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Acquisition of Brightness Discrimination in the Rat Is Impaired by Opiates with Psychotomimetic Properties

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TANG, A. H. AND S. R. FRANKLIN. *Acquisition of brightness discrimination in the rat is impaired by opiates with psychotomimetic properties.* PHARMACOL BIOCHEM BEHAV **18**(6) 873–877, 1983.—The acquisition of shock avoidance behavior by rats was studied in an automated Y-maze which incorporates a simultaneous brightness discrimination paradigm. When administered prior to each of 5 consecutive daily sessions, two opiate derivatives with psychotomimetic properties, cyclazocine and N-allynormetazocine, impaired the acquisition of brightness discrimination at doses which also increased movements between trials. These effects were similar to those produced by phencyclidine, ketamine, and a high dose of *d*-amphetamine. Pretreatment with morphine, pentazocine and scopolamine at motor stimulant doses before each training session did not affect acquisition of brightness discrimination. Nalorphine, naltrexone, and chlorpromazine also had no effect on brightness discrimination, even at motor depressant doses. Whereas the motor stimulation produced by morphine or pentazocine was blocked by naltrexone, the motor stimulation and discrimination disruption produced by cyclazocine or N-allylnormetazocine were only incompletely antagonized by naltrexone. The results demonstrate similarities between psychotomimetic opiates and phencyclidine-like compounds and may reflect the sensory or cognitive disturbance produced by these drugs in man.

Brightness discrimination Psychotomimetic opiates Automated Y-maze Phencyclidine Rats

IN 1954, Lasagna and Beecher [1] made the surprising discovery that nalorphine, which had been known only as a potent narcotic antagonist, was itself an analgesic in man. The finding was unexpected, partly because nalorphine exhibited no antinociceptive activities in most of the laboratory animal models of analgesia. Unlike morphine, however, nalorphine analgesia in man was associated with psychotomimetic effects in many of the patients [9]. This led to a search to find a useful analgesic among the narcotic antagonists which had a tolerable degree of psychotomimetic properties. Among a series of benzomorphans, Keats and Telford [10] found that potent analgesia, together with potent narcotic antagonism, was always associated with psychotomimetic effects in their human subjects.

The development of a non-addicting potent analgesic among the narcotic antagonists is limited by suitable animal models predicting psychotomimetic side effects. Schneider [17] found that higher doses of cyclazocine and levallorphan produced bizarre stereotypic behaviors in rats consisting of head turning from side to side, pivoting on hind legs and backward walking. Holtzman [4] studied the agonistic activities of cyclazocine and pentazocine in locomotor activities of rats and demonstrated a different mechanism from that which mediates the action of morphine. Canine delirium, which consists of violent struggles and visual tracking, was suggestive of hallucinations to Martin *et al.* [13] and provided the basis for the concept that the sigma receptor mediates the effects of psychotomimetic opiates. Drug discrimination studies have also provided a powerful method to compare the subjective aspects of pharmacological effects. Cyclazocine and N-allyl-normetazocine (SKF-10047), for instance, had similar discriminative properties in the rat, which were also shared by phencyclidine and ketamine, two dissociative anesthetics with psychotomimetic effects in man [5,18].

The opiates are known to have profound effects on operant behaviors in general. In food-reinforced behaviors of pigeons [16], and shock-avoidance in rats [6], cyclazocine and pentazocine increased response rate at lower doses and suppressed responding at higher doses. We feel that response rate measurement alone is inadequate to separate the desirable from undesirable properties of drugs. Barrett *et al.* [1] described a shock avoidance-escape procedure for rats in a symmetrical Y-maze. It incorporated a simultaneous brightness discrimination paradigm into the discrete-trial, shuttle avoidance task. Thus, stimulus control could be evaluated independently of movement stimulation or suppression. This procedure may be expected to be sensitive to disruption by drugs which alter sensory or cognitive functions. We further chose to evaluate the drug effects using acquisition of such behavior by naive rats rather than using well-trained animals. This was done to avoid cross-tolerance between drugs and to increase the sensitivity of the test procedure. The effects of opiates were compared to other psychotropic drugs, including phencyclidine-like compounds.

METHOD

Animals

About 400 male rats of the Fischer 344 strain weighing 180–200 g were used. They were housed individually in wire-mesh cages after arriving at the laboratory and during the 5 daily acquisition sessions, with free access to food and drinking water. Each rat was used only once.

Apparatus

The symmetrical Y-maze similar to that described by Barrett *et al.* [1], was constructed of clear Plexiglas. Each of the three arms had a dimension of 20×12×12 cm connected at 120° by a triangular area measuring 12 cm on each side. The floor of the Y-maze consisted of stainless steel bars 5 mm in diameter, arranged perpendicular to the side of the arms and separated by 10 mm from each other. The grid floor was connected to a shocker-distributor, constructed in our laboratory, to provide scrambled DC current. Behind the wall at the end of each arm were sets of three jewel lights which could be selectively illuminated as the discriminative stimuli. Each arm was further equipped with a photocell detector positioned midway (10 cm) from the end of each arm and 2.5 cm above the grid floor to register the movements of the rat. A clear Plexiglas cover served as the ceiling of the Y-maze and the Y-maze was housed in a sound-attenuated chamber equipped with masking white noise and an overhead houselight (three jewel lights) for general illumination. Four sets of identical Y-mazes were used for the experiments.

The stimulus input-outputs were interfaced in an adjacent room with a PDP8 computer which controlled the schedule contingencies and processed the experimental results.

Experimental Procedure

Each experimental session of the discriminated, avoidance-escape task in the automated Y-maze consisted of 25 discrete trials, separated by inter-trial-intervals (ITI's) of 40 sec. Sessions were signalled by the illumination of the overhead houselight. During ITI's none of the lights at the end of the arms were illuminated and movements of the rat from one arm to another had no scheduled consequence. A trial began with the illumination of two of the three arms, including the arm occupied at the start of the trial. The distribution of left or right arm illuminations, with respect to the occupied arm, was randomly selected. Movement of the rat into the unlighted arm immediately extinguished all arm illumination and started the next ITI. Movement into a lighted arm had no programmed consequence. Entry into either a lighted or darkened arm during the first 5 sec of a trial was recorded as an avoidance attempt. In the absence of a correct entry (into the dark arm) within the first 5 sec of a trial, shock (0.5 mA) was delivered through the grid floor and remained on until a correct entry into the dark arm was made, which immediately terminated the trial. Entry into a lighted arm during shock also had no programmed consequence. Shock was automatically terminated when no correct entry was made within 10 sec (15 sec after the beginning of a trial).

Performance of the avoidance-escape task in the Y-maze was expressed by the following measurements: (a) percent reduction of unavoided shock from a possible total of 25 (percent successful avoidance), (b) number of arm entries during ITI, (c) percent of trials in the session where the first arm entry (avoidance or escape attempt) was a choice of the dark arm (percent correct discrimination), and (d) percent of trials in the sessions where there was an avoidance attempt (with either correct or incorrect entries).

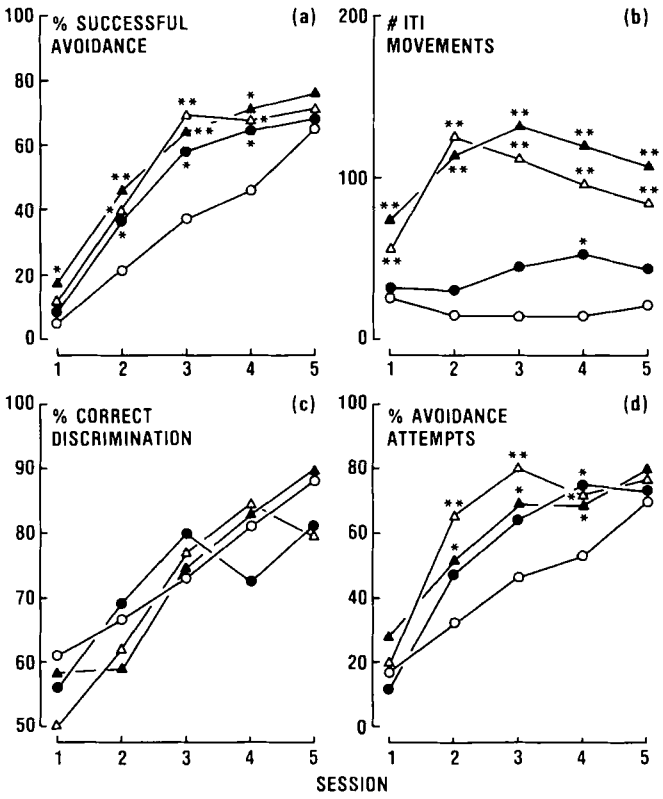

FIG. 1. Acquisition of shock avoidance-escape by rats in the Y-maze and the effects of morphine sulfate (○, saline; ●, 1 mg/kg; △, 3 mg/kg; ▲, 10 mg/kg, SC). Each data point represents the mean of 8 rats. $^{**}p<0.01$, $^{*}p<0.05$, two-tailed Dunnett's t-test comparing to the parallel saline group in the same experimental session. For the description of ordinates, see Method section.

Acquisition of the avoidance-escape behavior in the Y-maze was studied during 5 consecutive daily sessions with 25 trials each. Rats were divided into groups of 8, receiving injections of saline or drug solutions 30 min before each of the 5 experimental sessions. In the antagonism study, naltrexone (1 mg/kg) was administered with the test drug 30 min prior to each of 5 consecutive acquisition sessions. Drugs were always dissolved in saline and injected SC in volumes of 1 ml/kg. Cyclazocine was dissolved in distilled water with the addition of a small amount of citric acid (final pH=6.0).

For statistical evaluation, one-way analysis of variance was performed for treatment groups of each drug. If a significant value of F was found, data from each dose were further compared to the saline control group in that experiment, using Dunnett's t-test for multiple comparisons.

Drugs

Cyclazocine and pentazocine lactate (Talwin^{R} injections) were kindly supplied by the Winthrop Laboratory. N-allylnormetazocine HCl (SKF-10047) was provided by Dr. R. Willette, National Institute on Drug Abuse. Other drugs tested were obtained from commercially available sources: morphine sulfate, nalorphine HCl, naltrexone HCl (Endo Laboratories), phencyclidine HCl (Sernylan^{R}, Bio-Ceutic

TABLE 1

THE EFFECTS OF OPIATE COMPOUNDS ON THE AVOIDANCE ACQUISITION BY RATS IN THE AUTOMATED Y-MAZE (MEANS ± S.E.M.)

Drug	Dose mg/kg SC	N	% Successful Avoidance	ITI Movements	% Correct Discrimination	% Avoidance Attempts
Morphine SO_4	0	8	66 ± 4	22 ± 5	88 ± 2	71 ± 4
	1	8	66 ± 3	44 ± 10	81 ± 4	73 ± 3
	3	8	67 ± 4	85 ± 13†	80 ± 5	74 ± 3
	10	8	76 ± 3	108 ± 12†	89 ± 3	79 ± 3
Pentazocine lactate	0	8	46 ± 4	22 ± 6	90 ± 2	51 ± 5
	3	8	78 ± 4†	66 ± 21	84 ± 2	83 ± 4†
	10	8	86 ± 3†	143 ± 25†	88 ± 5	89 ± 3†
	30	8	79 ± 9†	74 ± 18	87 ± 4	82 ± 8†
Cyclazocine	0	8	71 ± 9	36 ± 5	80 ± 6	78 ± 7
	0.3	8	74 ± 6	107 ± 23†	86 ± 4	79 ± 6
	1	8	59 ± 5	110 ± 25*	78 ± 3	69 ± 6
	3	8	60 ± 7	196 ± 34†	63 ± 4*	78 ± 8
N-allyl-normetazocine HCl (SKF-10047)	0	8	56 ± 8	27 ± 5	78 ± 2	67 ± 8
	1	8	44 ± 6	25 ± 5	79 ± 3	56 ± 8
	3	8	48 ± 9	53 ± 24	83 ± 4	55 ± 9
	10	8	71 ± 8	216 ± 36†	62 ± 4*	83 ± 6
Nalorphine HCl	0	8	58 ± 9	40 ± 12	86 ± 4	63 ± 9
	1	8	58 ± 10	50 ± 14	88 ± 3	59 ± 10
	3	8	52 ± 5	65 ± 18	83 ± 4	59 ± 5
	10	8	56 ± 8	43 ± 11	87 ± 2	61 ± 8
Naltrexone HCl	0	8	61 ± 6	33 ± 6	90 ± 2	66 ± 6
	0.1	8	60 ± 4	22 ± 5	89 ± 4	67 ± 5
	0.3	8	50 ± 8	18 ± 6	87 ± 4	43 ± 5
	1	7	36 ± 7*	18 ± 10	85 ± 5	38 ± 7*

The results represent the fifth session performance.
†$p<0.01$; *$p<0.05$, two-tailed Dunnett's t-test for multiple comparisons to the parallel saline group.

Lab., Inc.), ketamine HCl (Ketalar^R, Parke-Davis), d-amphetamine sulfate, scopolamine HBr, and chlorpromazine HCl.

RESULTS

Rats exposed to the avoidance-escape contingencies in the automated Y-maze learned to reduce the number of shocks in 5 consecutive experimental sessions (Fig. 1a). This successful avoidance improvement in controls can be accounted for by both the acquisition of avoidance attempts (Fig. 1d) and correct brightness discrimination (Fig. 1c) which increased progressively during the 5 daily sessions. ITI movements, on the other hand, remained at the same levels. Figure 1 also shows that pretreatment with morphine before each training session increased the percentage of successful avoidances. This facilitating effect of morphine appears to be entirely due to an increase in avoidance attempts since the rates of discrimination acquisition between the morphine- and saline-treated groups were not different. The facilitation of avoidance attempts by morphine is further reflected by an increase in movements between trials (Fig. 1b) which was more demonstrable after the first session. The effects of morphine on avoidance acquisition, therefore, were related mainly to motor stimulation in the rat. Since for all other drugs tested in avoidance acquisition the drug effects were usually largest toward the end of the 5 training sessions, the remainder of experimental results are expressed by the fifth session performance only.

Table 1 summarizes the effects of several prototypical opiate analgesics on avoidance acquisition in the Y-maze. Pentazocine increased both avoidance attempts and ITI locomotor activities on the fifth session of training. Neither morphine nor pentazocine had a significant influence on brightness discrimination. Cyclazocine (0.3–3 mg/kg) and SKF-10047 (10 mg/kg) increased ITI movements. At the highest doses of these two compounds, brightness discrimination was completely disrupted so that the choice of arm entry during a trial appeared random. Brightness discrimination was unchanged by nalorphine or naltrexone, although the highest dose (1 mg/kg) of naltrexone reduced avoidance attempts significantly.

Table 2 lists the results of several non-opiate psychotropic drugs on the fifth session of avoidance acquisition. Phencyclidine and ketamine disrupted brightness discrimination and produced enhanced avoidance attempts as well as ITI movements. d-Amphetamine had a biphasic effect on ITI movement. At the highest dose (3 mg/kg) of d-amphetamine, which produced less motor stimulation than certain lower doses, brightness discrimination was also significantly impaired. Scopolamine, at the doses tested, increased ITI movements without any effect on brightness discrimination. A grossly depressant dose of chlorpromazine also had no effect on brightness discrimination.

TABLE 2

THE EFFECTS OF NON-OPIATE PSYCHOTROPIC DRUGS ON THE AVOIDANCE ACQUISITION BY RATS IN THE AUTOMATED Y-MAZE (MEANS ± S.E.M.)

Drug	Dose mg/kg SC	N	% Successful Avoidance	ITI Movements	% Correct Discrimination	% Avoidance Attempts
Phencyclidine HCl	0	8	62 ± 9	22 ± 5	86 ± 6	68 ± 6
	0.3	4	43 ± 11	17 ± 3	74 ± 5	45 ± 8
	1	8	66 ± 6	301 ± 43†	56 ± 6†	88 ± 4†
	3	8	46 ± 3	193 ± 8†	48 ± 5†	82 ± 3
Ketamine HCl	0	6	40 ± 10	31 ± 11	84 ± 4	49 ± 10
	3	8	74 ± 5†	102 ± 16*	90 ± 3	77 ± 4†
	10	8	77 ± 5†	111 ± 17*	86 ± 4	80 ± 4†
	30	8	52 ± 6	203 ± 19†	50 ± 10†	86 ± 5†
d-Amphetamine SO_4	0	8	40 ± 6	18 ± 3	86 ± 6	47 ± 6
	0.1	8	62 ± 7*	32 ± 6	86 ± 4	69 ± 7*
	0.3	8	86 ± 5†	117 ± 18†	80 ± 6	93 ± 3†
	1	8	81 ± 6†	120 ± 21†	83 ± 5	91 ± 4†
	3	8	68 ± 4*	49 ± 12	60 ± 5†	89 ± 3†
Scopolamine HBr	0	8	44 ± 7	26 ± 4	83 ± 3	50 ± 7
	0.1	8	47 ± 4	61 ± 17	81 ± 4	54 ± 4
	1	8	63 ± 6*	107 ± 16†	83 ± 6	66 ± 5
	10	8	62 ± 5	105 ± 18†	85 ± 2	63 ± 5
Chlorpromazine HCl	0	8	64 ± 7	45 ± 10	90 ± 3	68 ± 7
	0.1	8	56 ± 5	47 ± 9	90 ± 2	59 ± 5
	0.3	8	32 ± 6†	21 ± 7	95 ± 1	34 ± 6†
	1	8	6 ± 3†	4 ± 1†	93 ± 3	8 ± 3†

Results represent the fifth session performance.
†$p<0.01$; *$p<0.05$, two-tailed Dunnett's t-test for multiple comparison to the parallel saline group.

TABLE 3

ANTAGONISM OF THE EFFECTS OF SOME OPIATES ON THE AVOIDANCE ACQUISITION IN THE Y-MAZE BY NALTREXONE HCl (1 mg/kg) (MEANS ± S.E.M.)

Drug	Dose mg/kg SC	N	% Successful Avoidance	ITI Movements	% Correct Discrimination	% Avoidance Attempts
Saline	—	8	58 ± 6	24 ± 6	88 ± 3	64 ± 6
Morphine SO_4	10	8	62 ± 6	18 ± 5	88 ± 3	64 ± 6
Pentazocine lactate	10	6	65 ± 10	48 ± 18	83 ± 5	68 ± 10
Cyclazocine	3	8	69 ± 4†	161 ± 18†	68 ± 5*	82 ± 4†
N-allyl-normetazocine HCl	10	8	44 ± 6	92 ± 16†	56 ± 5†	65 ± 6

Both the opiate compound and naltrexone were injected 30 minutes before the experimental session. The results represent the fifth session performance.
†$p<0.01$; *$p<0.05$, two-tailed Dunnett's t-test for multiple comparisons to the parallel saline group.

When naltrexone (1 mg/kg) was given in combination with 10 mg/kg of morphine or pentazocine, the motor stimulation produced by the two analgesics (Table 1) was completely blocked (Table 3). But when the same dose of naltrexone was given with 3 mg/kg of cyclazocine or 10 mg/kg of SKF-10047, the motor stimulation was only partially blocked and the disruption in brightness discrimination was not reversed at all (cf., Tables 1 and 3).

DISCUSSION

Acquisition of brightness discrimination in the Y-maze presumably involves visual perception as well as associative learning. Such learning is shown in this study to be impaired by cyclazocine, SKF-10047, phencyclidine, and ketamine, all of which have psychotomimetic effects in man [10,12]. A high dose of *d*-amphetamine, exceeding that which stimu-

lated locomotor activities, also disrupted the acquisition of brightness discrimination. Clinically useful drugs such as chlorpromazine, morphine, pentazocine, and naltrexone did not impair discrimination acquisition at stimulant or depressant doses. It is tempting to relate this disruptive effect to the perceptual distrubances or confusional state produced by the psychotomimetic opiates and phencyclidine.

There are, however, reasons to be cautious with the above interpretation regarding the opiates. Nalorphine has been reported to have psychotomimetic effects in man qualitatively similar to those of cyclazocine [2,15], yet did not disrupt brightness discrimination in rats. Martin *et al.* [14] also reported that the maximum subjective effects of nalorphine in man are less intense than the maximum effects of cyclazocine. In many animal systems measuring antinociceptive or physiological functions, nalorphine has a lower efficacy than cyclazocine. The lack of effect by nalorphine on brightness discrimination may reflect the partial agonist nature of nalorphine on the particular subpopulation of opiate receptors [13]. There may also be a species peculiarity for the rats to be less sensitive to nalorphine. The bizarre behavioral effect produced in rats by cyclazocine, levallorphan, or phencyclidine did not occur with even very high doses of nalorphine [17].

It is important also to note that the subjective and behavioral effects of cyclazocine in man could be antagonized by a relatively high dose of naloxone [8]. In this study, a behavioral depressant dose of naltrexone did not reverse the effects of cyclazocine or SKF-10047 in discriminative learning. The increase in ITI movements from these two compounds was only partially reversed, although the motor stimulant effect of morphine and pentazocine was completely blocked. It calls into question the validity of the present model for the psychotomimetic properties of cyclazocine-like opiate compounds. Alternatively, it suggests that cyclazocine has nonopiate-related behavioral effects not yet characterized in human subjects.

Cyclazocine and SKF-10047 do share important pharmacological activities with phenycyclidine. Specific binding of (^{3}H)-phencyclidine to rat brain membrane preparations was displaced by SKF-10047 at sub-micromolar concentrations [19]. Likewise, binding of (^{3}H)-SKF-10047 was displaced by phencyclidine which was much weaker in displacing other opiate ligands [7]. In rats trained to discriminate cyclazocine from saline, the drug responses generalized to phencyclidine [18]. Rats trained to discriminate phenyclidine from saline also generalized to SKF-10047 [5]. Neither the stimulus effects of cyclazocine nor those of phencyclidine in rats were antagonized by naloxone. The rate-reducing effects of cyclazocine in schedule-controlled behaviors of rats were not blocked by naloxone [3]. The disruption of brightness discrimination learning further demonstrates a behavioral effect shared by cyclazocine and SKF-10047 on the one hand, phencyclidine and ketamine on the other. This effect appears not to be related to narcotic (naloxone-sensitive) mechanisms. Whether this phencyclidine-like property accounts for the psychotomimetic effects of cyclazocine and SKF-10047 in man requires further elucidation.

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