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Naloxone as a Negative Reinforcer in Rhesus Monkeys: Effects of Dose, Schedule, and Narcotic Regimen

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NARCOTIC antagonists have a variety of behavioral effects. Behavior can be elicited, punished, or maintained depending upon the dose, the temporal and contingency relationships between antagonist administration and behavior, and the concurrent or prior administration of a narcotic (7, 22). In morphine-dependent rhesus monkeys, for example, administration of the narcotic antagonist naloxone can elicit piloerection, vomiting, salivation, miosis, rhinorrhea, and hyperreflexia (the morphine-abstinence syndrome). Although the magnitudes of these elicited responses depend upon the dose of naloxone as well as the extent of previous or concurrent narcotic administration, such responses typically occur regardless of the contingency between antagonist administration and ongoing behavior (22).

Other behavioral effects of naloxone depend more critically upon the conditional relationship between drug administration and behavior. For example, operant responding maintained by intravenous codeine infusions can be suppressed when naloxone is added to the drug solution (23). This effect may be described as punishment (1) since response suppression extends across subsequent sessions when naloxone is no longer present. When comparable total amounts of naloxone are delivered independently of responding (*i.e.*, before the session), codeine-reinforced responding may be suppressed immediately but is unaffected in subsequent sessions when naloxone is no longer present (22). Operant responding maintained by intravenous cocaine infusions is unaffected by naloxone under identical conditions. Thus, suppression of responding by naloxone can depend upon the concurrent administration of a narcotic and upon the contingency between naloxone administration and behavior.

Narcotic antagonists such as naloxone also can function as negative reinforcers. That is, operant responding can be initiated and maintained by the response-contingent termination of infusions of narcotic antagonist or associated stimuli. It was found (8) that fixed-ratio performance could be maintained in morphine-dependent (12.0 mg/kg per day) rhesus monkeys when lever-press responding terminated a stimulus light that preceded nalorphine or naloxone infusions (avoidance) or the narcotic antagonist injections themselves (escape). It was subsequently reported (7, 11) that negatively reinforcing functions of several narcotic antagonists and narcotic-antagonist analgesics depended upon the doses of the drugs as well as upon the previous administration of narcotic. Pentazocine and propiram functioned as negative reinforcers in morphine-dependent rhesus monkeys but not in nondependent monkeys; pentazocine and propiram also functioned as positive reinforcers in nondependent monkeys (7, 10). Nalorphine and cyclazocine have been shown to function as negative reinforcers in both morphine-dependent and nondependent rhesus monkeys (11). Although naloxone maintained avoidance-escape responding in morphine-dependent monkeys, it has

not been possible to obtain reliable avoidance-escape performance with naloxone in nondependent animals (11). In the present paper, some of the experimental variables are further described which affect behavior maintained by the termination of naloxone infusions or the termination of stimuli that preceded naloxone infusions; in some cases, behavior also was maintained by naloxone presentation.

Rhesus monkeys (*Macaca mulatta*) weighing from about 3.5 to 5.5 kg were used. Each monkey was surgically prepared with a chronic jugular or femoral venous catheter and was then housed in an individual experimental chamber for the duration of the experiment. Monkeys were restrained within the chamber by a jointed metal arm and harness which protected the external portion of the catheter. Standard primate levers and colored light bulbs protected by acrylic panels were mounted on the wall of the cubicle. Drug infusions were accomplished by peristaltic pumps or gear-driven syringes. The monkeys were fed Purina monkey biscuits twice daily and fresh fruit twice weekly; water was freely available.

During most of the experiments to be discussed, morphine could be self-administered during four equally-spaced 1-hr sessions each day (4). Twenty-five infusions of morphine (0.1 mg/kg per infusion) could be obtained in each of the four daily morphine availability periods, thus limiting total daily morphine intake to 10.0 mg/kg per day. When one lever-press response was required to produce each infusion all monkeys typically received the maximal available amount of morphine each day. This amount of morphine is sufficient to establish and maintain physical dependence in the rhesus monkey (4).

Fixed-ratio schedules. When morphine intake appeared stable, 1-hr naloxone-escape sessions were interspersed twice daily among the periods of morphine availability. In the escape sessions, monkeys were exposed to a continuous intravenous infusion of naloxone (0.001 mg/kg per min) in the presence of a blue light; initially, each response interrrupted the naloxone infusion and extinguished the blue light for 1 min (time-out). During 1-min time-out periods, the chamber was illuminated by a white house light. In each monkey, reliable naloxone-escape performance emerged within 8 to 16 sessions. The number of responses required to interrupt the infusion and extinguish the light was raised eventually to 20 or 30 (a 20-response or 30-response fixed-ratio schedule). In some cases, it was necessary to advance the response requirement in small increments to prevent erratic performance or abrupt cessation of responding. In all instances, however, such strained responding could be eliminated by temporarily reducing the fixed-ratio value.

Under the 20-response fixed-ratio escape schedule (fig. 1), response rate increased to a maximum and then decreased as rate of naloxone infusion increased (fig. 1). At low rates of naloxone infusion, average (mean)

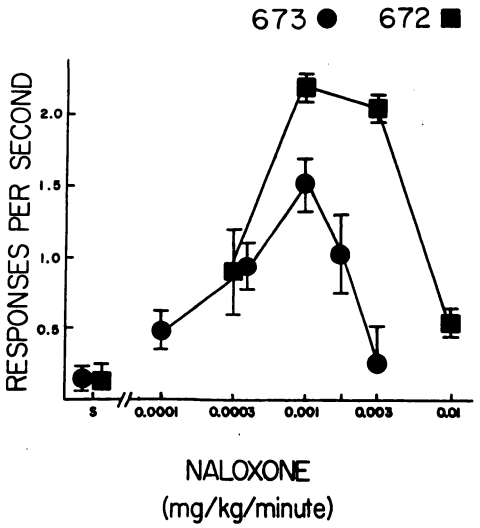

FIG. 1. Response rate as a function of naloxone infusion rate (mg/kg per min) or saline (S) in each of two monkeys under a 20-response fixed-ratio naloxone escape schedule. Each point represents the mean of the last three out of up to seven sessions at each dose averaged over from one to three infusion-rate replications in each monkey. Vertical lines indicate one standard error above or below each point. (Adapted from D. A. Downs and J. H. Woods, J. Exp. Anal. Behav. **23:** 415–427, 1975.)

response rates were low and were associated with long periods of no responding at the start of fixed-ratio components before the fixed-ratio component was completed by rapid responding. At high rates of naloxone infusion, low response rates usually were associated with progressive disruption of performance (fig. 2). Similar biphasic functions relating response rate to reinforcer magnitude have been obtained under a variety of schedules with different events maintaining responding (*e.g.*, fixed-ratio schedules of food presentation) (5). At all rates of naloxone infusion, responding seldom occurred during time-out periods, indicating that responding was controlled by the schedule contingencies rather than by a naloxone-induced stimulation of behavior.

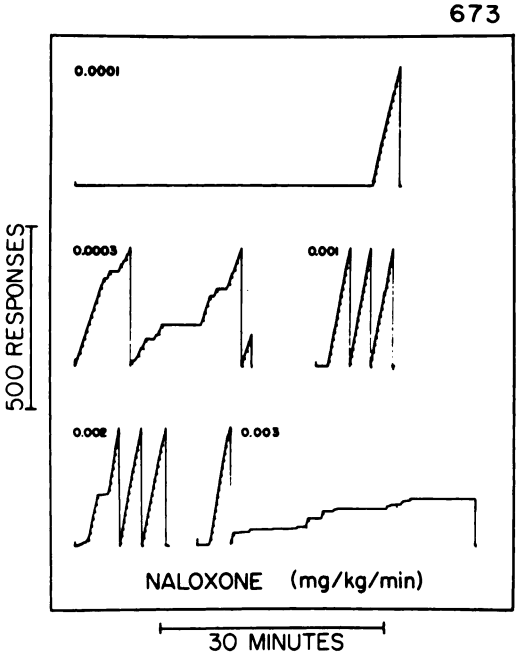

FIG. 2. Representative records of responding during individual 1-hr naloxone escape sessions in monkey 673 under a 20-response fixed-ratio schedule. Ordinates, cumulated responses; abscissae, time. Oblique deflections of the response pen indicate completion of 20 responses and presentation of a 1-min time-out. The paper drive did not run during time-outs. Naloxone infusion rates are expressed in mg/kg per min alongside each record.

Schedule-controlled responding has been maintained in morphine-dependent monkeys not only by naloxone termination (escape), but also by termination of a stimulus that preceded naloxone infusions (avoidance) (*e.g.*, 4, 8). In our avoidance-escape procedure (4), a blue light was illuminated for 30 sec before the onset of a 10-sec infusion of naloxone; completion of the fixed-ratio requirement within the 30-sec infusion period resulted in a 1-min time-out (avoidance). If the 10-sec infusions were not avoided, they could be terminated (escape) if the fixed-ratio requirement was completed during the infusion. That performances under a 30-response fixed-ratio schedule of naloxone (0.002 mg/kg per infusion) avoidance-escape were typical of fixed-ratio schedules is shown in figure 3. As in the escape experiment, responding seldom occurred during time-outs. However, response rate increased only slightly as the dose of naloxone was increased (fig. 4) and, in general, changes in dose resulted in changes in rate which were small compared to the effects of similar doses in the escape procedure.

The relative lack of sensitivity of response rate to changes in naloxone dose under the avoidance-escape schedule appeared to be correlated with infrequent naloxone infusions. One monkey originally trained under the avoidance-escape schedule received few naloxone infusions; consequently, dose changes or saline substitution had little immediate effect on response rate. In contrast, a monkey originally trained under the escape schedule received naloxone more frequently and showed a greater sensitivity to dose changes and saline substitution under the avoidance-escape schedule (4). These findings emphasize the interaction of experimental history, current schedule conditions, and dose as determinants of the behavioral effects of naloxone.

Effects of naloxone also are influenced by previous or concurrent narcotic administration (22). As noted earlier, it was found (11) that at doses from 0.005 to 0.1 mg/kg per infusion, naloxone failed to generate stable avoidance-escape respond-

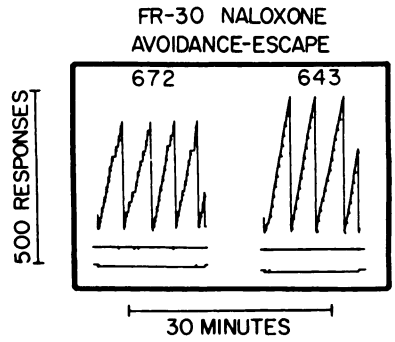

FIG. 3. Representative records of responding during individual 1-hr naloxone (0.002 mg/kg per infusion) avoidance-escape sessions in each of two monkeys under a 30-response fixed-ratio schedule (FR30). Ordinates, cumulative responses; abscissae, time. Oblique deflections of the response pen indicate completion of 30 responses and presentation of a 1-min time-out. The paper drive did not run during time-outs. Deflections of the center event pen indicate escapes (completion of fixed ratio after naloxone infusion onset). Upward deflections of the lower event pen indicate unavoided and unescaped naloxone infusions. (Adapted from D. A. Downs and J. H. Woods, J. Exp. Anal. Behav. **23**: 415–427, 1975.)

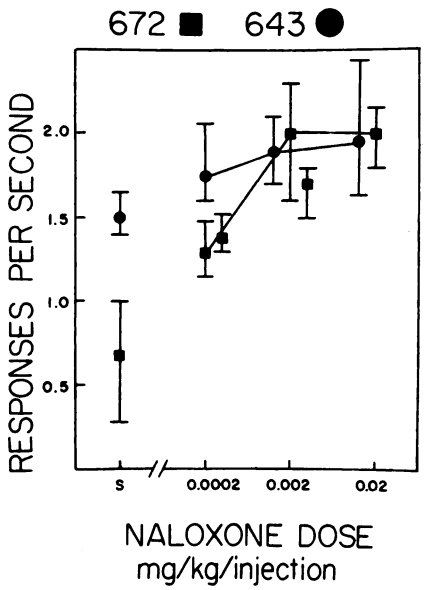

FIG. 4. Fixed-ratio response rate as a function of naloxone dose (mg/kg per infusion) or saline under the avoidance-escape schedule in each of two monkeys. Each point represents the mean of the last five of 20 sessions at each dose. One exception is the point at S for 672, which represents the mean of five sessions only. Vertical lines indicate the range about each mean. Replications are offset from original determinations. (Adapted from D. A. Downs and J. H. Woods, J. Exp. Anal. Behav. **23**: 415–427, 1975.)

ing in rhesus monkeys which were not morphine-dependent. We have found, however, that naloxone infusion rates above 0.1 mg/kg per min can generate and maintain escape responding in nondependent monkeys. Escape performance of one such monkey (990) at various naloxone infusion rates under an FR30 schedule is shown in figure 5. Monkey 990 had previous experience under fixed-ratio schedules of cocaine presentation but had never received narcotics. The naloxone-escape procedure in the nondependent monkey was essentially identical with that used in morphine-dependent animals. A major difference between naloxone-escape performance in morphine-dependent (*e.g.*, fig. 1) *vs.* morphine-naive monkeys lies in the range of naloxone infusion rates over which responding is maintained. Comparison of the cumulative records in figure 5 with those in figure 2 suggests that in the nondependent monkey, comparable escape responding is maintained at naloxone infusion rates which are roughly 1000 times greater than in the morphine-dependent monkey. Aside from rate of naloxone infusion, other features of naloxone-escape performance are quite similar. For example, naloxone infusion rate manipulations in morphine-dependent and nondependent monkeys typically caused changes in response rates within a few sessions (fig. 5). Reduced response rates at lower infusion rates generally were due to increased periods of no responding at the start of fixed-ratio components. Moreover, responding during time-outs was virtually absent. Thus, narcotic administration may cause a substantial shift in the quantitative effects of naloxone in the escape procedure but it is not a necessary condition for establishing or maintaining responding under fixed-ratio schedules of naloxone termination.

Fixed-interval schedules. In recent experiments, we also have studied naloxone under fixed-interval schedules in a morphine-dependent monkey. The monkey first was trained under a schedule where

each lever press terminated a continuous infusion of naloxone (0.001 mg/kg per min) and an associated blue light. The schedule was then changed to a 5-min fixed-interval schedule where illumination of a blue light for 5 min preceded a continuous naloxone infusion (0.001 mg/kg per min); the first response after the onset of the infusion resulted in a 1-min time-out (a 5-min fixed-interval schedule). Although responding was maintained consistently under this schedule, typical fixed-interval patterning (positively-accelerated responding) was observed infrequently within individual fixed-interval components (fig. 6a). The absence of pronounced positive acceleration during early exposure to the fixed-interval naloxone-escape schedule is similar to results obtained during early exposure to fixed-interval schedules of shock-avoidance (18).

Response rate under the 5-min fixed-interval schedule was relatively low in comparison to similar schedules of food or drug presentation. Response rate increased substantially, however, when the schedule was changed to a second-order fixed-interval schedule with fixed-ratio components (see 5, 14). Under the second-order schedule, every fifth response produced a 0.5-sec flash of light associated with time-outs (a 5-response fixed-ratio schedule) and the first fixed-ratio component completed after 5 min resulted in a 1-min time-out (fig. 6b). The increased response rate attributable to brief light presentations under the second-order schedule is similar to effects obtained under comparable schedules of food or drug presentation (6). Although response rate increased under the second-order schedule, instances of positively-accelerated responding within fixed-interval components were infrequent. The average time required for emission of one-fourth of the total responses in each fixed interval (quarter-life; see 9) provides an estimate of response patterning. With naloxone, quarter-life averaged from 21 to 25% of total fixed-interval time under each of the above conditions. In fact, responding

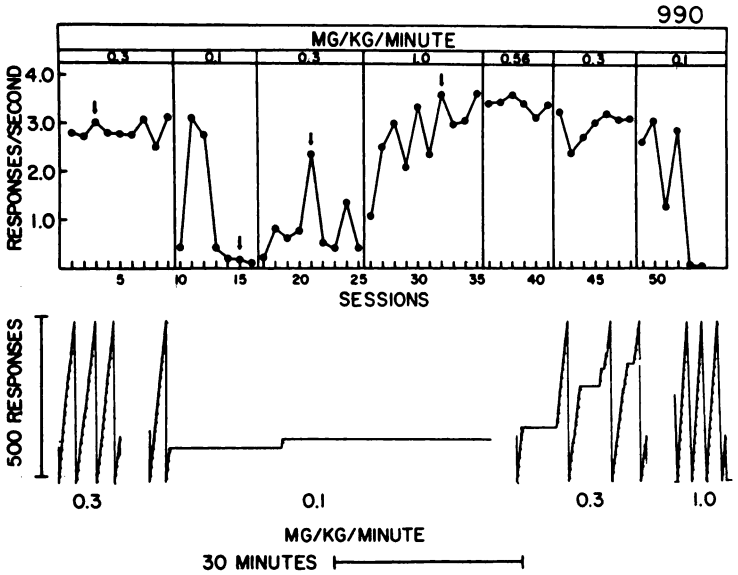

FIG. 5. Upper panel: Response rate (ordinates) across sessions (abscissae) under a 30-response fixed-ratio schedule of escape at various naloxone infusion rates (mg/kg per min) in a nondependent monkey (990). Lower panel: Cumulative response records of individual 1-hr naloxone escape sessions. Records are from sessions indicated by arrows in upper panel. Recordings as in figure 1. Note that 0.3 mg/kg per min of naloxone maintained higher response rates as part of a descending series of infusion rates than as part of an ascending series.

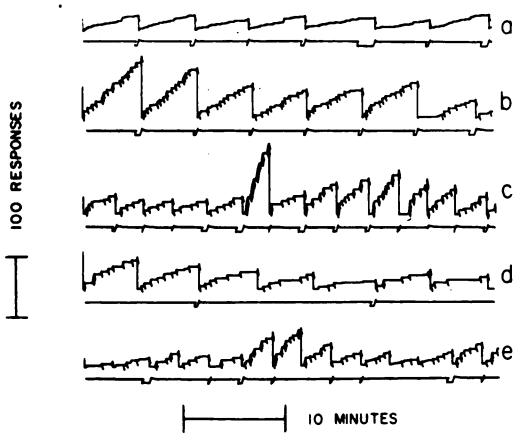

FIG. 6. Representative records of responding during portions of individual sessions under various fixed-interval or second-order schedules of escape from naloxone (0.001 mg/kg per min). Ordinates, cumulated responses; abscissae, time. The response pen reset and the paper drive did not run during each time-out. Downward deflections of the lower event pen indicate naloxone infusions. a. 5-min fixed-interval schedule. A continuous infusion of naloxone began after 5 min of blue light illumination; the first response after onset of the infusion resulted in a 1-min time-out. The blue light was extinguished and the house light was illuminated during time-outs. b. Second-order fixed-interval (5-min) schedule with five-response fixed-ratio components. Same as record a, except that every fifth response produced a 0.5-sec flash of the house light, as indicated by oblique deflections of the response pen, and the fifth response completed after onset of the naloxone infusion resulted in a 1-min time-out. c. Same as record b, except that the fixed-interval length was 2.5 min rather than 5 min. d. Same as record b, except that there was a 30-sec period at the end of each 5-min fixed-interval during which completion of a five-response fixed-ratio component resulted in a 1-min time-out (avoidance). e. Same as record c, except that there was a 30-sec period at the end of each 2.5-min fixed-interval during which completion of a five-response fixed-ratio component resulted in a 1-min time-out (avoidance).

within many fixed-interval components was negatively accelerated (*e.g.*, fig. 5b).

When the dose of naloxone was varied under the second-order schedule, maximal response rate was maintained at 0.001 mg/kg per min while higher (0.003, 0.01 mg/kg per min) or lower (0.0001, 0.0003 mg/kg per min) infusion rates typically maintained lower response rates. The shape of the function relating naloxone infusion rate to response rate under the second-order schedule was similar to that for the previously described fixed-ratio escape schedule. Although changes in naloxone infusion rate produced rapid changes in response rates under the second-order schedule, quarter-life remained virtually unchanged over the course of about 60 sessions regardless of naloxone infusion rate.

Several changes in the second-order schedule were studied with a naloxone infusion rate of 0.001 mg/kg per min in an attempt to find conditions which generated typical patterns of positively accelerated fixed-interval responding (*i.e.*, quarter-life greater than 25%). Decreasing the fixed-interval length from 5 min to 2.5 min (fig. 6c) resulted in only a slight increase in response rate but mean quarter-life increased from 21 to 36%. Another schedule change involved adjusting the time (t) between the end of the fixed-interval and the onset of the naloxone infusion. When the fixed-interval length was 5 min, introducing a 30-sec delay (t = 30 sec) between the end of the fixed-interval and the onset of naloxone, it resulted in a decrease in response rates but had no effect on patterning within fixed-interval components (mean quarter-life, 21%; see fig. 6d). Similarly, when the fixed-interval length was 2.5 min, introducing a 15-sec delay between the end of the fixed-interval and the onset of naloxone, it resulted in a decrease in response rates but quarter-life was essentially unchanged (mean quarter-life, 35%; see fig. 6e). Under fixed-interval schedules of electric shock avoidance, response rate also decreases as the time (t) between the end of the fixed-interval and the delivery of electric shock is increased from 0 to 15 sec (18).

The absence of pronounced positive acceleration within fixed intervals has been reported previously for escape from intense light (13) and during early exposure to fixed-interval schedules of shock avoidance (18). With electric shock, however, the development of positively-accelerated re-

sponding within fixed intervals is attributable at least in part to extended exposure to the fixed-interval schedule; moreover, some parametric changes (*e.g.*, reduction in t from 15 to 0 sec) can enhance the development of positive acceleration as well as increase response rate (18). In our experiment, increases in t decreased response rate but had no effect on quarter-life. In contrast, quarter-life was increased somewhat by decreasing the length of fixed interval. Thus, the optimal combinations of naloxone infusion rate and schedule parameters for obtaining positively-accelerated patterning under fixed-interval schedules with naloxone remain to be determined.

Continuous avoidance-escape schedule. In a preliminary study, one morphine-dependent monkey was first trained under a schedule where each lever press terminated a continuous infusion of naloxone (0.001 mg/kg per min) and an associated blue light. The schedule then was changed so that each response in the presence of a blue light terminated and/or postponed the onset of a continuous infusion of naloxone (0.001 mg/kg per min) for 20 sec. (fig. 7). As under the fixed-interval and fixed-ratio schedules described above, maximal response rates were obtained at 0.00178 mg/kg per min, while higher (0.003 mg/kg per min) and lower (0.001, 0.0003 mg/kg per min) rates of naloxone infusion maintained slightly lower response rates. However, after about 90 sessions under these conditions, regardless of naloxone infusion rate, a large percentage of total responses occurred immediately after each onset of the naloxone infusion. The monkey was "escaping" from the naloxone infusion instead of postponing its onset for sustained intervals. The escape contingency appeared to be a primary determinant of performance, since behavior was not maintained when it was eliminated. To eliminate the escape contingency, the schedule was changed so that responding during naloxone deliveries had no programmed consequences. Each response (except during naloxone delivery) postponed naloxone onset for 20 sec but once an infusion (0.002 mg/kg per infusion) was begun, it always continued for 6 sec. The interval between the end of one infusion and the beginning of the next was 10 sec. Under these schedule conditions, responding declined abruptly within a single session and failed to recover over nine subsequent sessions at 0.002 mg/kg per infusion. Higher (0.003 mg/kg per infusion) and lower (0.0003, 0.0001 mg/kg per infusion) doses of naloxone also failed to increase responding under the continuous avoidance procedure. When the original continuous avoidance-escape schedule was reinstated, however, responding recovered within a single session.

Since this monkey had previous exposure to a procedure in which responding was maintained by naloxone termination, and since responding seldom occurred in the absence of naloxone (*i.e.*, during response-produced time-outs) during that former procedure, it is possible that the

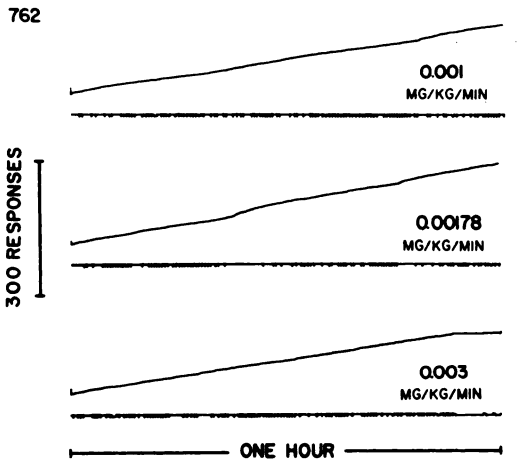

FIG. 7. Representative records of responding under a schedule of continuous avoidance-escape from naloxone in a morphine-dependent (10.0 mg/kg per day) rhesus monkey. Ordinates, cumulated responses; abscissae, time. Each response in the presence of a blue light terminated and/or postponed the onset of a continuous infusion of naloxone for 20 sec. The event pen was deflected downward during the naloxone infusion. Each session lasted for 1 hr. Rate of naloxone infusion (mg/kg per min) is indicated at the right of each record.

presence of naloxone was an important determinant of moment-to-moment performance under the continuous avoidance-escape schedule. Such findings emphasize further the potential effects of interactions among current and historical experimental conditions as well as pharmacological characteristics of drugs as reinforcers.

Superimposed and response-contingent naloxone. Under avoidance-escape schedules with electric shock, the delivery of unavoidable or inescapable additional shocks can sometimes increase response rates (3, 12, 19, 20). Several investigators have shown that electric shocks can also maintain responding when shocks are delivered as a consequence of responding (3, 15, 16). Under the 30-response avoidance-escape schedule with naloxone (0.002 mg/kg per infusion), response rates can be increased by unavoidable and inescapable infusions of naloxone (0.002 mg/kg), delivered after completion of every 5th or 10th fixed-ratio component (22). To determine whether response-contingent infusions of naloxone alone might also maintain responding, the schedule of naloxone delivery was changed with two monkeys. The avoidance-escape requirements were eliminated, the time-out following each 30-response fixed-ratio component was reduced to 1.5 sec (essentially a brief flash of the house light), and every 10th completed fixed-ratio component produced a 0.002 mg/kg per infusion of naloxone plus a 1-min time-out with the house light illuminated (22). Under this second-order fixed-ratio schedule of naloxone presentation, response rates ranging from 1.5 to 3.25 responses per sec were maintained for eight sessions in monkey 643 (fig. 8, lower panel). The naloxone pump was then disconnected and responding abruptly decreased. When the naloxone pump was reconnected and the number of completed fixed-ratio components required to produce naloxone infusion was decreased from 10 to 5, response rates increased to approximately 1.0/sec and were maintained for 10 additional sessions. The naloxone pump again was disconnected and responding declined to low rates within three sessions. When naloxone was available in subsequent sessions, however, responding was maintained poorly, although noncontingent infusions of naloxone (0.002 mg/kg per infusion) before a session caused pronounced increases in response rate during the session.

In a second monkey (672), response rates ranging from 1.6 to 3.65 responses per sec were maintained for 15 consecutive sessions under the second-order fixed-ratio schedule of naloxone delivery (fig. 8, upper panel). In the 16th session, however, responding decreased and only two infusions were obtained. In subsequent sessions, responding was maintained at low rates unless noncontingent infusions of naloxone were given before or during sessions.

These results suggest that naloxone can function much like electric shock in increasing responding maintained by naloxone

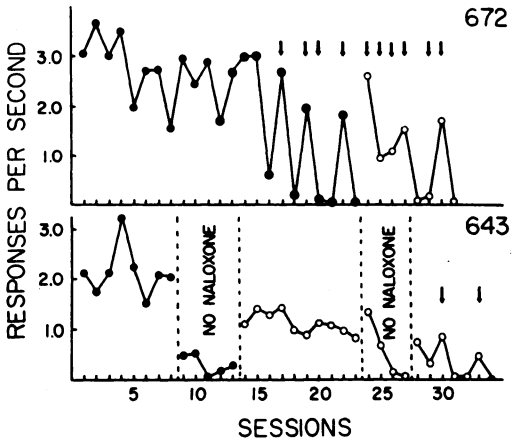

FIG. 8. Response rate (ordinates) across sessions (abscissae) in each of two monkeys under second-order schedules of response-contingent naloxone infusion (0.002 mg/kg). Every 30th response produced a 1.5-sec flash of the house light (a 30-response fixed-ratio schedule) and every 10th completed fixed-ratio component (closed symbols) or every 5th completed fixed-ratio component (open symbols) produced a 0.002 mg/kg infusion of naloxone plus a 1-min time-out, during which the house light was illuminated. Arrows indicate sessions in which noncontingent naloxone infusions were given before or during sessions. In monkey 643 (lower panel), the naloxone pump was disconnected in sessions 9 to 13 and in sessions 24 to 27.

one avoidance-escape as well as in maintaining responding when delivered as a response consequence. A major difference between the above results with response-contingent naloxone and previous results with response-contingent electric shock concerns the prolonged maintenance of such responding. Some schedules of response-produced electric shocks have been shown to maintain responding consistently over many more sessions than did naloxone in the present experiment (3, 15, 16). On the other hand, there may be decrements in response rates across sessions (17) or suppression of responding (15) when response-produced shocks are presented under fixed-ratio schedules. Whether prolonged maintenance of responding is possible with other schedules of response-produced naloxone remains to be determined.

Conclusions

General motivational properties often are attributed to drugs or other stimuli on the basis of the most dramatic or ubiquitous response-eliciting effects. Naloxone, as we noted earlier, at appropriate doses can elicit the narcotic abstinence syndrome in dependent animals. Thus, it may be tempting to consider other behavioral effects of naloxone as functions also of "precipitated abstinence." One might suppose, for example, that morphine-dependent monkeys escape from naloxone *because* it elicits the narcotic abstinence syndrome. But naloxone can elicit responses other than those associated with the abstinence syndrome (22). Moreover, naloxone can be a negative reinforcer in the absence of narcotic dependence. It is not apparent, then, which of several elicited effects are important determinants of the control over behavior by naloxone.

On the other hand, there are general similarities between behavioral effects of naloxone and those of other stimuli which clearly are attributable to operationally comparable variables. The behavioral outcome of naloxone administration has been shown to depend upon the temporal and conditional relationships of naloxone administration to behavior (schedule contingencies), physical dimensions of the stimulus (dose), and antecedent behavioral or pharmacological conditions (previous training; exposure to narcotic). These findings are consistent with the assumption (*e.g.*, 16) that the conditions under which stimulus events are presented can be at least as important as the nature of the events themselves as determinants of behavior.

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