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Discrete-Trial Choice Procedure: Effects of Naloxone and Methadone on Choice between Food and Heroin*

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INCREASING numbers of experimental studies involving drug self-administration purport to demonstrate specific effects of drug pretreatment on behavior maintained by injection of another drug. Unfortunately, in some cases there seems to be little appreciation of the methodological complexities involved. In general, experimental questions about the effects of a drug on behavior maintained by another drug are difficult to answer with standard self-administration procedures, which involve an operant response maintained by drug injections and emphasize rate of responding as the primary dependent variable. For example, suppose the effect of methadone on behavior maintained by injection of heroin was to be investigated. If pretreating the subject with methadone before an experimental session suppressed the rate of responding maintained by heroin injection, a variety of interpretations could be made. Methadone might be altering the ability of the subject to make the response, interacting with the rate or pattern of behavior under study, or interacting with the reinforcing effects of heroin. Clearly, the analysis of specific interactions between a drug and a self-administered drug with a standard self-administration procedure poses complex experimental questions.

The problem of analyzing the effects of a drug on behavior maintained by another drug is part of a more general problem of analyzing an interaction between a drug and any reinforcer. In reviewing a large number of studies in behavioral pharmacology, Kelleher and Morse (11) note that drugs generally do not interact specifically with the type of reinforcer. Rather, these investigators suggest that the baseline rate, or ongoing pattern of behavior, is a major determinant of how a drug will affect that behavior. For instance, various drugs have identical effects on behavior maintained by the delivery of food or by electric shock avoidance provided that the ongoing pattern of behavior is identical under both conditions (2, 10). The proposition that the ongoing pattern of behavior is a primary determinant of drug effect is known as the rate-dependency hypothesis and has become one of the major principles of drug-behavior interaction to be derived from basic behavioral pharmacology research. Given the importance of rate-dependent drug effects, Kelleher and Morse (11) suggest that the most satisfactory way to compare the effects of drugs on performance maintained by different reinforcers is to obtain, as nearly as possible, identical patterns of responding and then to establish dose-effect relations for drugs on these patterns.

Multiple schedules have been used successfully in examining the effect of drugs on behavior maintained by different reinforcers (1, 12). In these studies, multiple schedules were established in which two

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fixed-interval components, alternating throughout the session, were maintained by presentation of either food or electric shock. Schedule parameters were adjusted to maintain similar patterns of responding under both components. These studies suggest that *d*-amphetamine and cocaine do not differentially affect the behavior maintained by food or shock, whereas morphine, ethanol, chloriazepoxide, and pentobarbital all increase the responding maintained by shock at doses which decrease responding maintained by food. Although McKearney (12) is careful to point out that the results do not necessarily represent specific drug-reinforcer interactions (*e.g.*, differences may be attributable to unknown subject history differences with respect to shock and food), the method used seems to control several important sources of variability including stimulus control, response topography, nonspecific rate increasing or decreasing effects of drugs and rate and pattern of responding. Unfortunately, there are not equivalently rigorous studies with multiple schedules in which the interaction of drugs with self-administred drugs have been examined.

Another method which may be useful in the analysis of drug-reinforcer interactions is the discrete-trial choice procedure. On each trial the subject chooses between two mutually exclusive options, each associated with the delivery of a different reinforcer. Since the behavioral requirement is virtually identical for selecting either option, and since the major dependent variable is percent choice of the options, systematic changes in the choice baseline cannot be attributed to interactions with relatively nonspecific factors such as local response rates, or type of response. With such choice procedures, it has been demonstrated that the percent choice of a given option shows a positive relationship to the relative magnitude of reinforcer associated with that option. This relationship has been shown with both amount of food (13) and dose of intravenous cocaine (9). In other experiments, choice procedures have been used to evaluate the relative reinforcing properties of two different reinforcers: cocaine *vs.* methylphenidate (9); and secobarbital *vs.* chlordiazepoxide (5). In a recent experiment with volunteer alcoholic subjects, Griffiths *et al.* (6) have used a choice procedure to evaluate the influence of ethanol. More specifically, on a discrete trial basis, subjects chose between two mutually exclusive options involving either the availability of money or socializing. The results showed that the percent choice of selecting socialization over money was greater on sessions involving ingestion of an ethanol solution than on sessions involving ingestion of a control solution.

Since the choice procedure is relatively independent of a variety of nonspecific behavioral effects, it is well suited to the evaluation of the effect of a drug on performances maintained by different reinforcers. The current report describes how this procedure has been used to examine the effect of the narcotic antagonist, naloxone, and the opiate, methadone, on the choice between heroin and food reinforcers.

Method

Two male baboons (*Papio anubis*) weighing approximately 15 kg were used. Each animal was adapted to a standard restraint cart (4) and individually housed in a sound attenuated chamber approximately 0.8 × 0.8 × 1.2 m. Water was continuously available from a drinking tube.

An outline of the behavioral sequence involved in the choice procedure is illustrated in figure 1. A representation of a subject intelligence panel is illustrated in figure 2. The availability of a choice trial occurred at an interval of about 3 hr since completion of the preceding trial. 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 subject's intelligence panel. A five-response fixed-ration requirement on the initiate lever was necessary to proceed with the trial. Upon completion of this

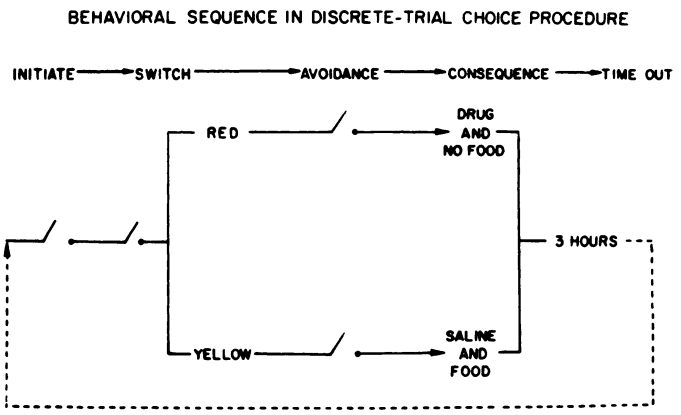

FIG. 1. Diagrammatic representation of behavioral sequence involved in choice procedure (see text for explanation).

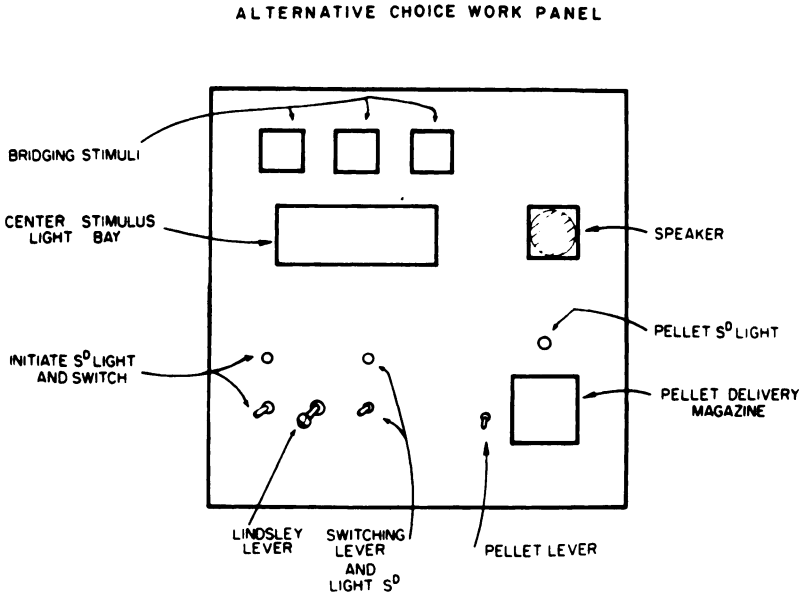

FIG. 2. Intelligence panel (see text for explanation).

initiate ratio, the baboon was presented with one of two colors (red or yellow) 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 left of center of the panel. Completion of a five-response fixed-ratio upon 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) a minimum of two times; it could then continue switching or proceed with the trial by completion of five responses on the Lindsley lever. This switching requirement assured that the subject was exposed to both stimulus conditions on each trial. Responding on the Lindsley lever "locked-in" the prevailing color in the light bay, extinguished the light over the switching lever, and set up an electric shock avoidance schedule on the same lever. Under

this schedule, every 2 min a 3-sec 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 15 responses within the 2 min. The avoidance requirement was identical for both red and yellow colors and was included to provide a possible measure of some of the nonspecific behavioral effects of the drugs. 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. At this time also, a smaller "bridging" stimulus light of the same color was illuminated in the upper right or left corner of the intelligence panel for a period of 1 hr.

Animals were surgically prepared with an intravenous catheter, by using the general procedure described by Deneau *et al.* (3). Placement of the catheter tip was near the right atrium by way of either the femoral or 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 (5). The catheter was attached to a valve system which allowed for the slow continuous administration (approximately 50 ml/24 hr) of saline *via* a peristaltic pump (Harvard No. 1201) to maintain catheter patency. Drug solution was infused into the valve system near the animal by means of a syringe pump (Sage #249-2) and then flushed into the animal with saline from a second syringe pump. This system necessitated a delay of approximately 15 sec between onset of drug delivery and actual infusion into the vein; however, the drug was delivered within a 1-min period. 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). Drug solutions were prepared by dissolving the hydrocholoride salts of heroin (diacetylmorphine), methadone, and naloxone in 0.9% saline. Drug doses were calculated on the basis of the salt.

The two baboons had participated in previous experiments involving the choice procedure with options associated with either food or heroin. Both animals had demonstrated that they would select consistently an option involving an infusion of heroin and delivery of food pellets more frequently than an option involving an infusion of saline and delivery of food pellets or an option involving an infusion of heroin alone. In the present study, both animals were maintained on a choice procedure involving a mutually exclusive choice between food and heroin reinforcers every 3 hr.[1] Completion of a trial in the presence of one color resulted in the immediate delivery of a saline injection and the immediate availability of 40 1-g of Purina monkey pellets (indicated by the illumination of a light over the pellet switch) on a schedule in which every five responses produced five pellets. Completion of a trial in the alternate color resulted in the immediate infusion of heroin HCl (0.32 mg/kg for S-14 and 0.96 mg/kg for S-15). For both animals, these values resulted in a performance which stabilized at a relatively low rate of selection of the heroin option (range: 1 to 3 heroin trials/day) and a correspondingly higher rate of selection of the food option (range: 5 to 7 food trials/day). Although free feeding would probably have resulted in consumption of somewhat higher overall numbers of pellets, the food available during the experimental trials along with a standard daily supplement of fresh fruit was adequate to maintain stable body weights in all animals throughout the experiment.

Administration of naloxone. Since the procedure involved a relatively low rate of choice behavior (eight trials/day) it was decided to evaluate the effects of naloxone over a 24-hr period in order to obtain a number of observations. One hour before the first trial of the experimental day

[1] The time-out period between trials was adjusted several minutes short of 3 hr and thus permitted the subjects to complete eight trials in a 24-hr period.

(11:00 A.M.) a relatively small amount of naloxone HCl (3.0 μg/kg) was administered acutely through the catheter.[2] After the acute administration, the remainder of the total dose of naloxone was administered over the next 24 hr in 50 ml of normal saline with the continuous infusion peristaltic pump. After 24 hr, naloxone was removed from the system. Saline trials were conducted with the same procedure; injections of normal saline equivalent in volume to the acute dose of naloxone were administered 1 hr before the first trial of the day, whereas 50 ml of normal saline was infused over the next 24 hr. Drug and saline trials were scheduled not more often than every 6th day with the requirement that the 3 days immediately preceding the trial were within the limits of the previously defined baseline performance (*i.e.*, range: 1 to 3 heroin trials per day. Doses of naloxone and saline were varied in an unsystematic order. Saline and each dose of naloxone were administered twice during the course of the study. The doses of naloxone HCl were: S-14: 0.09, 0.37, and 0.75 mg/kg/day; and S-15: 0.09, 0.23, and 0.28 mg/kg/day.

Administration of methadone. The effects of methadone on the choice procedure were evaluated by placing methadone in the continuous flush system so that methadone was infused at a continuous rate of 8.3 mg/kg/24 hr. After 12 days, the methadone was removed for one subject.

Results

Throughout the study, the animals continued to initiate trials at the maximum rate of eight per day. They generally completed trials (including the inititate, switching, and avoidance response requirements) within about 2 min of their initial availability. Performance in the avoidance component was insensitive to all experimental manipulations—neither baboon received any electric shocks during the entire course of the experiment. During control periods, the animals generally spaced their selection of the heroin option. The percent of heroin infusions as a function of the number of hours since the last heroin infusion during 10 consecutive control days in both baboons is shown in figure 3. The figure shows that both animals always selected the heroin option during the 6- to 15-hr period since the last heroin infusion. In no case did subjects select the heroin option on two consecutive trials.

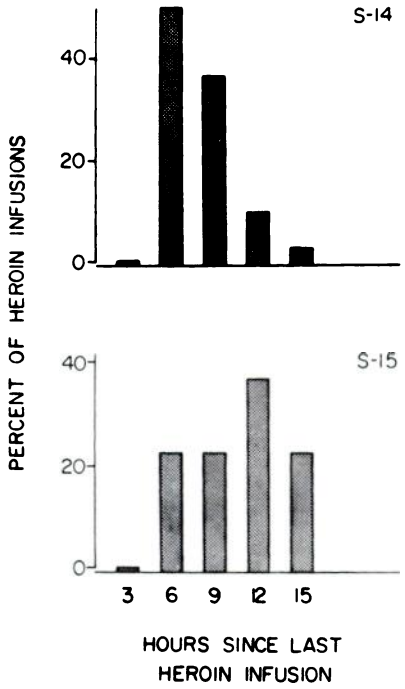

FIG. 3. Percent of heroin infusions as a function of the number of hours since last heroin infusion. Data were obtained during 10 consecutive control days. For both subjects, the maximum duration between successive heroin infusions did not exceed 15 hr.

Naloxone. The effect of naloxone upon choice performance in one baboon is shown in figure 4. The dose-response functions obtained for both animals are shown in figures 5 and 6. Naloxone produced dose-dependent increases in the percent of trials in which the animals selected heroin over food. Values from saline trials fell within

[2] Pilot research indicated that doses of naloxone in this dose range produced reliable changes in operant behavior, yet did not precipitate a full withdrawal syndrome in a heroin-dependent baboon receiving approximately 5 mg/kg/day of heroin HCl.

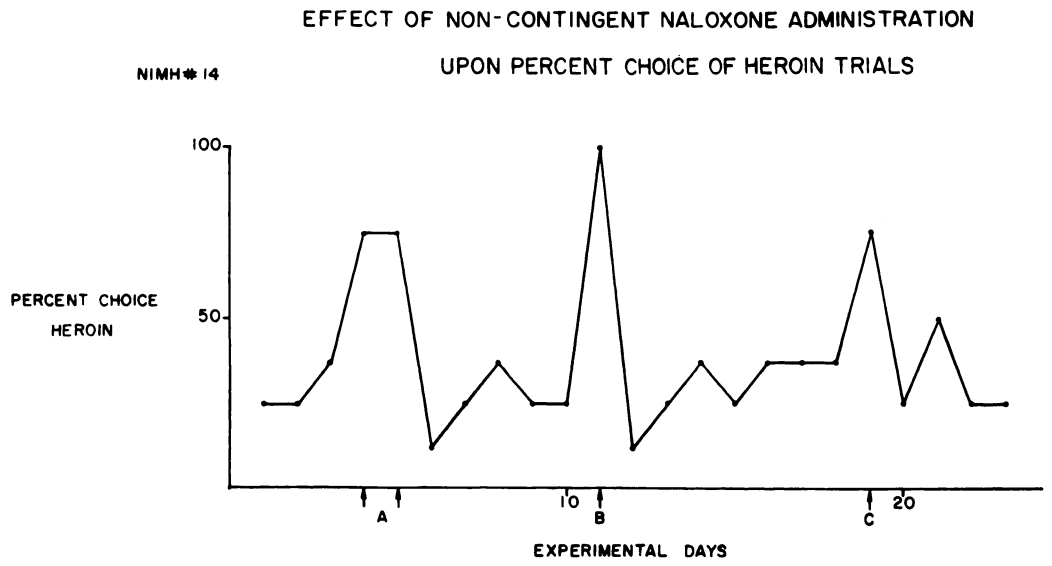

FIG. 4. Effect of naloxone administration on choice between heroin and food in S-14. The first administration ("A") was at a dose of 0.37 mg/kg/day and was maintained for a 2-day period (16 choice trials). Doses at "B" and "C" were both 0.75 mg/kg/day and were maintained for 1 day.

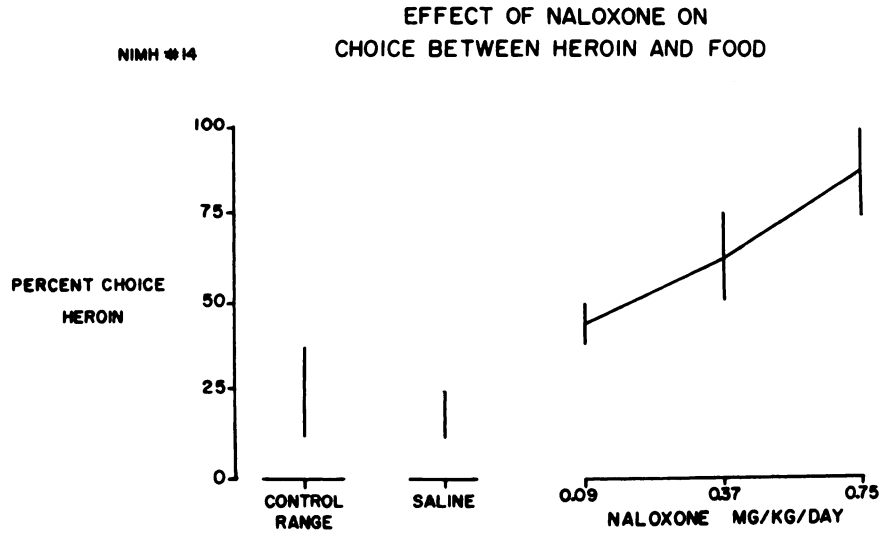

FIG. 5. Effect of naloxone on choice between heroin and food in S-14. Means and ranges are represented for naloxone and saline determinations. Control range represents the range of values obtained during the 3-day periods preceding all naloxone and saline trials (24 days total).

normal baseline control ranges. At the highest doses, naloxone produced signs of physical withdrawal, including agitation and sometimes vomiting.

Methadone. The results of the manipulations with methadone are shown in figure 7. Both animals maintained stable heroin intake before methadone administration. On the first day of methadone administration heroin intake dropped slightly in S-14. By the second day and consistently thereafter (except for 1 day with S-15) heroin intake was reduced in both animals. That the methadone effect was not clearly apparent until the 2nd day may reflect the slow build-up of significant methadone

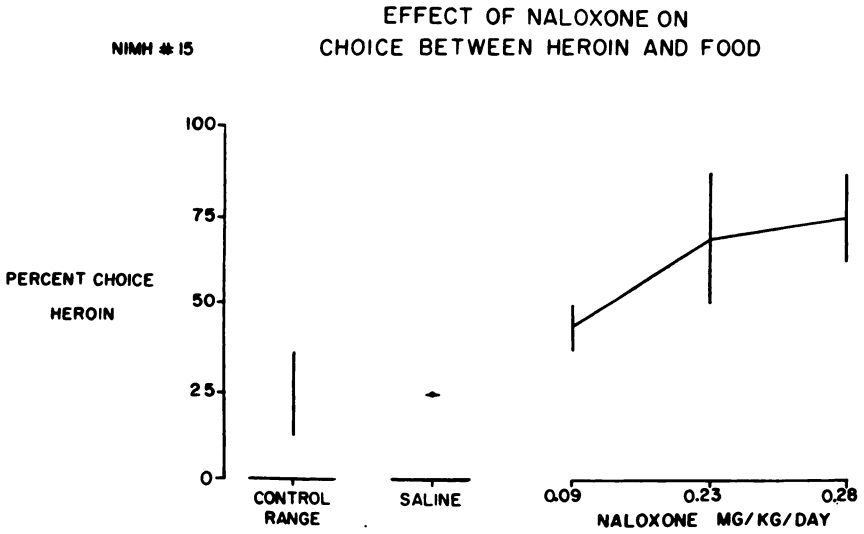

FIG. 6. Effect of naloxone on choice between heroin and food for S-15. Means and ranges are represented for naloxone and saline determinations. Control range represents the range of values obtained during the 3-day period preceding all naloxone and saline trials (24 days total).

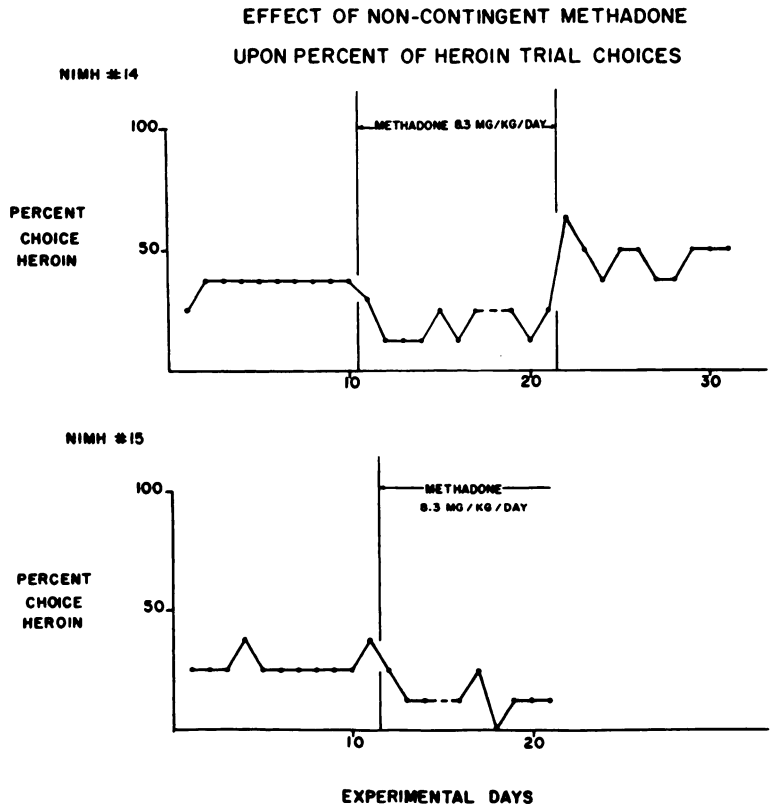

FIG. 7. Effect of methadone administration on choice between heroin and food.

levels due to the low infusion rate. On day 22, the methadone was eliminated entirely for S-14. Interestingly, the selection of heroin showed an immediate increase and then stabilized at a level somewhat higher than before methadone treatment. For subject S-15 the substitution of another drug for methadone at this point produced equivocal results which are not illustrated.

Discussion

The results of the current study indicate that naloxone produces dose-related increases in selection of heroin over food while methadone produces decreases in this same measure. Since the response requirements are virtually identical for completing a heroin or food trial, these results are not readily explained by a number of behavioral mechanisms. The results do not represent disruption of external stimulus control or disruption of the ability of the subjects to make a response. Such nonspecific drug effects would not have resulted in the systematic shift in choice performance observed in the present study. For instance, a total disruption of stimulus control which impaired the ability of the animals to discriminate between the two stimulus conditions would have been indicated by the selection of each option on a 50% basis. Furthermore, the results of the present study are not due to an interaction of the drugs with local rate or pattern of responding, nor are they explained by appealing to behavioral stimulant or depressant properties of the drugs. Again, such effects would have been equally distributed across both options and would not have resulted in the systematic shift in choice performance. One interpretation of the current results is that the drugs may interact with the relative reinforcing properties between the option involving heroin and the option involving food. More precisely, it is possible that doses of naloxone and methadone specifically alter the reinforcing properties of heroin. However, the data do not rule out several alternative behavioral mechanisms for the observed shift in choice behavior. For instance, the drugs may interact with the reinforcing properties of food, or they may interact with the scheduling differences between the two options—after fulfilling the avoidance requirement, the delivery of food was response contingent whereas the delivery of heroin was not.

The results of this study confirm and extend the findings of previous studies which have demonstrated that acute doses of a narcotic antagonist (naloxone or nalorphine) produce increases in morphine self-administration (7, 8, 15, 16). Other studies have also shown that pretreatment with opiates can decrease subsequent self-administration of opiate drugs (14, 15, 17). The contribution of the present research lies in the development of adequate controls for many of the nonspecific behavioral effects of the compounds studied. Accordingly, the data presented suggest that the choice procedure may provide an interesting tool for the further examination of drug-reinforcer interactions.

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