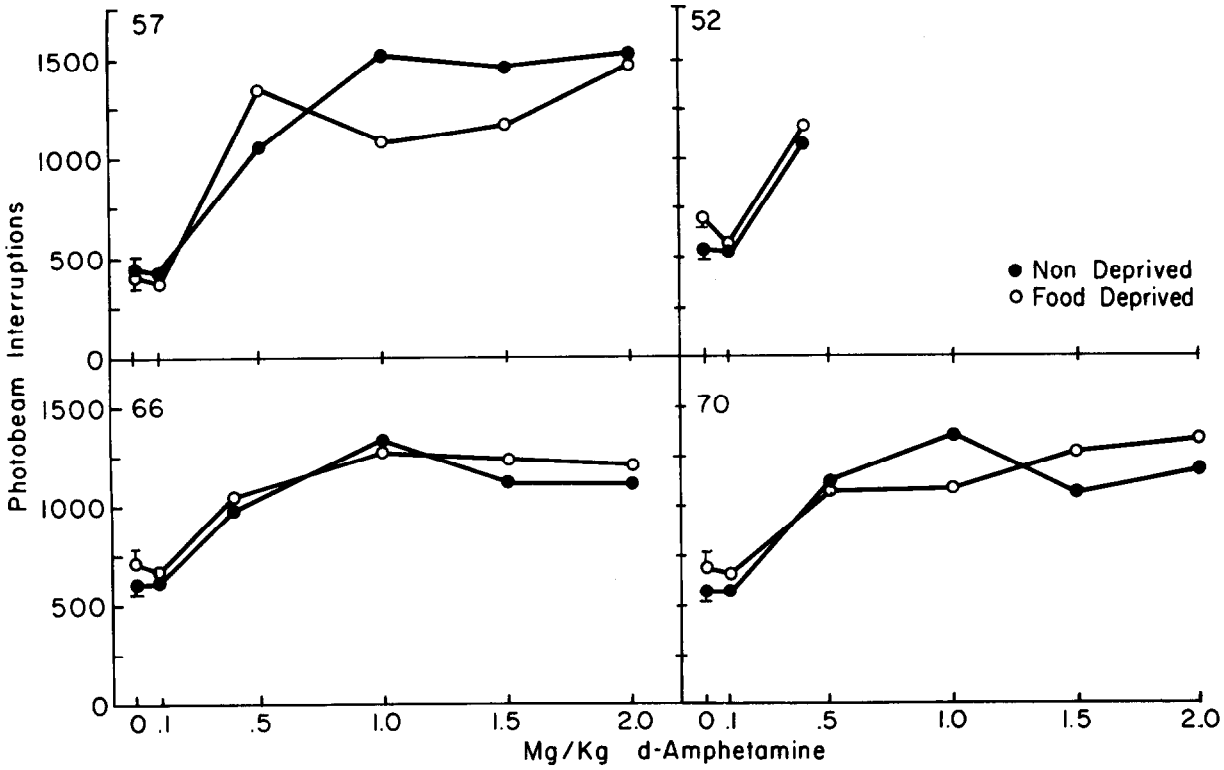

FIG. 3. Photobeam cage activity levels for individual animals as a function of d-amphetamine dose level. Vertical bars indicate the standard errors of the means for the nondrug days.

under the deprived and nondeprived conditions show that for this behavioral measure the effect of amphetamine was independent of the 10% change in body weight.

DISCUSSION

It is well-established that amphetamine differentially affects the reinforcing potency of food vs. ICSS. Specifically, amphetamine has an anorexic effect on food intake but enhances ICSS [5]. This differential effect was preserved in the present study when each of these reinforcers was made available on a FR 30 schedule. Thus, FR responding for food was always decreased under amphetamine, whereas FR responding for ICSS was markedly facilitated by amphetamine at least up through the 1.0 mg/kg dose level. While it has been frequently demonstrated that the reinforcement schedule under which a particular reinforcer is delivered is a powerful determinant of the effect of amphetamine, it would also appear that the reinforcer used to maintain behavior under a particular schedule also is an important determinant of the effect of amphetamine. A useful empirical generalization derived from studies on the effect of amphetamine on responding maintained under different reinforcement schedules is that the effects of amphetamine are rate dependent [2]. That is, amphetamine tends to increase low-rate responding but decrease high-rate responding. In the present study, however, large response-rate changes produced by alterations in deprivation level did not alter the direction of the effect of amphetamine. Since response-rate differentials generated by reinforcement schedules are maintained by subtle and complex differences in stimulus control, it is probably not too surprising that a response-rate differential produced by a deprivation level change is not affected in the same way by amphetamine.

The effect of amphetamine on FR responding for ICSS is interesting also in terms of error responses. Up through the 1.0 mg/kg dose level amphetamine resulted in a large increase in response rate but yet did not disrupt the accuracy of performance. That is, the animals stopped and started responding on the appropriate levers under the appropriate stimulus conditions. Thus, while amphetamine is usually disruptive to performance of a complex behavioral task, this was not the case for the FR 30 ICSS-reinforced schedule up through the 1.0 mg/kg dose level.

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