EFFECTS OF MORPHINE, CLONIDINE, AND INTENSITY CHANGE ON ELECTRIC-SHOCK DISCRIMINATION

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The effects of morphine, clonidine, and changes in stimulus intensity were examined in squirrel monkeys responding on one of two levers following brief presentations of one of two electric-shock intensities (0.1 and 0.5 mA). Responses were designated as correct or incorrect depending on which shock intensity had been presented and which lever was pressed. Morphine (0.42 to 1.80 mg/kg) and clonidine (0.075 to 0.18 mg/kg) decreased percentage correct responding. Morphine and clonidine also increased response latency and the number of shock presentations that were not followed by responses. Changes in shock intensity also decreased percentage correct responding but had no effect on response latency or on the number of shock presentations not followed by responses.

Key words: morphine, clonidine, shock discrimination, lever press, squirrel monkeys

Morphine and a variety of other analgesics have distinctive effects on behavior under the discriminative control of electric shock. For example, in squirrel monkeys trained to respond differentially in the presence or absence of shock, morphine decreases the percentage of correct responses in the presence of shock, but not in the absence of shock (Dykstra, 1979). Moreover, morphine-induced decreases in correct responding are greater when a shock intensity of 0.05 to 0.15 mA is used than when a shock intensity of 0.35 mA is used. Other analgesic opioids such as methadone, pentazocine, and cyclazocine, as well as the nonopioid analgesic levonantradol, also decrease correct responding in the presence of shock (Dykstra, 1980, 1981). In rats trained to respond differentially in the presence or absence of shock, morphine and other analgesics have similar effects (Hernandez & Appel, 1980; Lloyd, Appel, & McGowan,

1978; Poling, Simmons, & Appel, 1978). Morphine also decreases correct responding in rats trained to respond differentially following the presentation of two different shock intensities (Grilly & Genovese, 1979). In contrast, diazepam and chlorpromazine have different effects in these situations. In squirrel monkeys, diazepam decreases correct responding in the absence of shock, whereas chlorpromazine decreases correct responding in the absence of shock (Hernandez & Appel, 1979). These data suggest that morphine and other analgesics selectively alter responding in the presence of electric shock.

Data from electrophysiological investigations suggest that the analgesic effects of opioids are partly due to an attenuation of neural activity produced by noxious stimuli (Besson & LeBars, 1978; Gebhart, 1982). Therefore, opioid-induced alterations in responding in the presence of electric shock may be due to a reduction in the effective intensity of the electric shock stimuli. On the other hand, a number of studies indicate that morphine does not alter responding only under the discriminative control of noxious stimuli. For example, morphine decreases correct responding in rats trained to respond differentially following two shock intensities, as well as following two positions of a brief light flash (Grilly, Genovese, & Nowak, 1980) or during the presence or ab-

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sence of an auditory stimulus (Hernandez & Appel, 1979). Morphine also decreases correct responding in pigeons responding differentially to light intensity (West, Hernandez, & Appel, 1982).

In the present study, we investigated further the effects of morphine on responding under the discriminative control of electric shock. Squirrel monkeys were trained to respond differentially following the presentation of two different shock intensities. Earlier studies in our laboratory examined the effects of morphine on the discrimination between the presence or absence of shock. Specifically, we were interested in whether morphine would affect responding differently when the discrimination was between two different shock intensities.

In order to investigate whether morphine's effects on behavior controlled by electric shock were unique to an opioid analgesic, the effects of clonidine were also studied. Clonidine was chosen because many of its effects are similar to those of morphine. For example, clonidine has been shown to have analgesic effects in the rodent tail withdrawal and inflamed-paw tests (Fielding, Wilker, Hynes, Szewczak, Novick, & Lal, 1978; McCleary & Leander, 1981). Clonidine also reduces many of the symptoms of opioid withdrawal in opioid-dependent rats (Fielding et al., 1978; Shearman, Lal, & Ursillo, 1980) and in man (Gold, Pottash, Sweeney, & Kleber, 1980). On the other hand, clonidine does not produce morphine-appropriate responding in rats trained to respond differentially after injections of morphine or saline (Miksic, Shearman, & Lal, 1978). Moreover, its analgesic effects are not attenuated by naloxone (Fielding et al., 1978; McCleary & Leander, 1981).

We also compared the effects of morphine and clonidine on behavior under the discriminative control of electric shock with the effects of changes in the physical intensity of the shock stimuli. Although varying the physical intensity of the shock cannot be considered directly analogous to drug administration, the results from such a manipulation may be helpful in the inter-

pretation of drug effects on stimulus control.

METHOD

Subjects

Three experimentally naive adult male squirrel monkeys (*Saimiri sciureus*) served as subjects. The monkeys were housed individually with continuous access to water and were given sufficient Purina Monkey Chow to maintain them at approximately 80% of their free-feeding body weights (range 775 to 815 g). Their diet was regularly supplemented with fresh fruit and vitamin C tablets.

Apparatus

Experiments were conducted with monkeys placed in a small-primate cockpit (BRS/LVE 142-11), enclosed in a ventilated sound- and light-attenuating chamber. Each monkey was restrained in a seated position by a waist lock, and its tail was held motionless by a small stock. Electric current was delivered to the tail by two hinged brass bars that rested lightly on a shaved portion of the tail. The tail was massaged with a noncorrosive electrode paste (EKG Sol) to ensure a low-resistance electrical contact between bars and the tail. The electric shocks (1.0 s, 110 V, 60 Hz) were delivered through a variable series resistance and were calibrated prior to each session.

Two response levers (BRS/LVE 121-05) were mounted 9 cm apart on the front panel of the chamber. When either lever was pressed with a downward force of approximately 0.30 N or more, a response was recorded and an audible click was produced. Two in-line projectors (Grason-Stadler, 28 V 1820 lamps, clear lens) were mounted 8.5 cm above each of the levers. The chamber also contained a houselight (28 V 1820 lamp, blue lens) and a pellet dispenser that delivered 190-mg Noyes banana-flavored pellets. Continuous white masking noise was present inside the experimental chamber. Electromechanical programming and recording equipment were located in an adjacent room.

Procedure

Behavioral procedure. The monkeys were trained to respond on one lever following presentation of a 0.5-mA shock and on the other lever following presentation of a 0.1-mA shock. Experimental sessions consisted of 300 trials. Each trial began with the houselight illuminated for a 5-s period; responses during this period prolonged it by 5 s. After 5 s elapsed without a response, the lights above the levers were illuminated and a 1.0-s shock was presented. A response on either lever or the passage of 7.5 s terminated the trial. For two monkeys a response on the right lever was designated as correct when a 0.5-mA shock was presented, and a response on the left lever was designated as incorrect. When the 0.1-mA shock was presented, a response on the left lever was designated as correct and a response on the right lever was designated as incorrect. For the third monkey the designation of correct and incorrect responses for the two shock intensities was reversed. Incorrect responses were followed by a 10-s period during which the chamber was dark and responding had no programmed consequences. Every correct response was followed by a 30-ms, 2.5-kHz tone, and every ninth correct response for each stimulus (0.5 mA and 0.1 mA) was followed by a banana pellet. Sessions were conducted daily except Saturdays and Sundays and each consisted of 300 trials, half of which contained the 0.5-mA shock and half the 0.1-mA shock. Shocks were presented in a mixed order that excluded more than three consecutive trials with the same shock intensity.

Initially, the monkeys were trained to respond differentially following the presence or absence of a 0.5-mA shock. During this training period, each correct response was followed by presentation of the tone and a banana pellet. In addition, a correction procedure was used in which the trial following any incorrect response provided the same stimulus as the previous trial. Gradually the ratio of correct responses to pellets was increased to nine (FR 9), and the correction procedure was eliminated. When respond-

ing was stable and at least 90% of the responses were correct on both shock and no-shock trials, a 0.1-mA shock was introduced on trials on which shock had previously been absent. Training continued on this schedule until responding was again stable and at least 90% of the responses were correct on 0.5-mA and 0.1-mA shock trials.

Pharmacological procedure. Dosages of morphine sulfate and clonidine hydrochloride were calculated as mg of the salt per kg body weight. Each drug was dissolved in distilled water and dosages of each drug were given in mixed order with injections made into the leg muscle in a volume of 1.0 ml/kg body weight. Distilled water was used for vehicle injections. After injection, each monkey was returned to a holding cage for 30 min before being placed into the experimental chamber. Injections were given on Tuesdays and Fridays, with Thursdays serving as noninjection control days. Each monkey received four administrations of water and two administrations of each dosage of each of the drugs. The sequence of conditions was morphine, clonidine, and intensity manipulation. At least five baseline sessions separated each treatment regimen.

Stimulus manipulation procedure. Shock intensity was manipulated to obtain the following five conditions: (1) 0.0 mA versus 0.1 mA, (2) 0.5 mA versus 0.0 mA, (3) 0.2 mA versus 0.1 mA, (4) 0.5 mA versus 0.4 mA, (5) 0.0 mA versus 0.0 mA. During sessions when the shock intensities were manipulated, all other conditions were the same as during baseline sessions. Stimulus manipulation sessions were conducted on Tuesdays and Fridays, in a mixed order, and two sessions of each condition were conducted.

Data analysis. Treatment effects are expressed as absolute change in the percentage of correct responses, in the mean response latency, and in the number of shock presentations without a response. Control measures were calculated from at least five sessions during each series of experimental treatments (morphine, clonidine, or stimulus manipulation). If fewer than 50

responses occurred during a session, the data were excluded from further analysis (this happened only at drug dosages greater than those for which data are reported). To assess discrimination performance for both choice situations combined, the index A' (Pollack & Norman, 1964) was computed according to the formula provided by Grier (1971). A nonparametric index of sensitivity was used in order to avoid making assumptions about the underlying response distributions in the absence of complete operating characteristics. In the context of this experiment, A' is a measure of stimulus control and is related to the overall percentages of correct responses—that is, correct responding following both shock intensities. When $A' = 1.0$, perfect stimulus control is indicated, whereas a value of 0.5 indicates no stimulus control, or essentially random responding.

RESULTS

Baseline and Control Performance

Following approximately 100 training sessions, at least 90% of all responses occurred on the lever designated as correct following presentation of the 0.5-mA shock or the absence of shock. During the period when the 0.1-mA stimulus was introduced, correct responding initially decreased following both stimuli; however, correct responses returned to 90% within 15 sessions. During control sessions the percentage of correct responses was approximately equal for both intensities, with the largest average difference for any monkey being 6% (see Figures 3 and 4). For two monkeys the mean response latencies were similar following the presentation of both shock intensities (approximately 1.2 s), whereas for the third monkey the mean response latency following the 0.5-mA shock was shorter than that following the 0.1-mA shock (0.8 s vs. 1.2 s). The number of shock presentations that were not followed by a response never exceeded 42 per session for any monkey (typically there were 10 to 15), and usually these occurred at the beginning of the session.

Fig. 1. Average effects of morphine on A' in each of three monkeys. Dosages of morphine are in milligrams per kilogram. Points at V refer to vehicle injections; points at C refer to noninjection control sessions. Each point represents the mean of two sessions of each condition, except control points, which represent the mean of at least five sessions.

Fig. 2. Average effects of clonidine on A' in each of three monkeys. Dosages of clonidine are in milligrams per kilogram. Points at V refer to vehicle injections; points at C refer to noninjection control sessions. Each point represents the mean of two sessions for each condition, except control points, which represent the mean of at least five sessions.

Effects of Morphine and Clonidine

Figures 1 and 2 show the effects, in individual monkeys, of graded doses of morphine and clonidine on A' . Both morphine

and clonidine produced dosage-dependent decreases in A'. This effect was especially notable in S-873, where A' equaled 0.38 or 0.6 following 1.8 mg/kg morphine or 0.18 mg/kg clonidine, respectively.

Figures 3 and 4 show the effects, in individual monkeys, of graded doses of morphine or clonidine on the percentage of correct responses, response latency, and the number of shock presentations without a response following presentation of 0.5-mA shocks and 0.1-mA shocks. Morphine decreased the percentage of correct responses following the 0.5-mA shock in all three monkeys in a dosage-dependent fashion. Following presentation of the 0.1-mA shock, morphine had little effect on the percentage of correct responses for two monkeys, whereas morphine decreased the percentage of correct responses in the third

monkey in a dosage-dependent fashion. Morphine increased the number of shock presentations not followed by a response in a dosage-dependent manner, and this effect was approximately equal following each of the two shock intensities. Morphine also produced dosage-dependent increases in mean response latency, and there was no systematic difference between performances on the two shock intensities.

Clonidine decreased the percentage of correct responses following 0.1-mA shocks in a dosage-dependent fashion for two monkeys. For the third, S-873, substantial decreases were observed only following 0.18 mg/kg of clonidine. For S-874 all doses of clonidine had little or no effect on correct responding following 0.5-mA shocks. For the other two monkeys, clonidine produced slight decreases in correct responding follow-

Fig. 3. Average effects of morphine on the percentage of correct responses, mean response latency, and the number of stimulus presentations not followed by a response at 0.5-mA and 0.1-mA stimulus intensities in each of three monkeys. Dosages of morphine are in milligrams per kilogram. Points at V refer to vehicle injections; points at C refer to noninjection control sessions. The brackets at C represent one S.E.M. Each point represents the mean of two sessions for each condition, except control points, which represent the mean of at least five sessions.

Fig. 4. Average effects of clonidine on the percentage of correct responses, mean response latency, and the number of stimulus presentations not followed by a response at 0.5-mA and 0.1-mA stimulus intensities in each of three monkeys. Dosages of clonidine are in milligrams per kilogram. Points at V refer to vehicle injections; points at C refer to noninjection control sessions. The brackets at C represent one S.E.M. Each point represents the mean of two sessions for each condition, except control points, which represent the mean of at least five sessions.

ing 0.5-mA shocks, except after the 0.18 mg/kg dose, which produced substantial decreases. Clonidine also increased the mean response latency following both shock intensities in a dosage-dependent fashion, and increases were slightly greater following presentation of the 0.1-mA shock. Clonidine increased the number of shock presentations not followed by a response in a dosage-dependent fashion, and this effect was noticeably greater following presentation of the 0.1-mA shock than following the 0.5-mA shock. For example, in S-874, responding occurred on only 23% of the 0.1-mA shock presentations but on 92% of the 0.5-mA shock presentations following 0.18 mg/kg clonidine.

Effects of Changing the Stimulus Intensity

Changes in shock intensity did not alter the number of shock presentations without a response (range = 4 to 38) nor did changes in shock intensity alter mean response latency (range = 0.8 to 1.7 s), except in monkey S-874. During control conditions, S-874's mean response latency following presentation of the 0.5-mA shock (0.8 s) was shorter than that following presentations of the 0.1-mA shock (1.3 s). When the 0.5-mA shock was lowered to 0.2 mA or was eliminated, mean response latency increased (1.0 and 1.2 s, respectively). Likewise when the 0.1-mA shock was increased to 0.4 mA, mean response latency decreased from 1.3 s to 0.8 s.

Table 1

Effects of manipulating stimulus intensity on the percentage of correct responses in the presence of each shock intensity. Control values were calculated from the five sessions before stimulus-manipulation sessions.

Condition	Stimulus Intensity (mA)											
	0.5-0.1 control		0.0-0.1 1		0.5-0.0 2		0.2-0.1 3		0.5-0.4 4		0.0-0.0 5	
Subject												
S-873	96	98	33	80	96	95	64	98	97	14	32	69
S-876	97	93	17	86	99	90	81	93	88	35	42	55
S-874	96	97	06	98	99	91	92	98	92	22	04	96

Table 1 shows the effect of changing the shock intensity on the percentage of correct responses. Under the first condition, when the 0.5-mA stimulus was eliminated, correct responses on trials previously correlated with 0.5-mA shocks decreased dramatically in every monkey. Correct responding following 0.1-mA shocks decreased moderately for two monkeys and was virtually unchanged in the third. Under the second condition, when the 0.1-mA stimulus was eliminated, correct responding on trials previously correlated with 0.1-mA shocks decreased slightly in every monkey. Correct responding following 0.5-mA shocks increased slightly for two monkeys and was unchanged for the third. Under the third condition, when the 0.5-mA stimulus was changed to 0.2 mA, correct responding on trials previously correlated with 0.5-mA shocks decreased only slightly for one monkey, moderately for a second, and substantially for the third. Correct responding following 0.1-mA shocks was virtually unchanged in every monkey. Under the fourth condition, when the 0.1-mA stimulus was changed to 0.4 mA, correct responding on trials previously correlated with 0.1-mA shocks decreased dramatically in every monkey. Correct responding following 0.5-mA shocks was similar to baseline values in two monkeys and moderately decreased in the third monkey. Under the fifth condition, when both shock stimuli were eliminated, dramatic decreases in correct responding on trials previously correlated with 0.5-mA shocks were observed in every monkey. Correct responding on trials pre-

viously correlated with 0.1-mA shocks decreased substantially in two monkeys but was unchanged in the third. Under the fifth condition the overall percentage of correct responding (that is, the mean percentage of correct responses on all trials) was close to 50% in every monkey (S-873, 53%; S-876, 48%; S-874, 51%).

DISCUSSION

The effects of morphine, clonidine, and changes in shock intensity were examined in squirrel monkeys responding differentially following presentations of two different shock intensities. First of all, morphine produced dosage-dependent decreases in correct responding as indicated by reductions in A' ; however, morphine did not consistently affect correct responding following one stimulus more than the other. For example, whereas morphine consistently decreased correct responding following 0.5-mA shocks in every monkey, correct responding following 0.1-mA shocks was relatively unaffected for two monkeys but decreased in the third to a similar or greater extent than following 0.5-mA shocks.

In one sense these results contrast with previous studies (Dykstra, 1979, 1980) in which morphine and other opioids consistently decreased correct responding in the presence of a 0.35-mA or a 0.05 to 0.15-mA shock but not in the absence of electric shock. In the previous studies morphine-induced decreases in correct responding were greater in the presence of the lower

(0.05 to 0.15 mA) shock intensity than the higher (0.35 mA) shock intensity. In the present study morphine-induced decreases in correct responding did not depend on the shock intensity. These results suggest that morphine's effects differ when monkeys are responding differentially in the presence and absence of shock from when they are responding differentially in the presence of two different shock intensities. Previous studies, using rats, have also reported differences between results with the two types of discrimination tasks (Grilly & Genovese, 1979; Grilly et al., 1980; Lloyd et al., 1978; Poling et al., 1978).

Morphine produced approximately equivalent increases in response latency following the 0.5-mA and the 0.1-mA stimuli. This result is generally in agreement with previous research (Dykstra, 1979, 1980); however, the increases in response latency reported in those studies were greater than those seen here. The difference may be due to the limited response period used in the present study, which precluded response latencies greater than 7.5 s, and the limited duration of the stimuli. The previous studies employed unlimited response periods and shock was pulsed throughout the intervals.

Clonidine's effects were generally similar to those of morphine. That is, although clonidine decreased responding in the presence of both shock intensities, it did not consistently affect correct responding following one stimulus more than the other. Clonidine decreased correct responding following 0.1-mA shocks at the largest dose in all three monkeys, but the only decrease observed in one monkey occurred at this dose. Furthermore, only the largest dose of clonidine substantially reduced correct responding following 0.5-mA shocks in two monkeys but no decrease was seen in the third. Moreover, clonidine also increased response latency in a manner similar to that of morphine. Clonidine's effects did differ from those of morphine in one respect: Although both drugs increased the number of shock presentations not followed by a response, clonidine eliminated responding following 0.1-mA

shocks more frequently than following 0.5-mA shocks. In contrast, doses of morphine that eliminated responding did so to the same extent following both shock intensities.

Manipulation of shock intensity produced consistent changes in correct responding. In every case where one shock intensity was changed, the percentage of correct responses following the altered stimulus was affected more than that following the unaltered stimulus. When both shocks were eliminated, the overall proportion of correct responses was close to 50%; however, there were large individual differences in correct responses on the two levers, indicating a bias based on position and/or other factors. It is possible that similar biases were introduced by drug treatments. If biases such as these were present and were not the same in each monkey, they may account for the inconsistencies among monkeys. Further research is needed to investigate this proposition. For example, the effects of drug administration in combination with intensity change may be particularly interesting.

Even though large decreases in correct responding occurred when stimulus intensity was manipulated, mean latency to respond and the number of stimulus presentations not followed by a response were generally similar to control performances. It is clear from these results that changes in correct responding do not necessarily produce changes in response latency or in the number of presentations not followed by a response. Although the differences between drug administration and shock-intensity manipulation preclude a direct comparison of the two conditions, it is notable that performance following morphine or clonidine was not similar to performance involving manipulation of one of the two shock intensities.

Morphine and clonidine both produced dosage-dependent decreases in the stimulus control of two shock intensities. Previous studies, in which the discriminative stimuli were the presence and absence of shock, have shown that the opioid analgesics

decrease correct responding in the presence of shock but not in the absence of shock. Because an analogous effect was not observed in the present study, it is concluded that substantial differences exist in drug effects on performance under the two paradigms and that further work is necessary to determine the basis for these differences. Altering shock intensities also decreased the percentage of correct responses, but, unlike drug treatments, these manipulations consistently affected responding following the manipulated stimulus to a greater extent than following the one held constant. Although direct comparisons between drug effects and intensity manipulation effects are difficult to make, additional investigation of the interaction between the effects of stimulus change and drug effects on stimulus control may provide important information about the discrimination of electric shock.

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