Pharmacology Biochemistry & Behavior, Vol. 7, pp. 519–528.

Reduction of Heroin Self-Administration in Baboons by Manipulation of Behavioral and Pharmacological Conditions[1]

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(Received 6 April 1977)

WURSTER, R. M., R. R. GRIFFITHS, J. D. FINDLEY AND J. V. BRADY. *Reduction of heroin self-administration in baboons by manipulation of behavioral and pharmacological conditions.* PHARMAC. BIOCHEM. BEHAV. 7(6) 519–528, 1977. – Baboons responded on a discrete-trial choice task on which trials occurred every three hours throughout the day. Trials involved choosing between several mutually exclusive options, one of which was always associated with intravenous infusion of a unit dose of heroin. Experiments were undertaken to reduce the selection of the heroin option. Experiment 1 used methods analogous to clinical situations involving opioid maintenance and subsequent detoxification. During initial baseline conditions, baboons consistently preferred an option of heroin and food over an option of saline and food. Selection of heroin was almost entirely eliminated when there was a mutually exclusive choice between heroin and food and chronic non-contingent morphine was administered. Decreasing the dose of non-contingent morphine produced an increased selection of heroin. In Experiment 2, initial baseline conditions were similar to Experiment 1. Food availability was subsequently made contingent upon selection of options involving progressively lower doses of contingent heroin. These manipulations reduced heroin intake to about 15% of baseline levels. The experiments demonstrate the utility of animal models for studying procedures for the reduction of opiate self-administration.

Drug self-administration Heroin Morphine Choice procedure Animal models

THE PRIMARY focus of most research concerning infrahuman drug self-administration has been on the conditions for the establishment and maintenance of drug-taking behavior [14,30]. For example, environmental and pharmacological manipulations, including altering the drug dose [10], changing the response requirement [26,35], and pretreatment with another drug [6, 27, 33, 35, 36], have been shown to produce systematic changes in drug self-administration behavior. Schuster [29] has noted that animal drug self-administration may provide a model for evaluating factors which diminish drug-taking and which may have possible therapeutic applications. To our knowledge, there have been no infrahuman studies utilizing several simultaneous manipulations which specifically focused on reduction and elimination of drug self-administration as an endpoint.

In the current study, a discrete-trial choice methodology was used with baboons to examine two procedures designed to reduce intravenous heroin intake. The utility of the discrete-trial choice procedure for the analysis of environmental and pharmacological variables which may interact with drug reinforcement has been previously demonstrated and discussed [19,23]. The procedure involves discrete trials on which the animal chooses between two or more mutually exclusive options, each associated with different consequent events. Because the behavioral requirement is virtually identical for selecting any option, and because the major dependent variable is percent choice of the options, systematic changes in the choice performance can not be attributed to interactions with relatively non-specific factors such as local response rates, variations in stimulus control or the type of response required.

The distinguishing feature of the current choice experiments was that at all times, choice of one of the available options resulted in the intravenous infusion of a unit dose of heroin. After the baboons demonstrated consistent preference for heroin over saline, this study addressed the question of whether the preference for heroin could be reduced or eliminated by manipulating behavioral and pharmacological variables. The first experiment used methods analogous to clinical situations involving opioid maintenance and subsequent detoxification. Specifically, during baseline conditions baboons consistently preferred an option resulting in both the delivery of food and an

[1] Supported in part by NIDA Grants DA-01147 and DA-00018. The authors would like to thank J. Snell and D. Holland for their expert technical assistance.

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infusion of heroin over an option resulting in delivery of the same amount of food, but an infusion of saline. Selection of heroin was almost entirely eliminated when there was a mutually exclusive choice between heroin and food and chronic non-contingent morphine was administered. The dose of non-contingent morphine was subsequently decreased to zero over a twenty-day period, to determine whether the reduction in choice of the heroin option could be maintained in the absence of morphine. In Experiment 2, initial baseline performance was identical to that of the first study. Heroin self-administration was reduced by using contingent food delivery to reinforce the selection of options involving progressively lower doses of heroin, while the original (i.e., baseline) dose of heroin was always available as an option.

EXPERIMENT 1: REDUCTION OF HEROIN SELF-ADMINISTRATION USING FOOD, CHRONIC NON-CONTINGENT MORPHINE AND SUBSEQUENT MORPHINE WITHDRAWAL

METHOD

Animals

Two male baboons (*Papio anubis*), each weighing approximately 15 kg, served. One animal (CE) was experimentally naive prior to participating in the procedures to be reported; the other (MO) had participated in a previous experiment examining the effects of contingent electric shock upon choice behavior maintained by food delivery. Both animals were drug naive prior to this experiment.

Procedure

The baboons were individually housed in sound-attenuated cubicles measuring 0.8 × 0.8 × 1.2 m, and were restrained in a primate restraint chair described in detail previously [11]. The animals were seated facing a panel which formed the back wall of the cubicle, and which contained the manipulanda and stimulus lights. A speaker in the upper right of the panel delivered masking noise continuously. Water was continuously available through a drinking tube in the cubicle.

The discrete-trial choice procedure, which has been described previously [19], involved spaced trials on which the animal chose between two mutually exclusive options (represented by different colored lights), each associated with different consequent events. More specifically, the availability of a choice trial occurred at an interval of about 3-hr since completion of the preceding trial. The time-out period between trials was adjusted several minutes short of 3-hr, and thus permitted animals to consistently complete 8 trials in a 24-hr period. The beginning of a trial was indicated by an 8-sec tone followed by the illumination of a light directly over the initiate lever at the far left of the panel. A three-response fixed-ratio requirement on the initiate lever was necessary to proceed with the trial. Upon completion of this initiate ratio, the baboon was presented with one of two colors in the center stimulus light bay of the intelligence panel. The color initially presented for each trial alternated on a 50% basis regardless of the results of previous trials. Simultaneously, the light over the initiate switch was extinguished while a second light was illuminated over the switching lever located immediately to the left of center of the panel. Completion of a five-response fixed-ratio requirement on the switching lever changed the color presented in the stimulus light bay. In order to proceed with a trial, the baboon was required to change colors (switch) at least twice; the animal could then continue switching or proceed with the trial by completion of five responses on the Lindsley lever, also located on the left of the panel. This switching requirement assured that the animal was exposed to both stimulus conditions on each trial. After the switching requirement was met, responding on the Lindsley lever five times consecutively resulted in the extinction of the jewel light over the switching lever, and further responding on the switching lever had no programmed consequences. The color presented in the center bay at this time prevailed for the duration of the trial. Also at this time, an avoidance requirement on the Lindsley lever of an additional ten responses to be made within 2-min came into effect. Under this schedule, every two minutes a three-second illumination of a white light in the stimulus light bay was followed by an electric shock (2 mA, 0.25 sec) through a tail electrode, unless the animal made ten responses within the two minutes. Responses made in the presence of the white light had no programmed consequences. When the avoidance requirement was fulfilled, the center stimulus light bay was extinguished and the reinforcer which was contingent upon selection of a particular color was delivered if that color had been chosen. Simultaneously, a smaller stimulus light of the same color was illuminated over the central light bay for a period of one hr.

After initial behavioral training on the choice procedure using food reinforcement (described below), the animals were surgically prepared with an intravenous catheter by using the general procedure described by Deneau, *et al.* [7]. Placement of the catheter tip was near the right atrium by way of the jugular vein. The catheter passed subcutaneously and exited in the middle of the back. A detailed description of the infusion system has been presented previously [12]. Briefly, the system consisted of a number of *T* fittings and one-way valves (Becton-Dickinson) resting on a Plexiglas plate mounted on the rear of the restraint chair. The fittings were arranged such that the catheter lines from the pumps which were mounted on top of the animal's chamber joined at the chair to form a single common catheter pathway which entered the animal. This catheter system allowed for the slow continuous administration (50 ml per 24 hr) of saline via a peristaltic pump (Harvard No. 1201) to maintain catheter patency. Drug solution was infused into the valve system on the back plate by means of a syringe pump (Sage No. 239–2) and then flushed into the animal with saline from a second syringe pump. This system resulted in a delay of approximately fifteen seconds between onset of the drug delivery pumps and actual infusion of drug into the vein; however, the drug was completely delivered into the vein within a 1-min period (each pump was activated for a 30-sec duration). The total volume of fluid delivered during each infusion was 4.0 ml (2.0 ml of drug solution followed by 2.0 ml of saline). The total volume of fluid held by the cannula from the valve system to the vein was 1.0 ml. Drug solutions were prepared by dissolving the hydrochloride salt of heroin or morphine in 0.9% saline. Doses were calculated on the basis of the salt.

Early training of the animals on the choice procedure was done with food reinforcers. Initially, completing the work requirement in the presence of either color option

resulted in food availability. Food availability was signalled by the illumination of a light over the food switch at the right of the panel. Completion of a five-response fixed-ratio requirement on this switch resulted in the delivery of five (1-g) Purina monkey pellets into a hopper next to the switch. Animals obtained a total of fifty pellets per trial in this manner during initial training. When they consistently completed all trials available each day, the food was made contingent upon selection of only one of the two color options, while selection of the other option was associated with no programmed consequences. When the animals had demonstrated a consistent preference (88%–100%) for the option associated with food, the colors associated with food consequences and no consequences reversed, and preference was shifted to the previously unreinforced option. This procedure was repeated at least two times with food reinforcement. Subsequently, the magnitude of food reinforcement was made equal in both options, and the animals demonstrated no consistent preference for either option. In the final stage of training, the animals were catheterized and an infusion of heroin was associated with selection of one option, while a saline infusion was associated with the alternate option; the magnitude of food reinforcement remained equal in both options. When the animals demonstrated a consistent preference (75%–100%) for the heroin option, the colors associated with heroin and saline were reversed and their preference shifted to the previous non-drug option.

Baseline performance for this experiment was developed under conditions involving a choice between an option associated with both food and drug, and an option associated with only food. For one animal (MO) selection of the red option resulted in the delivery of 0.64 mg/kg/infusion of heroin plus the availability of 25 food pellets. As described above, pellets were made available by completing a five-response fixed-ratio requirement for five pellets, until the maximum number of pellets was obtained. For the second baboon (CE), selection of the blue option resulted in the delivery of 0.30 mg/kg/infusion heroin plus the availability of 35 pellets. For both animals, selection of the alternative option (green for MO, yellow for CE) resulted in the availability of the same number of pellets (25 for MO, 35 for CE), but with an infusion of saline volumetrically equal to the drug solution. The different drug doses assigned to the two animals were arbitrary; however, the number of pellets available was based on free feeding data for each baboon; total daily pellets available were 80% of the number of pellets eaten under free-feeding conditions. After baseline performance reached a criterion of at least eight days of selection of at least 75% of the combined drug-food option, food was removed from this option, leaving the animals with a choice between food or drug. On the same day, non-contingent infusion of morphine was begun, utilizing the continuous infusion system. For animal MO, infusion of non-contingent morphine was begun at a relatively low rate (125 mg/24 hr) and subsequently increased to 300 mg/24 hr, in order to achieve a shift of preference to the food-only option. Because CE's heroin dose was approximately one-half that of MO, non-contingent morphine was administered at a dose of 150 mg/24 hr to this animal; shift of preference to the food option was accomplished with no further dose manipulations. When both animals demonstrated stable preference (88%–100% choice) for the food option for a period of at least eight days, reduction of the dose of non-contingent morphine was begun at a rate of 20% per day, a reduction rate suggested for human opioid detoxification [22]. These conditions were maintained for 21 days.

RESULTS

During the course of this experiment, both animals initiated trials at the maximum rate of eight per day. They generally completed trials within approximately 2 min of initial availability. Performance in the avoidance component was insensitive to all experimental manipulations, in that neither baboon received any electric shocks during the entire course of the experiment.

Examination of Fig. 1, Segment A, shows that the choice performance of animal MO was stable for the eight consecutive days prior to the first experimental manipulation; during Days 1–8, selection of the combined drug-food (red) option never declined below 75%. The introduction of non-contingent morphine, along with the removal of food as a consequence of selecting the red option, was instituted on Day 9 for MO. During Experimental Days 9–15 (Fig. 1, Segment B), non-contingent morphine was administered at a daily rate of 125 mg; it is apparent that preference for the red option was reduced, with selection of the drug option dropping to 63% of the day's trials on Experimental Days 13 and 15. On Day 16, the non-contingent dose of morphine was increased to 200 mg/day and selection of the drug option was again decreased (Fig. 1, Segment C) to as few as 25% of the daily trials. On Day 26, the non-contingent morphine dose was incremented to 300 mg/day, and the baboon showed a stable decrease in preference (0–12%) for the drug option (Fig. 1, Segment D).

Preference for the drug-only option was increased in animal MO as the dose level of non-contingent morphine was systematically decreased (Fig. 1, Segment E). It can be seen that after the sixth day of this forced detoxification from morphine (Day 46), selection of the heroin option increased to 37% of the trials taken, and with the exception of one day (Day 48) remained at or above this level. Concomitantly, MO's food intake (Fig. 1, bottom panel) dropped, frequently dipping below a total of 100 monkey pellets per day, and stayed at a low level for the duration of the experiment. At the termination of the procedure on Day 60, MO had sustained a body weight loss of 30% although he continued to select the heroin option at a rate which limited food intake.

Baboon CE showed a pattern of responding similar to that of MO. After the simultaneous removal of food from the blue option (heroin) and introduction of non-contingent morphine at the rate of 150 mg/day (Fig. 2, Day 10), the selection of the heroin option dropped to zero within seven days and was maintained at that level for eight consecutive days (Fig. 2, Segment B). Systematic decreases in the morphine dose began on Experimental Day 24; by the eighth day (Experimental Day 31), CE's choice of the heroin option rose to 25% from a baseline of 0%, and stayed at or above this level for all but two days of the duration of the experiment. This animal's body weight remained almost constant throughout the course of these manipulations.

EXPERIMENT 2: REDUCTION OF HEROIN SELF-ADMINISTRATION WITH CONTINGENT FOOD AND CONTINGENT LOW-DOSE HEROIN

Experiment 1 demonstrated that selection of an option

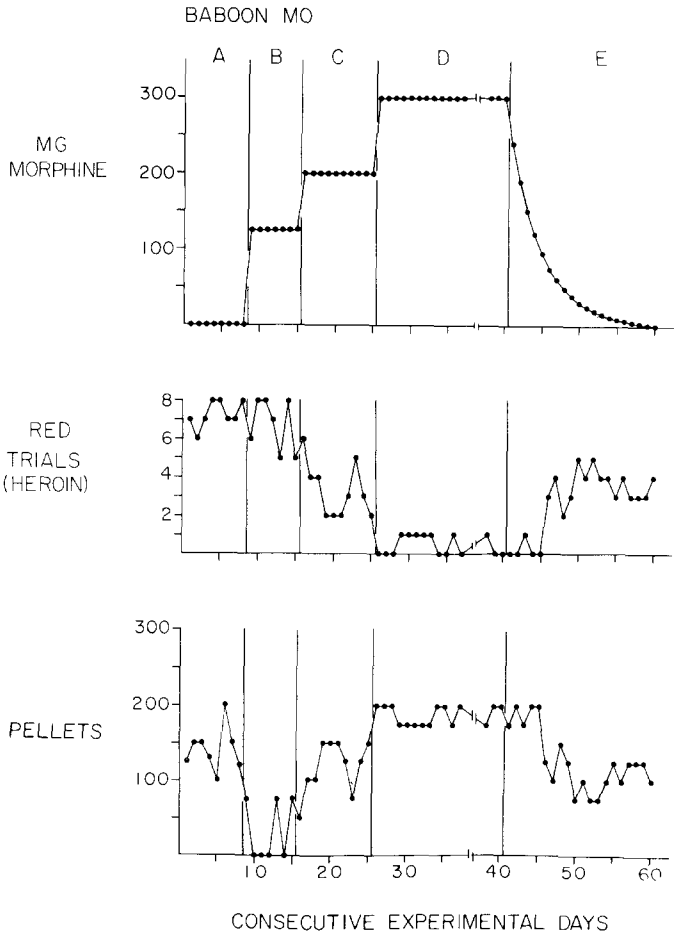

FIG. 1. Daily performance of Baboon MO during Experiment 1. The baboon completed eight trials a day, choosing between red and green options. The upper panel shows total daily morphine dose delivered non-contingently. The middle panel shows the number of times each day the red (heroin) option was chosen (choice between red and green was mutually exclusive; thus, the function representing choice of green was the inverse of that for red). The bottom panel shows the daily number of food pellets delivered. Experimental conditions varied during the course of the experiment as follows: Segment A: no morphine; red, 25 pellets and 0.64 mg/kg heroin; green, 25 pellets and saline. Segment B: 125 mg/24 hr morphine delivered non-contingently; red, 0.64 mg/kg heroin; green, 25 pellets. Segment C: 200 mg/24 hr morphine delivered non-contingently; red, 0.64 mg/kg heroin, green 25 pellets. Segment D: 200 mg/24 hr morphine delivered non-contingently; red, 0.64 mg/kg heroin; green, 25 pellets. Segment E: non-contingent morphine dose decreased at the rate of 20% per day; red, 0.64 mg/kg heroin; green, 25 pellets.

involving heroin could be eliminated almost entirely with a procedure involving non-contingent administration of morphine and food availability contingent on selection of an option involving saline infusions. However, when the dose of non-contingent morphine was systematically reduced, heroin self-administration increased. Experiment 2 utilized the same general methodology, but attempted to reduce preference for heroin using both contingent food and contingent low-dose heroin.

METHOD

Animals

Two male baboons *(Papio anubis)*, each weighing approximately 15 kg, served. Both were experimentally naive.

Procedure

Animals were housed, trained, and surgically prepared in a manner similar to that described for the first experiment, except that initial training on the choice procedure was extended to include three options. The behavioral sequence in the choice procedure was identical to that described previously, except that the baboons were required to change colors (switch) at least three times (instead of two) before completing a trial. During the training period for the three-option procedure, choice of one of the three options resulted in the availability of 50 food pellets, while choice of either of the other options had no programmed consequences. When the animals demonstrated a consistent preference for the food-reinforced option (75%–100%), the

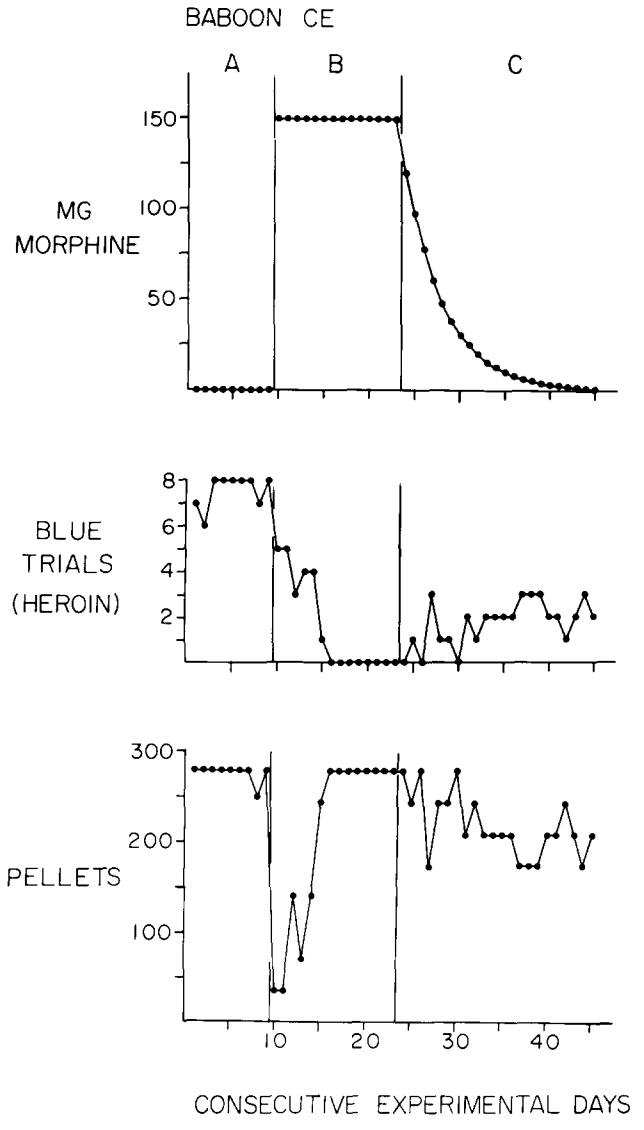

FIG. 2. Daily performance of baboon CE during Experiment 1. Panels follow same order as in Fig. 1. Choice was between a blue option and a yellow one. Conditions varied as follows: Segment A: no morphine; blue, 0.30 mg/kg heroin and 35 pellets; yellow, 35 pellets. Segment B: 150 mg/24 hr non-contingent morphine; blue, 0.30 mg/kg heroin; yellow, 35 pellets. Segment C: non-contingent morphine dose decreased by 20% per day; blue, 0.30 mg/kg heroin; yellow, 35 pellets.

color associated with food was changed. This procedure was repeated until the animals had demonstrated a preference for each color when it was associated with food. Subsequently, the animals were catheterized and the training sequence was repeated with heroin as the reinforcer, as described in Experiment 1.

At the beginning of this experiment, baseline performances were established under conditions similar to those of Experiment 1, with only two options presented during a trial. For one animal (DI) selection of the red option resulted in the delivery of an infusion of 0.32 mg/kg/infusion of heroin, plus the opportunity to earn 50 1-g Purina monkey pellets, while selection of the yellow option resulted in an infusion of saline plus the opportunity to earn 50 pellets. For the second animal (ST), selection of the yellow option resulted in the delivery of 0.83 mg/kg/infusion heroin plus the opportunity to earn 50 food pellets, while selection of the red option resulted in an infusion of saline plus the opportunity to earn 50 food pellets.

As in Experiment 1, under baseline conditions, there was a stable performance for the combined food-drug option. Subsequent experimental manipulations were arranged to attempt to reduce this preference for the heroin option by associating food and lower doses of heroin with other options. After the first dose-reducing manipulation a third color option was introduced in order to facilitate the introduction of still lower fractional heroin doses; and food was paired with the lowest of the available heroin doses. A summary of the sequence of options available for each animal during the course of the experiment is presented in Table 1.

RESULTS

As in the previous experiment, throughout this experiment both animals initiated trials at the maximum rate of eight per day. They generally completed trials within approximately 2 min of initial availability. Performance in the avoidance component was insensitive to all experimental manipulations, in that neither baboon received any electric shocks during the entire course of the experiment.

The first manipulation of contingencies (Experimental Day 13) designed to reduce daily heroin intake in animal DI occurred after the animal had demonstrated a clear preference for the combined drug-food option (red) (Fig. 3, Segment A). For this manipulation, a fraction of the drug dose associated with the red option was made available in the alternative (yellow) option. Thus, the baboon could choose between the initial dose (0.32 mg/kg/infusion) associated with the red color option, or a fractional dose (one-third original dose: 0.11 mg/kg/infusion) associated with the yellow option. In addition, the food consequences were altered so that only trials completed in the yellow fractional dose option resulted in food reinforcement (opportunity to earn 25 pellets). Examination of Segment B of Fig. 3 shows that under these conditions the baboon demonstrated an orderly shift of preference to the option involving the food-fractional drug dose combination. As a consequence of this shift in preference, the total heroin intake progressively decreased during the ten days after the manipulation from approximately 35 mg/day to less than 16 mg/day.

After performance stabilized under these contingencies, a second manipulation was undertaken on Day 30. In order to achieve continued reduction in drug intake without eliminating higher dose options, a third color option (green) was added. Selection of the green color option was associated with an even smaller fractional dose of heroin (one-sixth original dose: 0.055 mg/kg/infusion), and the availability of food (25 pellets); the red option was associated with 0.32 mg/kg/infusion heroin and no food; the yellow option was associated with 0.11 mg/kg/infusion heroin and no food. The addition of a third choice option along with a lower dose of heroin paired with food produced results similar to those seen after the first manipulation. Although the animal was required to choose between three options, there was an orderly preference

TABLE 1

ORDER OF OPTIONS IN EXPERIMENT 2.

ORDER	BABOON DI	BABOON ST
A	0.32 mg/kg heroin plus 50 pellets(red) vs. saline (yellow)	0.83 mg/kg heroin plus 50 pellets(yellow) vs. saline (red)
B	0.32 mg/kg heroin(red) vs. 0.11 mg/kg heroin plus 25 pellets(yellow)	0.83 mg/kg heroin(yellow) vs. 0.42 mg/kg heroin plus 25 or 20 pellets(red)
C	0.32 mg/kg heroin(red) vs. 0.11 mg/kg heroin (yellow) vs. 0.055 mg/kg heroin plus 25 pellets(green)	0.83 mg/kg heroin(yellow) vs. 0.42 mg/kg heroin (red) vs. 0.21 mg/kg heroin plus 20 pellets(blue)
D	0.32 mg/kg heroin(red) vs. 0.055 mg/kg heroin (green) vs. saline plus 25 pellets (yellow)	0.83 mg/kg heroin(yellow) vs. 0.21 mg/kg heroin (blue) vs. 0.10 mg/kg heroin plus 20 pellets (red)
E	0.32 mg/kg heroin(red) vs. 0.055 mg/kg heroin plus 25 pellets(green) vs. saline (yellow)	0.83 mg/kg heroin(yellow) vs. 0.10 mg/kg heroin (red) vs. 0.05 mg/kg heroin plus 20 pellets(blue)
F	0.32 mg/kg heroin(red) vs. 0.055 mg/kg heroin (green) vs. 0.025 mg/kg heroin plus 25 pellets(yellow)	0.83 mg/kg heroin vs. 0.05 mg/kg heroin (blue) vs. saline plus 20 pellets(red)
G	0.32 mg/kg heroin(red) vs. 0.025 mg/kg heroin (yellow) vs. saline plus 20 pellets (green)	

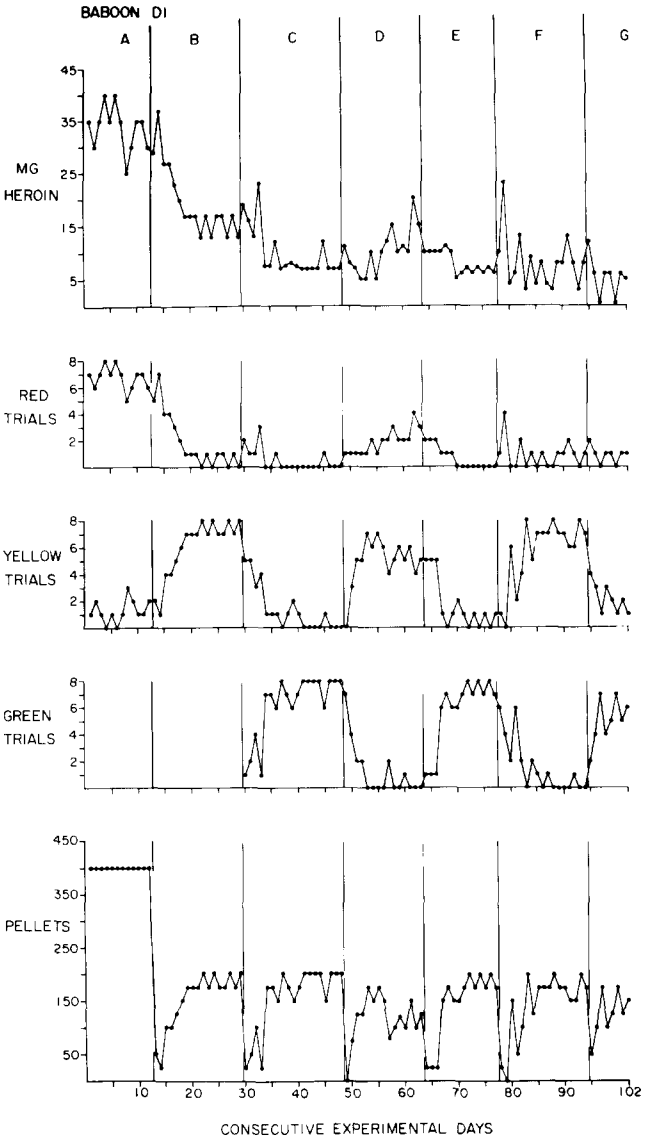

FIG. 3. Daily performance of Baboon DI in Experiment 2. The upper panel shows daily amount of heroin HCl self-administered by the animal. The bottom panel shows the daily number of food pellets delivered. The three center panels show the number of times each day that a particular color was chosen. Consequences of selection of a color varied during each phase of the experiment: Segment A: red, 0.32 mg/kg heroin and 50 pellets; yellow, saline and 50 pellets; green not presented. Segment B: red, 0.32 mg/kg heroin; yellow, 0.11 mg/kg heroin and 25 pellets; green not presented. Segment C: red, 0.32 mg/kg heroin; yellow, 0.11 mg/kg heroin; green, 0.06 mg/kg heroin and 25 pellets. Segment D: red, 0.32 mg/kg heroin; yellow, saline and 25 pellets; green, 0.06 mg/kg heroin. Segment E: red, 0.32 mg/kg heroin; yellow, saline; green, 0.06 mg/kg heroin plus 25 pellets. Segment F: red, 0.32 mg/kg heroin; yellow, 0.03 mg/kg heroin and 25 pellets; green, 0.06 mg/kg heroin. Segment G: red, 0.32 mg/kg heroin; yellow, 0.03 mg/kg heroin; green, saline and 25 pellets.

shift toward the green option which involved the lowest drug dose plus food (Fig. 3, Segment C). Accompanying this shift in preference was a corresponding decrease in total drug intake from approximately 16 mg/day to a frequently reached minimum of 6.7 mg/day.

The next manipulation, on Day 49, was undertaken to attempt to eliminate heroin intake entirely. The heroin dose was eliminated from the yellow option (which was only rarely selected) and injections of saline were substituted; additionally, food availability (25 pellets) was made contingent upon selection of the yellow option. As before, selection of the red option resulted in infusion of the original dose of drug (0.32 mg/kg), and selection of the green option resulted in an infusion of 0.055 mg heroin; the opportunity to work for food, however, was only available as a consequence of selecting the yellow option. Examination of Fig. 3, Segment D indicates that although the number of trials ending in saline and food (yellow) increased substantially, the number of trials ending in the

original heroin dose (red) also increased. Although total drug intake during this period reached a low of 5.0 mg/day on three occasions, drug intake did not attain the stability exhibited after prior manipulations, as is evidenced by the fact that drug intake ranged from 5.0 mg/day to 20.2 mg/day.

The period from Days 64 to 77 (Fig. 3, Segment E) involved the reestablishment of the previous conditions of low drug intake and behavioral stability. This was accomplished by leaving the drug doses associated with the three color options unchanged, while shifting the availability of the food reinforcer from the yellow option (no drug) to the green option (0.055 mg/kg). As shown in the figure, this manipulation resulted in a restabilization of a decreased level of heroin intake in the range of 5.8 to 6.7 mg/day.

In an attempt to reduce drug intake further, the next manipulation utilized the previous strategy of associating food availability with the selection of lower drug doses. The red option was associated with the original dose of 0.32 mg/kg; the green option with one-sixth original dose of 0.055 mg/kg; and the yellow option with 0.025 mg/kg or one-twelfth the original dose. Additionally, selection of the yellow option resulted in food availability (25 pellets). Figure 3, Segment F, shows that under these conditions a majority of trials were completed in the yellow (drug-food) option; however, it is also apparent that selection of the red option (original dose) occurred regularly, effectively maintaining a daily level of heroin intake in the 5 to 10 mg range.

The final manipulation for animal DI consisted of eliminating drug and substituting saline in the green option while simultaneously making food availability contingent upon selection of the same (green) option. The last fractional dose remained available in the yellow option, while the original dose remained, as always, available in red. The results of this manipulation are presented in Fig. 3, Segment G. While preference shifted to the selection of green (food only) trials, selection of both the yellow and red options occurred frequently enough so that heroin intake was not consistently lower than the level already achieved in earlier manipulations.

The successful phases of results with animal DI were systematically replicated in a second animal (ST) which started at a higher initial level of heroin intake (approximately 100 mg/day). As shown in Fig. 4, Segment A, the initial baseline performance was a stable preference for the combined drug-food option (yellow) which was associated with an infusion of 0.83 mg/kg and the availability of 50 pellets. The red option was associated with similar food availability, and an infusion of saline.

The first experimental manipulation on Day 18 involved the introduction of a fractional dose of heroin (one-half original dose: 0.43 mg/kg/infusion) in the red option along with food availability (25 pellets). The original dose of heroin remained associated with the yellow option, but with no food availability. As shown in Fig. 4, Segment B, this manipulation resulted in an orderly shift of preference with a concomitant decrease in daily heroin intake. On Experimental Day 34, the number of pellets associated with selection of the food option was reduced to 20 in an attempt to further reduce heroin intake, with little effect. The addition of a third color option (blue) associated with a smaller fractional dose of drug (one-fourth original dose: 0.21 mg/kg/infusion), plus food availability resulted in another shift of preference to the drug-food option (Fig. 4, Segment C). The next two experimental manipulations (Segments D and E of Figure 4) utilized the same procedure of associating food availability with successively lower fractional doses of heroin (one-eighth original dose: 0.10 mg/kg/infusion and one-sixteenth original dose: 0.05 mg/kg/infusion). The last manipulation involved associating food with an option (red) resulting in saline only. As shown in Fig. 4, although orderly preference shifting was demonstrated during these manipulations, the overall downward progression of drug intake was disrupted during the latter manipulation (Fig. 4, Segments E and F), due to increased selection of the yellow option associated with the original heroin dose.

DISCUSSION

The present studies utilized a discrete-trial choice procedure in which baboons chose between several mutually exclusive options, one of which consistently involved self-administration of a unit dose of heroin. The studies demonstrated that the selection of the heroin option could be reduced systematically by manipulating various parameters. Experiment 1 demonstrated that selection of the heroin option could be eliminated almost entirely when morphine was chronically administered and food availability was made contingent on selection of an option involving saline infusions. When the dose of non-contingent morphine was systematically reduced, the baboons increased selection of the heroin option, at the cost of lowered food intake. In Experiment 2, reduction of selection of the heroin option was accomplished using contingent food availability to reinforce selection of options involving progressively lower doses of heroin. The initial manipulations in this experiment almost entirely eliminated the selection of the option associated with the original heroin dose. However, in subsequent manipulations when food availability was contingent upon selection of options involving progressively lower doses of heroin, an apparent threshold was reached (approximately 15% of the original dose), and the animals began to increase their selection of the original dose.

Other studies using choice procedures have shown that rhesus monkeys and baboons consistently demonstrate preference for an option associated with infusions of various psychomotor stimulant drugs (e.g., cocaine, methylphenidate, diethylpropion), over options associated with saline infusions [3, 24, 25]. In addition, it has been demonstrated that animals will show a preference for a higher dose of a psychomotor stimulant drug over a lower dose of the same compound, both when selection of one option precludes selection of the other option (e.g., [3, 24, 25]), and when availability of different doses is determined by a concurrent variable-interval scheduling procedure in which the relative rate of responding for each dose option is the dependent variable [20,21]. Other research with choice procedures has indicated that they may be utilized to examine preference for one drug over a second drug [4, 24, 25]. In the present experiment, baboons consistently preferred an option associated with heroin over an option associated with saline when food contingencies were similar in both options (see Segment A of Figs. 1, 2, 3 and 4).

Choice procedures have also been used to examine how environmental manipulations may alter choice between different cocaine doses [23]. When behavioral requirements are similar, monkeys will generally select the higher dose

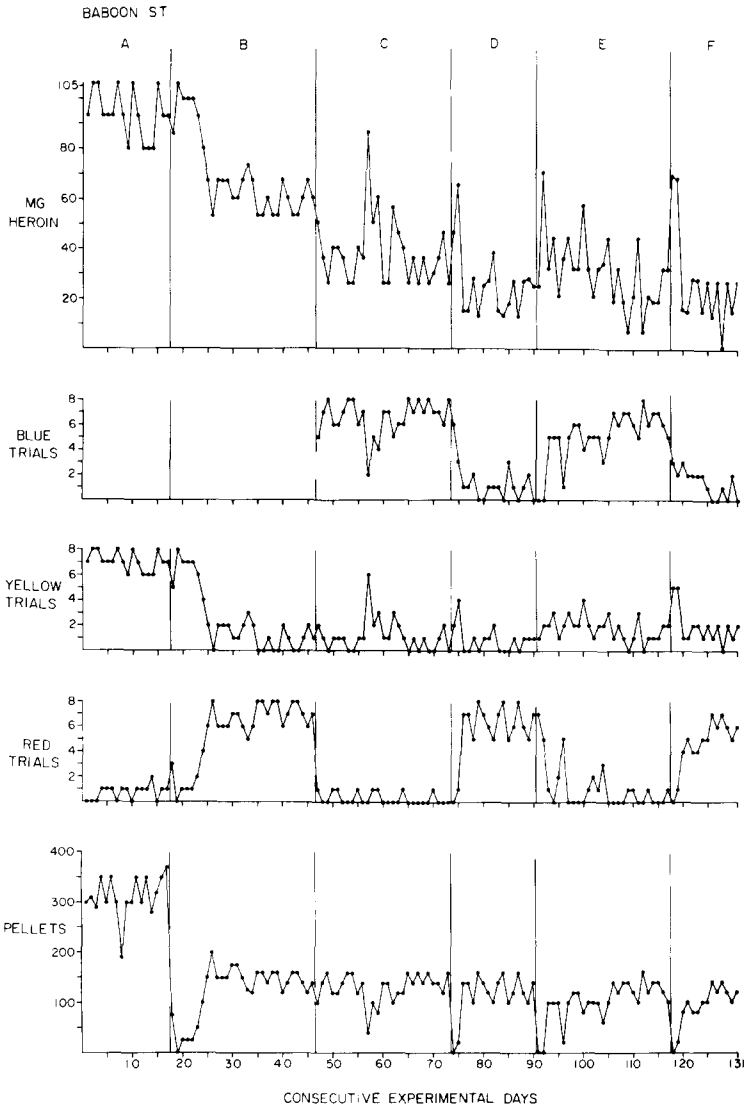

FIG. 4. Daily performance of Baboon ST in Experiment 2. Panels labeled as in Fig. 3. Consequences of selection of a color varied during each phase of the experiment: Segment A: yellow, 0.83 mg/kg heroin and 50 pellets; red, saline and 50 pellets; blue not presented. Segment B: yellow, 0.83 mg/kg heroin; red, 0.43 mg/kg heroin and 25 or 20 pellets (see text); blue not presented. Segment C: yellow, 0.83 mg/kg heroin; red, 0.43 mg/kg heroin; blue, 0.21 mg/kg heroin and 20 pellets. Segment D: yellow, 0.83 mg/kg heroin; red, 0.10 mg/kg heroin and 20 pellets; blue, 0.21 mg/kg heroin. Segment E: yellow, 0.83 mg/kg heroin; red, 0.10 mg/kg heroin; blue, 0.05 mg/kg heroin and 20 pellets. Segment F: yellow, 0.83 mg/kg heroin; red, saline and 20 pellets; blue, 0.05 mg/kg heroin.

option over the lower dose option: however, monkeys will change their preference to the lower dose option when either electric shock or an increased work requirement is added to the higher dose option. The present studies extend the research on environmental factors influencing drug preference by demonstrating two conditions (Experiments 1 and 2) under which contingent food delivery can be used to reduce an established preference for a given heroin dose.

The results of Experiment 1 suggest that discrete-trial choice procedures provide effective methodologies for examining the effects of drug pretreatment (i.e., non-contingent drug administration) on drug self-administration performance. Numerous previous studies have examined the effects of drug pretreatment on opiate self-administration [15, 31, 32, 33, 35]. Unfortunately, some of the results of these studies are difficult to interpret because of an absence of controls for the direct behavioral effects of the pretreatment drug. Griffiths, Wurster and Brady [19] overcame some of these methodological problems by using a discrete-trial choice procedure similar to that described in the present experiments. Stable baseline performance involving a mutually exclusive choice between food availability and a

heroin infusion was established in baboons. Non-contingent naloxone administration superimposed upon the choice baseline produced dose-dependent increases in the percent of trials in which heroin was selected over food; non-contingent methadone administration superimposed upon this same choice baseline produced consistent decreases in the percent trials on which heroin was selected over food. Because the behavioral requirements were virtually identical for selecting either option, these changes in choice performance probably represent direct interaction of the pretreatment drugs with the heroin and/or the food. The results of Experiment 1 of the current report extend the research of drug effects on choice behavior by demonstrating that progressive decreases in the dose of non-contingently administered morphine produced shifts in the choice performance toward an option involving heroin infusions and away from an option involving food availability.

The current experiments may be thought of as animal models for examining opiate addiction processes. Animal models for the study of aberrant physiological and behavioral processes via the production of symptoms analogous to those of a relevant pathology have been extant in behavioral pharmacology for a number of years [13,34]. Because it has been noted that a close correspondence exists between drugs which are readily self-administered by animals and man [7, 18, 30], animal self-administration procedures have been utilized as a model for screening of the reinforcing properties of drugs. Schuster [29] has also proposed that animal drug self-administration experiments may provide a basis for the assessment of pharmacological and environmental factors which diminish drug-taking behavior and therefore have possible therapeutic application.

In the current studies, a situation somewhat analogous to a clinical drug abuse situation was developed in which a full dose of heroin was always an option. The studies focused on pharmacological and environmental manipulations designed to decrease the intake of heroin which was self-administered. The first experiment involved the non-contingent administration of an opiate (morphine) along with food reinforcement of an alternative non-drug option – a situation analogous to methadone maintenance [9,22]. Subsequent progressive decreases of the non-contingent morphine produced a model similar to clinical detoxification from a maintenance level of opioid administration. When low doses of non-contingent morphine were reached, both animals in the study increased selection of their original dose of heroin – a situation analogous to relapse in humans. Similar phenomena have been noted in clinical methadone detoxification studies, where it has been observed that some addicts report discomfort and relatively frequent relapse to heroin use when the maintenance dose of methadone declines below 20–30 mg/day [17]. In terms of an overall treatment strategy, Dole [8] has argued that indefinite maintenance may be the best course for some addicts, and studies comparing maintenance programs to detoxification-abstinence programs have indicated that long-term maintenance strategies may be more successful than detoxification programs in terms of patient retention and recidivism rates [2,5].

In Experiment 2, the animal's selection of options that were progressively associated with lower doses of heroin was reinforced with food. Clinically, this situation is analogous to a detoxification program in which patients can self-prescribe their drug dose. The few clinical studies which have permitted subjects to self-prescribe their methadone [1,13] or heroin [28] dose have yielded conflicting results, including increases, decreases, and no change in the amount of drug self-administered. The initial manipulations of Experiment 2 produced a rapid shift of preference to alternative low heroin doses, with a corresponding decrease in total heroin intake. These data may have implications for situations in which an opiate drug such as morphine is allowed to be self-administered in a clinical setting. Goldstein [16] has noted the failure of traditional detoxification treatment strategies and proposed an alternative approach involving sequential treatment employing pharmacological supports (STEPS). The client is encouraged to progress through the following graded sequence of steps: (1) intravenously self-administer morphine 3–4 x day; (2) subcutaneously self-administer morphine 3–4 x day; (3) oral methadone daily; and (4) oral levo-alpha-acetylmethadol (LAAM) daily. An important rationale for this approach is that alteration of drug self-administration behavior can be most easily accomplished by using a series of graded steps. The rationale for Experiment 2 was similar, to the extent that baboons' overall heroin intake was decreased in a graded sequence of steps in which the selection of progressively lower doses of heroin was reinforced.

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