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Morphine Effects upon Discriminated Approach and Discriminated Avoidance in Rats: Antagonism by Naloxone

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Abstract. The effects of various doses of morphine (5, 10 and 20 mg/kg) alone or in combination with a constant dose of naloxone (1.25 mg/kg) were examined in rats trained on a discriminated approach schedule (in which bar pressing in the presence of a stimulus light produced food), or on a discriminated avoidance (in which the same response produced stimulus-shock termination). Since the performance of rats in the discriminated avoidance varied widely, drug effects were examined separately in groups of good, intermediate or poor performer rats. Comparable patterns of responding in the presence of light were found in the approach group and in the good performer avoidance group. Morphine induced a dose-related decrease of this responding which was identical in both cases. Other effects of morphine were a dose-related increase of escape failures in all the avoidance groups and stimulatory or depressant effects upon bar presses performed during the no light periods. All the effects of morphine were antagonized by naloxone. The data suggest that comparable patterns of responding maintained by different reinforcements can be similarly affected by morphine.

Key words: Morphine – Naloxone – Discriminated approach – Discriminated avoidance – Escape

It has been repeatedly stated that the effects of drugs upon behavior seem to depend more on the schedules of reinforcement and the pattern of responding that is engendered rather than on the nature of the reinforcement itself (Morse and Kelleher 1970; Iversen and Iversen 1977). Nevertheless by comparing the effects of different drugs on similar patterns of responding maintained by fixed-interval schedules of food presentation, shock presentation or stimulus-shock termination in squirrel monkeys, McKearney (1974, 1975) found that morphine decreased food-reinforced but increased shock-reinforced responding. This could suggest that the effects of morphine are more dependent on the character of the reinforcing stimulus than the effects of other behaviorally active drugs. On the other hand, recent evidence suggests that the effect a drug can have upon behavior is far more complex than that previously considered. The work of Barrett (1976) and of Katz and Barrett (1978) would in fact suggest that the nature of the influence of a given drug upon behavior results from an interaction between the kind of behavior under study, the events that maintain it and the schedule under which these events are presented; in fact differential effects of drugs were observed under FI, but not under FR schedules.

In the present experiments the effects of morphine upon two similar but differentially reinforced behaviors were compared using rats as subjects. Under the approach schedule the first lever response in the presence of a signal light produced a food pellet; under the avoidance schedule the same behavioral response in the presence of a signal light avoided a shock. Therefore the conditions under which the two different events were presented and the patterns of responding that were produced were equal in the two schedules.

It is very well known that the narcotic antagonist naloxone can effectively block most of the behavioral, as well as the other, effects of morphine (Takemori et al. 1969; Holtzman 1976; Downs and Woods 1976; Markowitz et al. 1976). Some evidence indicates, however, that the effectiveness of naloxone blockade varies according to the behavioral effect of the alkaloid which is being studied (McMillan 1973; Downs and Woods 1976). It was therefore of interest to observe if naloxone would differentially influence morphine effects upon responding under the two above mentioned schedules.

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Materials and Methods

Subjects

A total of 33 male Sprague-Dawley rats (Nos farm) weighing 300–450 g served as subjects. They were housed three to a cage in a nearby animal quarter with the room temperature kept at 22° ± 1°C and a 12 h light-dark cycle (lights on 7 a.m.) maintained by electric lighting. The 18 animals used in the discriminated approach experiments were maintained at 85% of their free-feeding weights throughout the experiment. For the other rats food was freely available. All animals had water available ad lib. in the home cages.

Apparatus

The experiments were conducted in standard operant chambers equipped with sound attenuating and ventilating devices. In the approach experiments a lever, a stimulus light and a food tray (for a 72 mg pellet reinforcement) were located on one wall of the chamber. In the avoidance experiments the chambers were equipped with the lever and the stimulus light only; in addition a 0.8 mA constant current shock (3 s duration) could be delivered to the grid floor of the chamber via an electromechanical scrambler. Programming of stimulus events and response contingencies was accomplished using conventional circuits located in an adjoining room. The data were recorded on digital counters and pen recorders.

Drugs

The drugs used were morphine hydrochloride and naloxone hydrochloride. Both were dissolved with saline and injected I.P. Doses are expressed in terms of the total salts.

Procedure

Discriminated Approach. A total of 18 rats were trained to press a lever in the presence of a stimulus light to earn a food-pellet reinforcement. The light came on according to a variable-interval schedule (mean 1 min) and, in the absence of a response, remained on for 7 s. The first lever press during this light period turned off the light and produced a pellet of food. Lever presses outside light periods had no programmed consequencies. Each rat was trained on this schedule every day and the daily session terminated after completion of a total of 60 light cycles. The total numbers of lever presses performed during the light periods as well as outside the light periods (intertrial responses) were recorded separately for each animal.

Drug treatments were started when all rats showed stable performances. Drug sessions were run on Wednesday and the preceeding day a control session was always performed in which rats were treated with saline. In the drug session groups of 8–11 rats received saline or naloxone (1.25 mg/kg) and, 5 min later, saline or morphine (5, 10, 20 mg/kg). Trials began 15 min after the latest treatment. Drug sessions were always spaced at least a week apart. Treatment order was randomized and each animal received 3–4 different treatments over a period of about 2 months.

Discriminated Avoidance. A total of 15 rats were trained to press a lever in the presence of a stimulus light to avoid an electric shock. In this case too the light sequences were programmed according to a variable-interval schedule (mean 1 min). The light preceded a shock by 7 s and remained on during the 3 s of the shock period. Pressing the lever during the first 7 s of light avoided the shock and turned the light off. The same response during the shock period terminated both the shock and the light. Bar pressing outside these periods had no programmed consequences. A daily session terminated after the completion of 60 light cycles. Data recorded for each animal included the total number of avoidances, the total number of times the rat failed to press the lever in the presence of shock (escape failures) and the total number of lever presses outside the light periods (intertrial responses).

After 14 sessions of training the rats reached a stable performance. The level of performance, however, was very variable from animal to animal. In fact, for some rats the percent of avoidances was very near to 100 whilst other rats showed no avoidance at all. The animals were therefore divided into three groups as follows: rats making at least 85% of avoidances were defined as "good performers", those making 30–75% as "intermediate performers" and the animals making less than 15% of avoidances as "poor performers". All groups were submitted to drug treatments which followed the same general design described for the discriminated approach experiments. In this case however each animal received all the eight treatments (saline or naloxone alone and saline or naloxone plus morphine) in a randomized order over a period of about 2 months.

Data Analysis

For each animal the data were always expressed as differences between scores obtained under drug treatment and scores obtained on the preceeding day under saline. The percentages of approach, avoidances or escape failures were arc sin transformed and the rates of intertrial responses (bar presses/min) were log transformed before the analysis. Both transformations were used to stabilize the within group variances.

Data related to the approach experiments were subjected to analyses of variance for a 2 (naloxone levels) × 4 (morphine levels) completely randomized factorial design (fixed model). An unweighted mean solution (Winer 1971) was employed as the number of observations were unequal in different cells.

Data related to the avoidance experiments were separately analyzed for the good, intermediate and poor performer groups. In this case the analyses of variance were applied to a three factor design (naloxone and morphine as fixed factors and animals as random factor). The choice of the error term was made according to the rule suggested by Winer (1971) for mixed model designs.

For each experiment dose-effect lines were computed by regression analyses.

Results

Control Performances

As can be seen from Table 1, rats belonging to the approach group were able to obtain almost total possible reinforcements. In the avoidance groups the percent avoidance obviously decreased from the "good" to the "poor" performers, but the escape failures were very few in all groups. In any case there were some intertrial responses, the maximum rate being exhibited by the approach group.

Drug Effects

Discriminated Responding. Data relative to drug effects upon discriminated responding are summarized in Fig. 1 and 2.

As regards approach experiments, rats receiving morphine before the trial showed a dose-dependent linear decrease in responding in the presence of the

Table 1. Mean values ± SE of various measures of control performance. Data refer to pre-drug sessions

	Approach ($n = 18$)	Avoidance		
		"good" ($n = 5$)	"intermediate" ($n = 5$)	"poor" ($n = 5$)
Pellets obtained or shocks avoided (%)	99.60 ± 0.21	88.92 ± 2.62	57.34 ± 9.88	3.80 ± 2.28
Escape failures (%)	–	0.006 ± 0.006	0.132 ± 0.099	0.494 ± 0.251
Intertrials (resp/min)	4.479 ± 0.910	1.775 ± 0.236	2.204 ± 0.165	2.358 ± 0.481

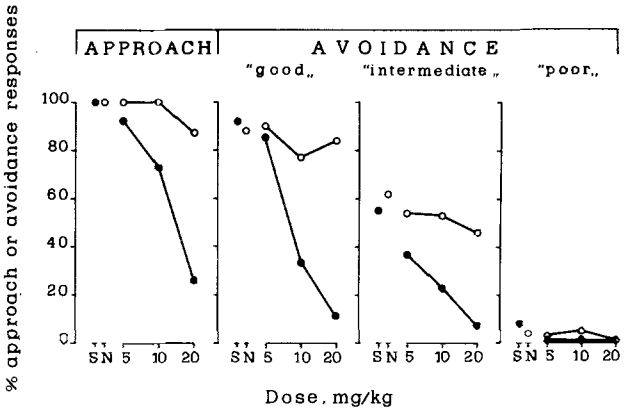

Fig. 1. Effects of morphine (●) and naloxone plus morphine (○) upon approach or avoidance responding. S and N refer to animals treated with saline or naloxone alone. Each point represents the mean of 5–11 values

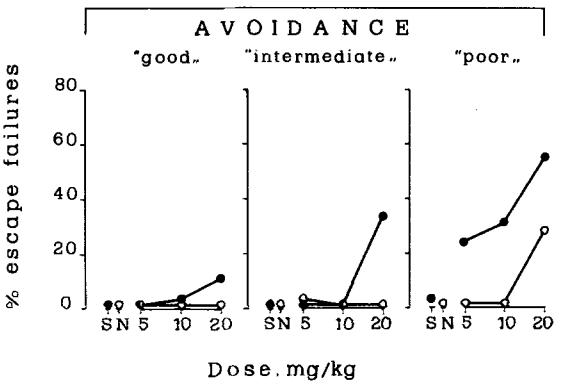

Fig. 2. Effects of morphine (●) and naloxone plus morphine (○) upon escape failures. S and N refer to animals treated with saline or naloxone alone. Each point represents the mean of 5 values

stimulus light ($F = 31.80$; df 1/59; $P < 0.01$); this effect was completely antagonized by pretreatment with 1.25 mg/kg of naloxone. The antagonist alone had no significant effects.

In the good performer avoidance group morphine caused a dose-dependent decrease in avoidance responses which was completely antagonized by naloxone. A significant inverse linear relationship was found between morphine dose and bar presses ($F = 52.65$; df 1/28; $P < 0.01$), while the avoidance number of naloxone pretreated animals receiving morphine was not significantly different from that of the naloxone group. The antagonist alone did not influence the avoidance responses.

Data related to the intermediate performer group are similar to those of the good performer rats. In this case too, the linear decrease in bar pressing was significant ($F = 7.24$; df 1/28; $P < 0.05$) while naloxone, which did not affect performance when given alone, completely restored the avoidance responses in rats treated with morphine.

The number of avoidances in the poor performer group was, on the contrary, unaffected by morphine, by naloxone, or by naloxone plus morphine.

Data related to the effects of morphine, naloxone and naloxone-morphine combination on the escape failures in the three groups of rats are presented in Fig. 2. In all groups morphine caused a significant linear increase of escape failures ("good": $F = 27.33$; df 1/28; $P < 0.01$; "intermediate": $F = 17.08$; df 1/28; $P < 0.01$; "poor": $F = 5.79$; df 1/12; $P < 0.05$) which was more pronounced from the first to the last group. Naloxone completely antagonized morphine effects in the "good" and "intermediate" groups while the effects were still evident but significantly reduced in intensity ($F = 19.98$; df 1/16; $P < 0.01$) in the poor performer group. Naloxone given alone had no influence upon escape failures.

Intertrial Responding. Figure 3 summarizes the drug effects on the number of responses the animals made outside the light periods. For the approach experiment the analysis of variance gave a significant inverse linear relationship between morphine doses and rate of intertrial responding ($F = 13.73$; df 1/59; $P < 0.01$). Again naloxone had no significant effects given alone, but completely antagonized the depressant action of the alkaloid; in fact all the data related to naloxone-

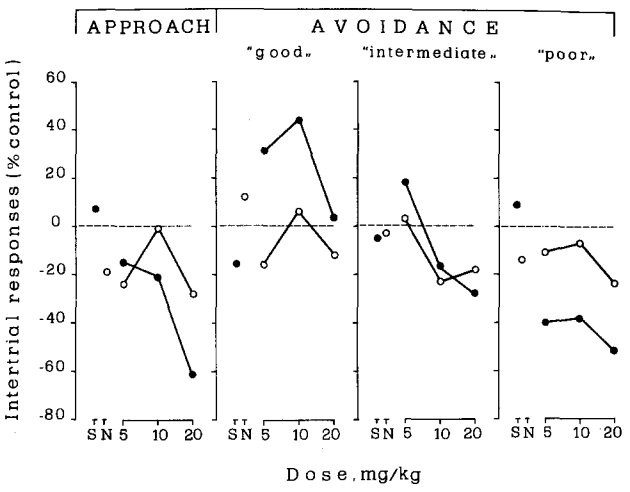

Fig. 3. Effects of morphine (●) and naloxone plus morphine (○) upon intertrial responses. S and N refer to animals treated with saline or naloxone alone. Each point represents the mean of 5–11 values

morphine combinations were close to, and not significantly different from, those obtained with naloxone alone. Morphine significantly increased intertrial responding in the good performer avoidance group but the effect was unrelated to the dose (overall morphine vs saline comparison: $F = 8.60$; df 1/28; $P < 0.01$); whereas it changed these responses in a dose related way in the "intermediate" group ($F = 6.72$; df 1/12; $P < 0.05$) and decreased them in the "poor" group, but was without a significant dose-effect relationship (overall morphine vs saline comparison: $F = 26.2$; df 1/24; $P < 0.01$). Naloxone completely antagonized morphine effects in all groups but had no significant effects when given alone.

Discussion

The main purpose of the present work was to compare the effects of morphine upon operant behaviors maintained by similar schedules of reinforcement but by different reinforcing events. The two discriminated schedules that have been used were formally comparable but the behavior they generated was not the same in the two experimental situations. In fact under the approach schedule all rats behaved alike under control conditions whilst under the avoidance schedule animals varied widely in the level of performance achieved. Therefore any conclusion about the importance of reinforcing events in determining morphine effects can only be drawn by considering these effects in groups of rats showing comparable patterns of responding under control conditions. In the present experiment this is the case if one compares the approach group with the good performer avoidance group. As can be seen from Fig. 1 the effects of morphine in these two groups were similar, that is in both cases there was not only a dose-dependent decrease in schedule-controlled responding but also a very similar shape of this decrease. In fact the regression coefficients were −26.68 for the approach group and −26.45 for the good avoider group. The present results would therefore be in line with those (Kelleher and Morse 1964; 1968) which suggest that, when comparable patterns of responding are studied, the effects of a given drug will be the same regardless of differences in the nature of the reinforcer. However, in McKearney's studies (1974, 1975) morphine increased shock-reinforced responding (shock being used as a negative or a positive reinforcer) and decreased food-reinforced responding when these reinforcers were scheduled in the same way. In the present experiments, morphine had similar effects under the food and shock avoidance schedules. However it should be noted that schedule factors were very different in the experiments of McKearney and ourselves; thus, the effects of morphine on responding maintained by different events, as well as the effects of other drugs (e.g. Katz and Barrett 1978), can be similar or dissimilar depending on how those events control behavior. Since McKearney's reports and the present one are the only studies where morphine effects on similar but differently reinforced behaviors are compared, more work seems necessary to assess the relative importance of the many factors influencing behavioral responses to morphine.

Some other features of morphine actions upon the avoidance behavior are worth discussing. In both good and intermediate performer groups morphine caused a dose-dependent inhibition of avoidance behavior which was almost complete at the highest dose used. Thus morphine effects upon avoidance do not seem to depend on the rate of avoidance itself. The lack of morphine actions in the poor performer group is not in accordance with the study of Davis et al. (1973) who showed that 10 or 20 mg/kg of morphine markedly improved avoidance rates of poor performer rats in a one way avoidance situation. In that case however a different (and easier) response topography was required.

The intensity of depressive effects of morphine upon the escape behavior was most pronounced in the poor and least in the good avoider group. It seems therefore that the entire performance was better maintained in the good performers and that this rendered it more resistant to drug effects.

As regards the intertrial responses, morphine effects were quite different in the approach group and in the three avoidance groups. The effect seems roughly rate dependent, maximum increases being exhibited by the group with the lowest rate (good avoidance performers) and greatest decreases by the group with the initially highest control rate (approach). In fact a correlation

coefficient between control rates and effects within each dose of morphine gave a score of −0.40 for 5 mg/kg, −0.54 for 10 mg/kg and −0.88 for 20 mg/kg dose.

Finally the results obtained treating rats with naloxone before receiving morphine indicate that 1.25 mg/kg of the antagonist is sufficient for complete antagonism of most of the morphine depressant effects (even at the highest dose used) upon approach, avoidance and escape behavior and upon intertrial responses. Only morphine actions upon escape behavior of poor avoiders were not completely removed, but a shift in the dose-effect curve was apparent. On the other hand, when given alone, the dose of naloxone used in no instance affected the behaviors studied, which is in accordance with the finding that the drug is generally devoid of significant effects upon behavior unless very high doses are employed (Holtzman 1976).

Naloxone antagonizes morphine effects upon various operant behaviors maintained by food presentation in various species (McMillan 1973; Downs and Woods 1976). There is no report however about a naloxone-morphine interaction in a discriminated approach situation like that described in the present report. The fact that in this case too a complete removal of morphine effects has been demonstrated adds to the generality of naloxone-morphine antagonism. Naloxone has also been reported to antagonize the effect of morphine on a discrete trial avoidance schedule in rats (Reynoldson and Bentley 1974) and that of various narcotics on a continuous avoidance schedule (Holtzman 1973) in the same species. Although quantitative comparisons between the naloxone actions exhibited in those works and in the present one are difficult to make, because of parametric variations between different studies, in both cases a qualitatively similar effect of the antagonist is quite evident. Thus the present report confirms the considerable generality of naloxone antagonism upon morphine effects on operant responding.

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