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NON-OPIOID PSYCHOTOMIMETIC-LIKE DISCRIMINATIVE STIMULUS PROPERTIES OF N-ALLYLNORMETAZOCINE (SKF 10,047) IN THE RAT

GARY T. SHEARMAN * and ALBERT HERZ

Department of Neuropharmacology, Max-Planck-Institut für Psychiatrie, Kraepelinstrasse 2, D-8000 München 40, F.R.G.

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The purpose of this study was to characterize the discriminative stimulus property of dl-SKF 10,047 in the rat and to investigate if this property is the result of an interaction with opiate receptors or dopaminergic mechanisms. Male Sprague Dawley rats were trained in a two-lever food-reinforced procedure to discriminate between the effect of saline and of dl-SKF 10,047 (5 mg/kg). The trained rats dose dependently generalized the effect of dl-, d- and l-SKF 10,047, as well as cyclazocine, phencyclidine and ketamine but did not generalize the effect of either fentanyl, morphine, bremazocine, ethylketocyclazocine, pentazocine, nalorphine, naloxone, MR 2266, d-lysergic acid diethylamide, apomorphine or d-amphetamine. Neither naloxone, MR 2266, fentanyl, ethylketocyclazocine nor haloperidol antagonized the discriminative stimulus produced by dl-SKF 10,047. These data suggest that the discriminative stimulus property of dl-SKF 10,047 in the rat is not due to its interaction with either opiate receptors or dopaminergic mechanisms but may be related to its psychotomimetic effect in man.

Narcotic drug discrimination Opiate receptors SKF 10,047 Ethylketocyclazocine Morphine
d-Lysergic acid diethylamide Phencyclidine Naloxone Dopamine

1. Introduction

N-Allylnormetazocine (SKF 10,047) was reported to produce analgesia and psychotomimetic subjective effects in man (Keats and Telford, 1964). Canine delirium and psychotomimetic effects produced by SKF 10,047 were proposed to result from its agonistic interaction with a so-called σ opiate receptor (Martin et al., 1976). Although SKF 10,047-induced canine delirium was antagonized by naltrexone (Martin et al., 1976) other effects of SKF 10,047 in the dog were not and it was suggested that the σ-effects of SKF 10,047 could result from its interaction with several receptors (Martin et al., 1980). SKF 10,047 and other proposed σ-opiate receptor agonists, including cyclazocine (Gilbert and Martin, 1976), bind with high affinity to a site where phencyclidine (PCP) binds and it was suggested that the σ effects of opiates may be mediated through a PCP binding site (Zukin and Zukin, 1981; Quirion et al., 1981; Itzhak et al., 1981). It has also been suggested that some agonistic actions of SKF 10,047 could involve an activation of dopaminergic systems (Martin et al., 1976; Iwamoto, 1981) and in addition to its agonistic effects, SKF 10,047 has antagonistic properties at μ- and κ-opiate receptors (Martin et al., 1974; Iwamoto, 1981; Shearman and Herz, 1981a, 1982).

Narcotic drug discrimination procedures have been used to characterize the discriminative stimulus properties of narcotic drugs (for reviews see Lal et al., 1977; Holtzman et al., 1977; Colpaert, 1978) and to investigate the receptor (Teal and Holtzman, 1980a; Herling and Woods, 1981; Shearman and Herz, 1981a,b; 1982) as well as the

* To whom all correspondence should be addressed.

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neurochemical (Colpaert, 1978) mechanisms underlying such discriminative stimuli. It was the purpose of our study to characterize the discriminative stimulus property of SKF 10,047 in the rat and to investigate if this property is the result of its interaction with opiate receptors or with dopaminergic mechanisms.

2. Materials and methods

2.1. Discrimination training

The procedure used was identical to that reported in detail previously (Shearman and Herz, 1981a,b; 1982). Briefly, rats (n = 24) were trained to discriminate between the effect of dl-SKF 10,047 and saline by responding (FR 10) for food reinforcement (45 mg food pellets) with a lever on one side of the food cup 30 min after an injection of dl-SKF 10,047 (5 mg/kg) and by responding with a lever on the other side 30 min after a saline (1 ml/kg) injection. SKF 10,047-saline sessions were carried out 7 days a week and the rats were trained to a criterion of emitting four or less responses with the incorrect lever (i.e. SKF lever after saline injection or saline lever after SKF injection) prior to the first reinforcement (10 responses with the correct lever) in 9 out of 10 consecutive sessions.

2.2. Discrimination testing

The rats were used for testing when they reached the criterion level of performance. Test sessions lasted 15 min and were separated by at least two 'practice' sessions in which no more than four responses were emitted with the incorrect lever before lever selection.

2.3. Data analyses

Data are expressed as a percentage of rats selecting the SKF lever following each drug treatment. ED_{50} were calculated with slope (m) and y-intercept (b_0) of log-linear regression lines using the equation $y = m\log x + b_0$.

2.4. Drugs

The following drugs were used: ethylketocyclazocine methanesulfonate, dl-cyclazocine base and pentazocine hydrochloride (generously supplied by Sterling-Winthrop Research Institute, Rensselaer, N.Y., U.S.A.), dl-SKF 10,047 base (N-allylnormetazocine, obtained from Addiction Research Center, U.S. Public Health Service, Lexington, KY, U.S.A.); d- and l-SKF 10,047 methanesulfonate and MR 2266 (1-2-(3-furylmethyl-5,9-diethyl-2′-hydroxy-6,7-benzomorphan), generously provided by Dr. Merz, Boehringer Ingelheim Ltd., Ingelheim, F.R.G.), dl-bremazocine hydrochloride (2-(1-hydroxycyclopropylmethyl)-5-ethyl-9,9-dimethyl-2′-hydroxy-6,7-benzomorphan; kindly provided by Dr. Römer, Sandoz, Basle, Switzerland), nalorphine hydrochloride (Boehringer Ingelheim, Ltd., Ingelheim, F.R.G.), morphine hydrochloride (Merck, Darmstadt, F.R.G.), fentanyl citrate (Janssen Pharmaceutica Beerse, Belgium), ketamine hydrochloride (Parke, Davis and Co., Munich, F.R.G.), phencyclidine hydrochloride (a gift from Dr. A. Trevor, Department of Anaesthesia, Stanford University School of Medicine, Stanford, California, U.S.A.), haloperidol (Haldol®, Janssen Pharmaceutica, Beerse, Belgium), naloxone hydrochloride (Endo Laboratories, Garden City, New Jersey), d-lysergic acid diethylamide and apomorphine (Sandoz AG, Basle, Switzerland) and d-amphetamine sulfate (Sigma, Chemical Co., Taufkirchen, F.R.G.). All drugs were dissolved in 0.9% saline except dl-SKF 10,047, MR 2266 and cyclazocine which were dissolved in 8.5% lactic acid, 1.0 N NaOH and saline in a 3:2:5 ratio. All drugs were administered s.c. in a vol of 2 ml/kg. Drug doses were calculated in terms of the free base and were administered in an irregular order.

3. Results

3.1. Acquisition of the SKF 10,047-saline discrimination

All of the rats acquired the SKF 10,047-saline discrimination to the required criterion. The num-

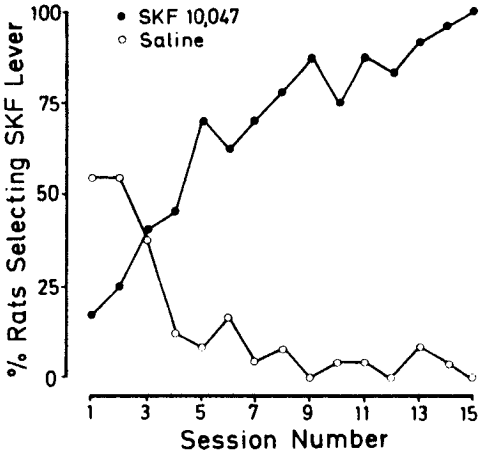

Fig. 1. Acquisition of dl-SKF 10,047 (5 mg/kg) vs. saline discrimination by rats. Percent of rats selecting the SKF lever (*ordinate*) vs. training session number (*abscissa*). n=24 for each training session except for the first SKF 10,047 session where n=23 since one rat did not make a lever selection.

ber of sessions needed to reach this criterion ranged from 17 to 35 with the mean (±1 S.E.) being 22 ± 1. Acquisition of the SKF 10,047-saline discrimination is shown in fig. 1.

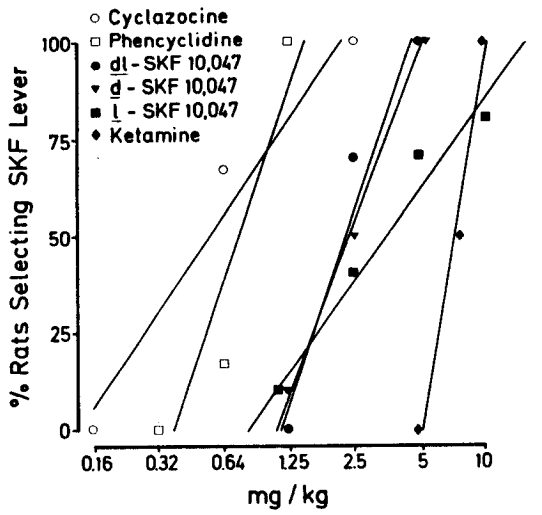

Fig. 2. Generalization tests with cyclazocine, phencyclidine, dl-SKF 10,047, d-SKF 10,047, l-SKF 10,047 and ketamine in rats trained to discriminate between the effect of saline and dl-SKF SKF10,047 (5 mg/kg). Percent of rats selecting the SKF lever (*ordinate*) vs. dose (log scale) of test drug (*abscissa*) in mg/kg. n=10 for all enantiomers of SKF 10,047 at each dose and 6 for all other drugs.

3.2. *Generalization tests*

During generalization tests the rats never emitted an average of more than three responses with the non-selected lever before lever selection. The data summarized in fig. 2 show that SKF 10,047-saline-trained rats dose relatedly selected the SKF lever after injection of cyclazocine, phencyclidine, dl-SKF 10,047, d-SKF-10,047, l-SKF 10,047 and ketamine. ED_{50} were 0.55, 0.72, 2.29, 2.38, 3.54 and 7.21 mg/kg respectively. The rats did not generalize the effect of either fentanyl, morphine, bremazocine, ethylketocyclazocine, pentazocine, nalorphine, naloxone, MR 2266, d-lysergic acid diethylamide, d-amphetamine or apomorphine to the discriminative stimulus produced by 5 mg/kg dl-SKF 10,047 (table 1). SKF 10,047-saline-trained rats did not make a lever selection after injection of higher doses of fentanyl (0.08 mg/kg) morphine (5 mg/kg), ethylketocyclazocine (0.64 mg/kg), bremazocine (0.16 mg/kg) or d-amphetamine (2.5 mg/kg).

TABLE 1

Drugs that were not generalized by rats trained to discrimininate the effect of dl-SKF 10.047 (5 mg/kg).

Test drug [a]	Doses tested (mg/kg)	Percentage of six rats selecting SKF lever
Fentanyl	0.02/0.04	0/17
Morphine	1.25/2.5	0/17
Ethylketocyclazocine	0.16/0.32	0/0
Bremazocine	0.04/0.08	17/0
Pentazocine	5/10	0/0
Nalorphine	2.5/10/40/160	0/0/0/0
Naloxone	1.25/5/10	0/0/0
MR 2266	0.32/1.25/5/10	0/0/0/0
d-LSD	0.04/0.08/0.16	0/0/17
d-Amphetamine	0.64/1.25	0/0
Apomorphine	0.16/0.64	0/0

[a] Thirty min following injection of the test drug, the rats were placed in their assigned Skinner boxes and allowed to make a lever selection. The lever with which the animal first emitted ten responses was considered the selected lever.

TABLE 2

Drugs that did not antagonize the discriminative stimulus produced by dl-SKF 10,047 (5 mg/kg).

Test drug	Pretreatment [a] time (min)	Doses tested (mg/kg)	Percentage of 6 rats selecting SKF lever
Naloxone	10	1.25/5/10/20	100/100/83/83
MR 2266	10	0.32/1.25/5	83/67/100
Fentanyl	30	0.04/0.08	100/100
Ethylketocyclazocine	30	0.32/0.64	100/100
Haloperidol	60	0.04/0.08/0.16	100/100/100

[a] Test drugs were injected at these times before the test sessions. SKF 10,047 (5 mg/kg) was always injected 30 min before the test session.

3.3. Antagonism tests

During antagonism tests the rats never emitted an average of more than two responses with the non-selected lever before lever selection. The data summarized in table 2 show that neither naloxone, MR 2266, fentanyl, ethylketocyclazocine nor haloperidol antagonized the discriminative stimulus produced by dl-SKF 10,047 (5 mg/kg).

4. Discussion

The present study showed that rats can learn to discriminate between the effect of saline and dl-SKF 10,047 (5 mg/kg). The number of training sessions required for the rats to reach the discrimination criterion was similar to the number needed to reach an equivalent criterion for fentanyl (0.04 mg/kg)-ethylketocyclazocine (0.32 mg/kg) and bremazocine (0.04 mg/kg)-saline discriminations using this procedure (Shearman and Herz, 1981b; 1982).

The lack of stereoselectivity and the inability of the narcotic antagonists naloxone and MR 2266 to antagonize the discriminative stimulus produced by SKF 10,047 suggests that this property is not mediated by an agonistic action at an opiate receptor since the activity of opiate drugs is typically characterized by a high degree of stereoselectivity for the levorotatory enantiomer and by sensitivity to antagonism by narcotic antagonists (Pert and Snyder, 1973; Teal and Holtzman, 1980c). Although naloxone displaced [^{3}H]SKF 10,047 binding to rat brain membranes (Pasternak et al., 1981) this displacement may have occurred at μ-, κ- or σ-sites since SKF 10,047 probably binds as an antagonist at μ- and κ-receptors (see below). Our data agree with the results of other behavioral (Ward et al., 1978; Harris, 1980) and biochemical (Wood and Stotland, 1982) studies done with rodents and showing a lack of antagonism of SKF 10,047 effects by naloxone and therefore suggest that the discriminative stimulus effect of SKF 10,047 in rats is a non-opioid effect. Since naloxone and MR 2266 were not generalized to the SKF 10,047 discriminative stimulus and neither fentanyl nor EKC antagonized this effect, it is suggested that the discriminative stimulus property of SKF 10,047 is not related to its previously demonstrated antagonistic actions at μ- and κ-opiate receptors (Martin et al., 1974; Iwamoto, 1981; Shearman and Herz, 1981a, 1982).

In the present study it was found that SKF 10,047-saline-trained rats dose dependently generalized the effect of cyclazocine, a dysphorogenic-psychotomimetic analgesic (Haertzen, 1970) and proposed κ/σ-opiate agonist (Martin et al., 1976), as well as the effect of the structurally related dissociative anesthetics PCP and ketamine (Domino et al., 1965). However, nalorphine and pentazocine, also proposed mixed κ/σ-opiate agonists (Martin et al., 1976) and LSD, a potent hallucinogen were not generalized. Furthermore, neither fentanyl nor morphine, euphorogenic analgesics (Gorodetzky and Martin, 1965) that were proposed to be μ-opiate agonists (Martin et al., 1976, 1978) nor EKC, a dysphorogenic analgesic (W.R.

Martin, personal communication), or bremazocine, proposed κ-opiate agonists (Martin et al., 1976; Römer et al., 1980) were generalized to the SKF 10,047 discriminative stimulus. Although the subjective effects of nalorphine and cyclazocine are similar (Haertzen, 1970), psychotomimetic effects occurred in only 20% of patients after nalorphine injection (Keats and Telford, 1964). Unlike SKF 10,047 or cyclazocine, pentazocine did not produce psychotomimetic effects in man but produced predominantly morphine-like effects and, in high doses, nalorphine-like effects (Jasinski et al., 1970). Furthermore, the hallucinogenic effects of LSD in man are qualitatively different from the psychotomimetic effects of PCP (Cohen et al., 1962) or cyclazocine (Haertzen, 1970). Thus, there is a good relationship between the drugs that were generalized to the SKF 10,047 discriminative stimulus and their psychotomimetic efficacy in man. Our data support previous studies demonstrating similarities in the discriminative stimulus properties of SKF 10,047, cyclazocine, PCP and ketamine (Teal and Holtzman, 1980b; Holtzman, 1980; Shannon, 1981; Brady and Balster, 1981).

The discriminative stimulus properties of SKF 10,047 in the rat does not appear to involve the activation of brain dopaminergic mechanisms since neither apomorphine nor d-amphetamine were generalized to the SKF 10,047 discriminative stimulus and haloperidol did not antagonize this effect. Some other effects of SKF 10,047 may, however, involve such an activation (Martin et al., 1976; Iwamoto, 1981).

In conclusion, our findings suggest that the discriminative stimulus property of SKF 10,047 in the rat is not due to an interaction with opiate receptors or activation of dopaminergic mechanisms. In addition, our data further demonstrate similarities between the discriminative stimulus properties of SKF 10,047, cyclazocine, PCP and ketamine and may support the suggestion that the effects of these drugs are exerted via a common receptor (Zukin and Zukin, 1981; Quirion et al., 1981). The lack of generalization by euphoric dysphoric, psychotomotor stimulant drugs or LSD to the SKF 10,047 discriminative stimulus and the close relationship between the potency of those drugs that were generalized to the SKF 10,047 discriminative stimulus and their clinical psychotomimetic potency (Keats and Telford, 1964; Domino et al., 1965; Haertzen, 1970) lead us to suggest that the discriminative stimulus property of SKF 10,047 in the rat may be related to its psychotomimetic effect in man and that rats trained to discriminate SKF 10,047 may be used to evaluate the potential psychotomimetic effects of certain new chemicals.

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