Pharmacology Biochemistry & Behavior, Vol 24, pp 597–604, 1986 © Ankho International Inc Printed in the U S A 0091-3057/86 $3 00 + 00

Morphine Discrimination in the Pigeon Using a Color Tracking Procedure[1]

MERLE G PAULE[2] AND GALEN R. WENGER

Department of Pharmacology and Interdisciplinary Toxicology
University of Arkansas for Medical Sciences, Little Rock, AR 72205

Received 24 September 1984

PAULE, M G AND G R WENGER *Morphine discrimination in the pigeon using a color tracking procedure* PHARMACOL BIOCHEM BEHAV **24**(3) 597–604, 1986 —Pigeons were trained to discriminate 5 0 mg/kg morphine from saline After morphine, subjects tracked the location of red response keys and after saline, the location of green keys When stimulus generalization to other drugs was investigated *dl*-methadone produced morphine-like responding and this response generalization was primarily due to the *l*-isomer Pretreatment with 1 0 mg/kg naloxone shifted the morphine generalization curve 10-fold to the right but only shifted the rate suppression curve 3-fold to the right *dl*-Cyclazocine generated dose-related increases in responding on the red key location and in 3 of 5 birds, responses after 1 0 mg/kg were indistinguishable from those after morphine training doses Meperidine did not produce responding on the red keys, nor did diazepam, cocaine, *d*-amphetamine, phencyclidine or pentobarbital The discriminative stimulus effects of morphine are thus stereoselective and pharmacologically specific Generalization of responding to *dl*-cyclazocine but not to phencyclidine suggests that the morphine-like discriminative *dl*-cyclazocine cue was not due to interaction at sigma opiate receptors

Drug discrimination Opiate discrimination Morphine discrimination Color tracking procedure
Key peck Food reinforcement Pigeons

SINCE the first demonstration that drugs can serve as stimuli that control behavior [7] numerous investigators have studied the discriminative stimulus properties of drugs (e g , [11, 24, 30, 44]) It has even been suggested that drugs be classified according to their discriminable effects [1] Many investigations involving drug discriminations have been particularly concerned with the elucidation of the nature of 'opiate' discriminative stimuli [8, 26, 36, 38] and reviews on the subject have been published [2, 9, 13]

Typically, drug discrimination procedures require that the experimental animal discriminate between a drugged state and a non-drugged state or between two drugged states Such discriminations are evidenced by the occurrence of one behavior in the drugged state and the occurrence of another behavior in the non-drugged state or the other drugged state A frequently used design for these experiments has utilized reinforcement of responses at one position in the presence of a drug and at another position in the absence of the drug [25, 33, 42, 45]

With such procedures, the delivery of a reinforcer at one position can serve as a cue concerning which response position will be reinforced on subsequent trials [21] Such information is independent of the stimulus control engendered by the drug state under study Furthermore, it has been shown that in tests of stimulus generalization (i e , tests to determine if other drugs or other doses of the training drug produce responding similar to that noted after administration of the training drug), certain drugs can induce position responding (i e , responding exclusively to the left or right positions [22]) Such drug-induced position responding might confound interpretation of generalization data in procedures that utilize position responding as a criterion for drug discrimination

To circumvent such problems, a color-tracking procedure has been developed in which the experimental subjects track the location of one color in the drugged state and another color in the non-drugged state [20,21] Subjects make observing responses (responses to a white center key) that randomly vary the location of the colors on the side keys and a second-order schedule [15] is used to generate large amounts of behavior before any cues are provided by the reinforcer

Morphine, which has been shown to function as a discriminative stimulus in squirrel monkeys [29, 36, 38], rats [11, 26, 28, 33], and pigeons [8, 35, 39, 45] served as the training drug The purpose of the present investigation was to begin pharmacological characterization of the morphine discriminative stimulus in pigeons under a color-tracking procedure by determining response generalization to other

[1]This research was supported by NIDA grant DA 02251-06 A preliminary report of some of the work described here was presented earlier at the 1983 FASEB meetings in Chicago [25]

[2]Present address Division of Reproductive and Developmental Toxicology, Pharmacodynamics Branch, HFT-132, National Center for Toxicological Research, Jefferson, AR 72079

[3]Requests for reprints should be addressed to Dr Merle G Paule, Division of Reproductive and Developmental Toxicology, Pharmacodynamics Branch, HFT-132, National Center for Toxicological Research, Jefferson, AR 72079

opioid (meperidine, methadone, cyclazocine, naloxone) and non-opioid (diazepam, cocaine, amphetamine, phencyclidine, pentobarbital) compounds

METHOD

Subjects

Five experimentally naive male White Carneaux pigeons, 7 to 8 years old and weighing 500 to 570 grams at the beginning of these experiments were used The birds were food deprived to and maintained at approximately 80% of these initial weights throughout the experiments Water and oyster shell grit were available ad lib in their home cages

Apparatus

A pigeon test cage (Gerbrands model G-7313) equipped with three response keys arranged horizontally served as the experimental chamber The chamber was enclosed inside a sound and light-attenuating enclosure (Gerbrands model G-7211) For auditory feedback, a small relay mounted on the chamber operated with each effective (0 05 N minimum force) key peck Houselights (two 28 volt-DC bulbs, No 1819) illuminated the experimental chamber during the session except during feed cycles when only the grain hopper was illuminated White noise was supplied continuously to the room housing the behavioral chambers and enclosures

Training Procedure

The training procedure was similar to that described previously for birds trained to discriminate phencyclidine from saline [21] Briefly, pigeons were trained to eat from the lighted grain hopper after pecking the center response key when it was transilluminated with a white light Each peck produced an 8-sec access to grain Once center key responding was established, the reinforcement requirements were changed so that a peck on the center white key extinguished the center key and transilluminated one of the two side response keys with a green light Pecks on the green key produced food Pecks on the darkened center or side key had no programmed consequences The location of the green side keys varied randomly after each response on the lighted center key After several sessions (one session per day, Monday through Friday), pigeons were injected IM 15 minutes prior to the next session with 1 0 mg/kg methadone hydrochloride (1 ml/kg volume) After methadone injections, pecks on the white center key extinguished the center key and randomly transilluminated one of the two side keys with a red light Pecks on the red key produced food After several sessions, IM saline injections (1 ml/kg volume) were made 15 min prior to sessions in which the green side key was randomly presented and reinforced Saline sessions and methadone sessions were mixed such that neither substance was administered for more than 2 consecutive sessions

The reinforcement requirements were increased during these sessions so that after a single observing response (one peck to the center white key-FR1), five responses (FR5) to the lighted side keys were required for food magazine operation Reinforcement contingencies were increased further such that the final schedule required the completion of 15 observing responses, each one followed by 5 responses to the correct lighted side keys prior to reinforcement

During the next sessions, pecks on the center observing key extinguished the center key and transilluminated both side keys, one with a red light and one with a green light

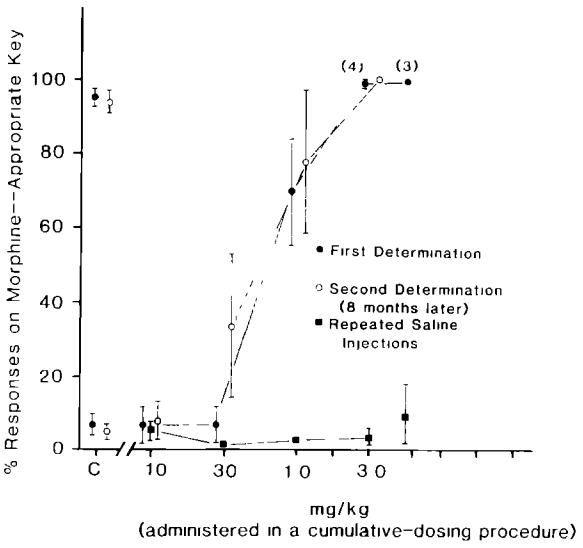

FIG 1 Dose-response curves for morphine and repeated saline administrations Repeated saline injections were made to control for the effects of repeated injections in the cumulative-dosing procedure Abscissa represents actual doses administered per injection (not total dose given) in the cumulative-dosing procedure Data are presented as averages±S E 's calculated for data from 5 birds except where noted (n) Data at C represent values obtained from control days (Wednesdays and Thursdays only) for the weeks during which the dose-response data were collected Upper point represents data obtained after the training dose of 5 0 mg/kg morphine Lower point represents data obtained after saline administrations Dose response data for the first morphine and the repeated saline administration dose-response curves were obtained from single observations in each bird at the beginning of this study The second morphine dose-response curve was determined similarly approximately 8 months later

Positions of the colored side keys again varied randomly after each peck on the center key Pecks on the green key produced food if the pigeon had received saline or no injection prior to the session and pecks on the red key produced food if the pigeon had received methadone hydrochloride prior to the session Completed ratios (FR5's) on the incorrect key reilluminated the center white key to initiate another trial (FR5) The food magazine operated only after the completion of 15 FR5's on the "correct" side key Thus, prior to the first reinforcement of each session, a minimum of 75 responses to one key color had been made Training sessions continued for 60 min or until 15 reinforcements had been presented During the subsequent 6 or more weeks, little or no control over responding was demonstrated by methadone or saline injections (i e , the color 'tracked' was not related to the substance injected) and therefore the 'training' drug was changed to morphine (1 8 mg/kg, IM) Extensive training with this and a higher (2 5 mg/kg) dose of morphine (40 and 4 weeks, respectively) failed to produce acceptable levels of "morphine discrimination" (greater than 75% correct responding prior to the first reinforcement on Wednesday through Friday sessions), therefore, the morphine training dose was increased to 5 0 mg/kg This training dose was used for the remainder of the study as an acceptable level of morphine discrimination was evident within 2 weeks after this dose increase

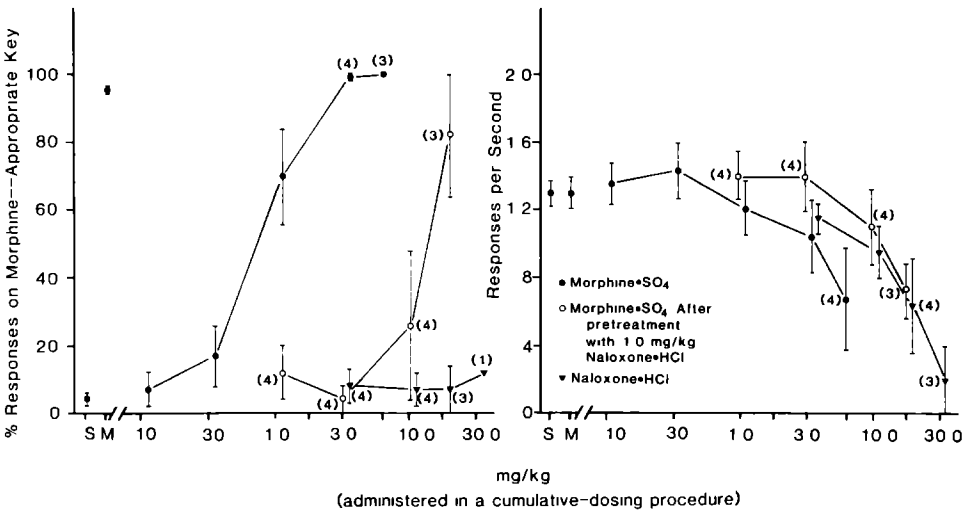

FIG 2 Dose-response curves for morphine alone and for morphine after pretreatment with 1 0 mg/kg naloxone and for naloxone alone Abscissa represents actual doses administered per injection (not total dose given) in the cumulative-dosing procedure Data at S represent values obtained from 5 control days (Wednesdays and Thursdays only) after saline administration for the weeks during which the dose-response data were collected Data at M represent values obtained from 5 control days after the administration of the training dose (5 0 mg/kg) of morphine Dose response data were obtained from single observations in 5 birds except where noted (n) All data presented as means±S E 's Note that the shift to the right (approximately 10-fold) of the morphine dose-response curve for stimulus generalization (left panel) is more than that noted (approximately 3-fold) for morphine response-rate suppression (right panel)

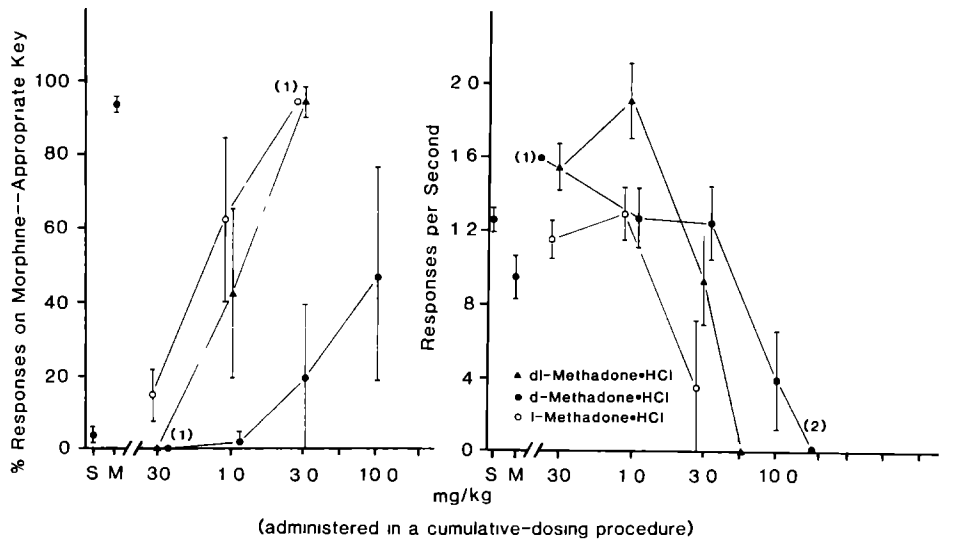

FIG 3 Dose-response curves for racemic methadone, *l*-methadone and *d*-methadone Data presented as in Fig 2 Note that *l*- and *dl*-methadone (3 0 mg/kg) produced responding that was no different from that seen after training doses of morphine whereas much higher doses of *d*-methadone did not (left panel) *l*-Methadone suppressed responding at lower doses than did *d*-methadone and racemic methadone increased response rates at 0 3 and 1 0 mg/kg

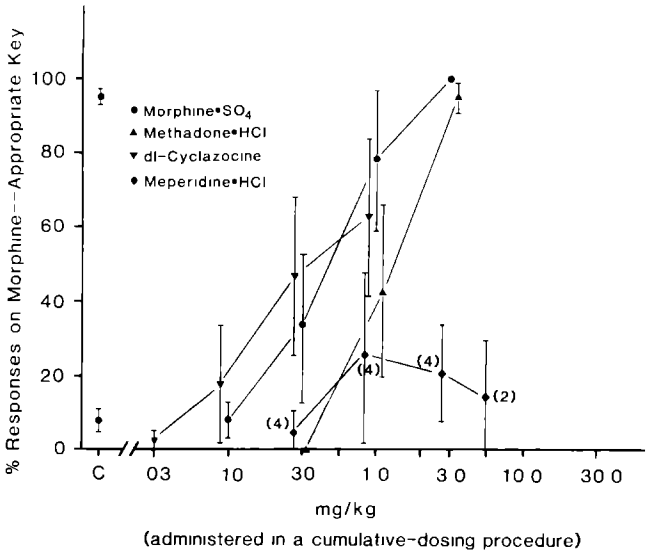

FIG 4 Generalization curves for morphine, *dl*-methadone, *dl*-cyclazocine, and meperidine Data presented as in Fig 1 Note the dose-related increase in the percent of responses made on the morphine-appropriate key after the administration of *dl*-cyclazocine The curves for morphine and methadone are those shown in previous figures

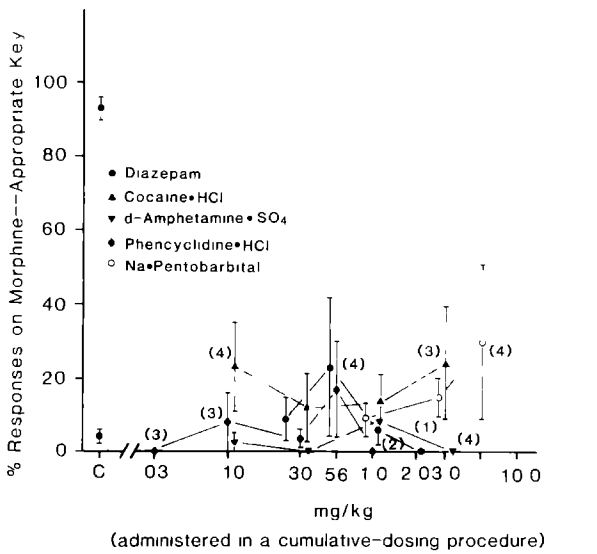

FIG 5 Dose-response curves for *d*-amphetamine, cocaine, diazepam, pentobarbital and phencyclidine Data presented as in Fig 1 Note that none of these compounds at the doses tested produced morphine-appropriate responding

Substitution Testing

Once a stable discrimination had been developed (test animals averaged at least 75% of the FR responses on the correct key color prior to the first food reinforcement on Wednesdays, Thursdays and Fridays for 2 consecutive weeks), other doses of morphine (MSO_4) were administered on Fridays In these experiments, a cumulative ascending series of MSO_4 doses or repeated saline injections were administered to each pigeon for a series of 3 to 6 sessions on the test day [21,40] For example, a 0 10 mg/kg dose of MSO_4 was administered, the bird was placed in the experimental chamber and 15 min later the session began Immediately after the first food presentation (completion of 15 FR5's to either key color), the session ended, the bird was removed and a second dose [0 30 mg/kg (0 40 mg/kg total at this point)] of MSO_4 was given and so on until a dose was reached that eliminated responding for 10 min The test was then concluded and the procedure repeated with another bird Similar substitution procedures were performed with the other drugs used In almost all cases, birds responded as soon as the session started and completed the required responses within three to five minutes Thus, discrimination behavior was recorded 15–20 minutes after each drug or saline administration and the interinjection intervals did not vary from bird to bird

A few weeks after the start of substitution testing, a repeated saline administration resulted in a shift of responding from the saline-appropriate key to the morphine appropriate key, i e , one subject shifted from tracking the green keys to tracking the red keys, apparently, as a function of the number of repeated saline injections or the number of reinforcers delivered Therefore, data collected before this occurrence was discarded and subsequent training of the subjects included some sessions during which repeated saline injections were administered and only responses on the green keys were rewarded Animals were then considered stable and under adequate stimulus control when more than 75% of their responses prior to the first reinforcement were correct for all repeated saline injections for 2 such consecutive tests Occasionally, training doses of morphine were administered to subjects after a variable number of saline injections In all instances, responding was morphine-appropriate after morphine injections

Drugs

Morphine sulfate, cocaine hydrochloride (Mallinckrodt, Inc , St Louis, MO), naloxone hydrochloride (Endo Laboratories, Garden City, NJ), *d*-amphetamine sulfate (Smith, Kline and French, Philadelphia, PA), *dl*-methadone hydrochloride, *d*-methadone hydrochloride, and *l*-methadone hydrochloride (Eli Lilly, Indianapolis, IN), sodium pentobarbital (Sigma Chemical Co , St Louis, MO), meperidine hydrochloride (Wyeth Laboratories, Philadelphia, PA), and phencyclidine hydrochloride (NIDA, Rockville, MD) were dissolved in 0 9% saline *dl*-Cyclazocine (Sterling-Winthrop Research Institute, Rensselaer, NY) was dissolved in 0 9% saline acidified to pH 5 0 with lactic acid Diazepam (Roche Products, Manati, Puerto Rico) was dissolved in a solution of 10% ethanol, 40% propylene glycol and 50% saline All drugs were injected in 1 ml/kg volumes and, except for diazepam and *dl*-cyclazocine, doses given refer to the salts Control injections consisted of equal volumes of diluent appropriate to the drug studied

Data Analysis

Drug discrimination data are presented as averages of the percent of responses occurring on the morphine-appropriate (red) key prior to the first reinforcement of the session or of

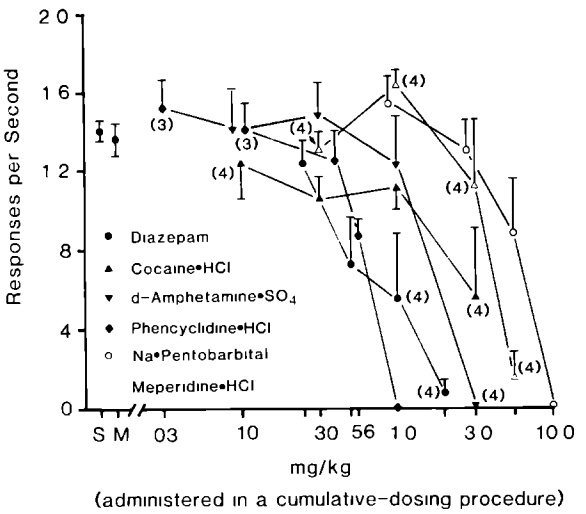

FIG 6 Dose-response curves for rate suppression for compounds not producing morphine-appropriate responding Data presented as in Fig 2 for responses per second

the test trial during cumulative dosing tests Response rates are expressed as averages of the responses per second and refer only to side key (both red and green) responding (i e , observing response latencies and reinforcement time are omitted from this calculation) Response rate data, but not generalization data were used for animals that did not complete 15 (FR5s) Responding after repeated administrations of the cyclazocine diluent (0 9% saline plus lactic acid) was not different from that noted after repeated saline injections and is not shown

RESULTS

Stability of Morphine Dose-Response Curve Over Time

Morphine produced a dose related increase in the percentage of responses made on the morphine appropriate (red) response key (filled circles Fig 1) Using the cumulative dosing procedure, it was determined that at least 3 of 5 birds responded primarily on the morphine-appropriate key after 1 0 mg/kg MSO_4, and that 4 of 4 birds did so after the 3 0 mg/kg dose (only 4 birds responded after this dose) A redetermination of the MSO_4 dose-response curve 8 months later resulted in very similar results (open circles Fig 1) Repeated injections of saline produced responding no different from that noted after single injections of saline

Antagonism of the Discriminative Stimulus Properties of Morphine

After naloxone alone, animals responded primarily on the saline key at doses as high as 30 mg/kg Pretreatment with 1 0 mg/kg naloxone 15 minutes prior to the start of a morphine cumulative-dosing procedure shifted the MSO_4 dose-response generalization curve 10-fold to the right (left panel, Fig 2) Treatment with 1 0 mg/kg naloxone only, as shown by others in our laboratory, does not affect response rate or produce any morphine-appropriate responding (Wessinger and McMillan, personal communication) Naloxone also shifted the morphine dose-effect curve for rate of responding to the right (right panel, Fig 2), but the shift was only about 3-fold

Stereoselectivity of the Morphine-Appropriate Cue

Morphine generalized completely to *dl*-methadone as indicated by its dose-response curve in Fig 3 (left panel) All 5 birds responded on the morphine-appropriate key after 3 0 mg/kg racemic methadone Subsequent determinations of the dose-response curves for *d*- and *l*-methadone indicate that the morphine-like discriminative stimulus properties of racemic methadone are due primarily to the levo-isomer (left panel, Fig 3) The *l*-isomer of methadone is also the more potent of the isomers in suppressing response rates (right panel, Fig 3) Racemic methadone at lower doses (0 3 and 1 0 mg/kg) increased response rates, an effect not seen after administration of either optical isomer alone

Cyclazocine and Meperidine

Three of five birds responded on the key color associated with morphine after administration of 1 0 mg/kg *dl*-cyclazocine (i e , greater than 88% on the red key) One bird responded only on the green keys and the remaining bird responded on both key colors The average dose-response curve is shown in Fig 4 Responding was markedly suppressed at doses higher than 1 0 mg/kg

Meperidine hydrochloride generated morphine-appropriate responding in only one animal at only one dose (1 0 mg/kg) This animal responded on both keys after 3 0 mg/kg The dose-response curve for meperidine is also shown in Fig 4 Naloxone and repeated saline injections resulted in responding on the green keys

d-Amphetamine, Cocaine, Diazepam Pentobarbital and Phencyclidine

Figure 5 shows the dose-response curves obtained after various doses of compounds that did not produce a morphine-like discriminative stimulus One of four birds given 5 6 mg/kg of pentobarbital made 91% of its responses on the red key and the same bird made 78% of its responses on the red key after 0 5 mg/kg diazepam After 0 56 mg/kg phencyclidine, this same bird made 64% of its responses to the red key None of these compounds elicited responding on the red key in other birds

Response Rates for Compounds Not Eliciting Morphine-Appropriate Responding

Figure 6 shows that behaviorally active doses were used in determining whether the morphine discriminative stimulus cue generalized to diazepam, cocaine, d-amphetamine, phencyclidine, pentobarbital or meperidine All compounds suppressed response rates at doses that did not produce morphine-appropriate responding

DISCUSSION

The results of this study show that the discriminative stimulus properties of morphine sulfate in the pigeon under a color-tracking procedure are stereoselective and phar-

macologically specific The stereoselectivity of the morphine interoceptive cue was demonstrated by the differences in potencies between *l*- and *d*-methadone in producing morphine-like responding and by the failure of *d*-methadone to substitute completely for morphine even at doses that markedly decreased response rates The pharmacological specificity of the morphine discrimination was evidenced by the shift of the morphine dose-effect curve in the presence of the narcotic antagonist naloxone, the ability of methadone to produce morphine-appropriate responding, and the inability of *d*-amphetamine, cocaine, diazepam, phencyclidine and pentobarbital to produce morphine-like responding

The morphine discrimination was very stable over time in that the response generalization from the morphine training dose to other morphine doses was essentially unchanged over an eight month period Such stability of drug discriminations has also been noted by others for morphine [5,33], and phencyclidine [20]

Naloxone shifted the morphine generalization curve 10-fold to the right Response rate suppression by morphine was also blocked by pretreatment with naloxone but the shift to the right of the response rate dose-effect curve was only about one-third of that noted for antagonism of the stimulus generalization curve This finding is similar to that described by Herling *et al* [10] and suggests that the discriminative stimulus effects of morphine may be subserved by different substrates than those responsible for the rate suppression by morphine

Naloxone antagonism of morphine discrimination has also been demonstrated in rats [12, 31, 32, 41, 43], squirrel monkeys [29,36] and pigeons [39,45] As morphine has been postulated to have high activity at both mu and kappa opiate receptors while having low or no activity at sigma receptors [19], it is probable that the naloxone antagonism of the effects of morphine occurs at either or both mu and kappa receptors

Morphine generalized completely to racemic methadone, a morphine-like opiate agonist (i e , dose-dependent increases in morphine-appropriate responses were noted after administration of *dl*-methadone) Such observations are consistent with previous reports in the rat [6, 31, 32], pigeon [14] and squirrel monkey [29] The stereoselectivity of the morphine-appropriate discriminative stimulus of methadone in the pigeon was demonstrated by the marked differences in potencies of the *l*- and *d*-isomers of methadone in producing morphine-appropriate responses The levorotatory methadone isomer was approximately ten-fold more potent than the dextrorotatory isomer Such stereoselectivity of the morphine-like discriminative state has been reported for methadone in squirrel monkeys [38] and for other morphine-like agonists in rats [32,43] and squirrel monkeys [29,38], for which the *l*-isomers were also far more potent than the *d*-isomers

Response generalization from morphine to *dl*-cyclazocine was variable between animals Three of the five animals tested did, however, clearly respond in a morphine-appropriate fashion after receiving *dl*-cyclazocine Our results with *dl*-cyclazocine are similar to those obtained by other investigators using rats trained to discriminate 3 0 mg/kg morphine sulfate from saline [32] In their studies, three of five rats responded in a morphine-appropriate fashion after 0 3 mg/kg cyclazocine Higher doses tended to decrease the percent of trials completed on the morphine lever

In contrast, pigeons trained to discriminate 10 0 mg/kg morphine sulfate from saline did not respond in a morphine appropriate manner after receiving cyclazocine at doses up to 3 2 mg/kg [8] These observations contrast with those of the present study but may reflect differences in the morphine training doses and/or the discrimination procedures The training dose has been shown by others to affect results of generalization tests in drug discrimination procedures [3, 16, 37], and in particular, morphine generalization to cyclazocine [34]

Meperidine has been shown to substitute for morphine as a discriminative stimulus in rats [26,32], squirrel monkeys [29] and rhesus monkeys [46] Previous results obtained in the pigeon [8] appeared equivocal in that one of three birds tested made 100%, another bird 86% and another 63% of its responses to the morphine appropriate key after 5 6 mg/kg meperidine hydrochloride These authors concluded from their data that meperidine did not produce stimulus control over behavior that was similar to that produced by the training dose (10 0 mg/kg) of morphine sulfate In the present study, three of four birds tested responded primarily on the saline appropriate key after receiving a range of doses of meperidine The fourth bird clearly responded in a morphine-appropriate fashion after 1 0 mg/kg meperidine hydrochloride, but such responding decreased with higher doses to intermediate responding and finally to saline-appropriate responding These data suggest that meperidine does not produce a morphine-like discriminative stimulus in pigeons trained to discriminate 5 0 mg/kg morphine from saline Additionally, pigeons trained to discriminate meperidine from water do not respond in a meperidine-appropriate fashion after morphine administration and the discriminative stimulus effects of meperidine are not blocked by naloxone [17], thus, it is probably not mediated via mu receptors in pigeons as it appears to be in mammals [26 29, 32, 46] Also, meperidine does not show cross tolerance with methadone in pigeons [18]

As others have noted, pigeons do not appear to distinguish between mu agonists and kappa agonists [9] Morphine may have generalized to cyclazocine in the present study because cyclazocine has partial mu agonist activity It has been shown previously that in animals trained to discriminate low doses of mu agonists, those agonists will generalize to cyclazocine [4,34]

Compounds other than opiates did not produce morphine-appropriate responding in the majority of cases *d*-Amphetamine and cocaine produced responding primarily to the saline-appropriate color One animal exhibited dose-related increases in morphine-like responding after diazepam, phencyclidine and pentobarbital It is interesting to note that, for this particular animal, stimulus control of saline responding was weak (i e , large variabilities in the percent responses made on the saline key on saline training days) whereas stimulus control of morphine responding was strong These observations suggest that the response bias of the bird for the morphine-response key may have influenced its responding when tested with other drugs Such findings parallel those of [23] where dose-response curves for the generalization of the training drug (phencyclidine) to other doses of the training drug and to other drugs were shifted after a response bias was induced by changes in the reinforcement schedule

In summary, the morphine discriminative stimulus in the pigeon, while stereoselective and pharmacologically specific is qualitatively different from that observed in rats, squirrel monkeys and rhesus monkeys Generalization of the morphine discriminative stimulus to *dl*-cyclazocine (kappa and

sigma receptor agonist) but not phencyclidine (sigma receptor agonist) suggests that the morphine-like discriminative *dl*-cyclazocine cue was not due to interaction at sigma opiate receptors

ACKNOWLEDGEMENTS

The authors with to thank William Hardwick for technical assistance, D E McMillan for review of the manuscript and Tina Sykes for preparation of the manuscript

REFERENCES

1 Barry, H , III Classification of drugs according to their discriminable effects in rats *Fed Proc* **33**· 1814–1824, 1974
2 Colpaert, F C Theoretical Review Discriminative stimulus properties of narcotic analgesic drugs *Pharmacol Biochem Behav* **9**: 863–887, 1978
3 Colpaert, F C Pharmacological specificity of opiate drug discrimination In *Drug Discrimination Applications in CNS Pharmacology*, edited by Colpaert and Slangen Amsterdam Elsevier Biomedical Press, 1982, pp 3–16
4 Colpaert, F C , C J E Niemegeers and P A J Janssen On the ability of narcotic antagonists to produce the narcotic cue *J Pharmacol Exp Ther* **197**: 180–187, 1976
5 Colpaert, F C , C J E Niemegeers and P A J Janssen Change of sensitivity to the cueing properties of narcotic drugs as evidenced by generalization and cross-generalization experiments *Psychopharmacology (Berlin)* **58**: 257–262, 1978
6 Gianutsos, G and H Lal Effect of loperamide, haloperidol and methadone in rats trained to discriminate morphine from saline *Psychopharmacologia* **41**. 267–270, 1975
7 Girden, E and E A Culler Conditioned responses in curarized striate muscle in dogs *J Comp Psychol* **23**: 261–274, 1937
8 Herling, S , E H Coale, Jr , R I Valentino, D W Hein and J H Woods Narcotic discrimination in pigeons *J Pharmacol Exp Ther* **214**. 139–146, 1980
9 Herling, S and J H Woods IV Discriminative stimulus effects of narcotics Evidence for multiple receptor-mediated actions *Life Sci* **28**· 1571–1584, 1981
10 Herling, S , R J Valentino, R E Solomon and J H Woods Narcotic discrimination pigeons Antagonism by naltrexone *Eur J Pharmacol* **105**· 137–142, 1984
11 Hill, H E , B E Jones and E C Bell State dependent control of discrimination by morphine and pentobarbital *Psychopharmacologia* **22**. 305–313, 1971
12 Hirschhorn, I E and J A Rosecrans A comparison of the stimulus effects of morphine and lysergic acid diethylamide (LSD) *Pharmacol Biochem Behav* **2**. 361–366, 1974
13 Holtzman, S G Discriminative stimulus properties of opioid agonists and antagonists In *Theory in Psychopharmacology*, vol 2, edited by S J Cooper New York Academic Press, 1983, pp 1–45
14 Jarbe, T U C Discriminative effects of morphine in the pigeon *Pharmacol Biochem Behav* **9**· 411–416, 1978
15 Kelleher, R T Conditioned reinforcement in second order schedules *J Exp Anal Behav* **9** 475–485, 1966
16 Koek, W and J L Slangen The role of fentanyl training dose and of the alternative stimulus condition in drug generalization *Psychopharmacology (Berlin)* **76**: 149–156, 1982
17 Leander, J D Meperidine as a drug cue in pigeons Not a narcotic effect *Fed Proc* **38**· 863, 1979
18 Leander, J D and D E McMillan Meperidine effects on schedule-controlled responding *J Pharmacol Exp Ther* **201**. 434–443, 1977
19 Martin, R W , C G Eades, J A Thompson, R E Huppler and P E Gilbert The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog *J Pharmacol Exp Ther* **197**: 517–532, 1976
20 McMillan, D E Generalization of the discriminative stimulus properties of phencyclidine to other drugs in the pigeon using color tracking under second order schedules *Psychopharmacology (Berlin)* **78**: 131–134, 1982
21 McMillan, D E , D A Cole-Fullenwider, W C Hardwick and G R Wenger Phencyclidine discrimination in the pigeon using color tracking under second-order schedules *J Exp Anal Behav* **37**: 143–147, 1982
22 McMillan, D E and G R Wenger Effects of barbiturates and other sedative hypnotics in pigeons trained to discriminate phencyclidine from saline *J Exp Anal Behav* **40**: 133–142, 1983
23 McMillan, D E and G R Wenger Bias of phencyclidine discrimination by the schedule of reinforcement *J Exp Anal Behav* **42** 51–66, 1984
24 Overton, D A Dissociated learning in drug states (state dependent learning) In *Psychopharmacology, A Review of Progress 1957–1967*, edited by D H Efron Washington, DC U S Government Printing Office, 1968
25 Overton, D A A comparison of the discriminable CNS effects of ketamine, phencyclidine and pentobarbital *Arch Int Pharmacodyn* **215**· 180–189, 1975
26 Overton, D A and S K Batta Investigation of narcotics and antitussives using drug discrimination techniques *J Pharmacol Exp Ther* **211**· 401–408, 1979
27 Paule, M G and G R Wenger Morphine discrimination in the pigeon using the color tracking procedure *Fed Proc* **42**: 770, 1983
28 Rosecrans, J A , M H Goodloe, Jr , G J Bennett and I D Hirschhorn Morphine as a discriminative cue Effects of amine depletors and naloxone *Eur J Pharmacol* **21**: 252–256, 1973
29 Schaefer, G J and S G Holtzman Discriminative effects of morphine in the squirrel monkey *J Pharmacol Exp Ther* **201**: 67–75, 1977
30 Schuster, C R and R L Balster The discriminative stimulus properties of drugs In *Advances in Behavioral Pharmacology*, vol 1, edited by T Thompson and P B Dews New York Academic Press, 1977
31 Shannon, H E and S G Holtzman Blockade of discriminative effects of morphine in the rat by naltrexone and naloxone *Psychopharmacology (Berlin)* **50**· 119–124, 1976
32 Shannon, H E and S G Holtzman Evaluation of the discriminative effects of morphine in the rat *J Pharmacol Exp Ther* **198**· 54–65, 1976
33 Shannon, H E and S G Holtzman Further evaluation of the discriminative effects of morphine in the rat *J Pharmacol Exp Ther* **201**. 55–66, 1977
34 Shannon, H E and S G Holtzman Morphine training dose a determinant of stimulus generalization to narcotic antagonists in the rat *Psychopharmacology (Berlin)* **61**. 239–244, 1979
35 Swedeberg, M D B and T U C Jarbe Morphine cue saliency Limits of discriminability and third state perception of pigeons In *Drug Discrimination Applications in CNS Pharmacology*, edited by F L Colpaert and J L Slangen Amsterdam Elsevier Biomedical Press, 1982, pp 147–164
36 Teal, J J and S G Holtzman Stimulus effects of morphine in the monkey Quantitative analysis of antagonism *Pharmacol Biochem Behav* **12**: 587–593, 1980
37 Teal, J J and S G Holtzman Discriminative stimulus effects of cyclazocine in the rat *J Pharmacol Exp Ther* **212** 368–376, 1980
38 Teal, J J and S G Holtzman Stereoselectivity of the stimulus effects of morphine and cyclazocine in the squirrel monkey *J Pharmacol Exp Ther* **215**· 369–376, 1980

39 Valentino, R J , S Herling, J H Woods, F Medzihradsky and H Merz Quaternary naltrexone Evidence for the central mediation of discriminative stimulus effects of narcotic agonists and antagonists *J Pharmacol Exp Ther* **217** 652–659 1981
40 Wenger, G R Cumulative dose-response curves in behavioral pharmacology *Pharmacol Biochem Behav* **13** 647–651, 1980
41 White J M and S G Holtzman Three-choice drug discrimination in the rat Morphine, cyclazocine and saline *J Pharmacol Exp Ther* **217** 254–262, 1981
42 Winger, G and S Herling Discriminative stimulus effects of pentobarbital in rhesus monkeys Tests of stimulus generalization and duration of action *Psychopharmacology (Berlin)* **76** 172–176, 1982
43 Winter, J C The stimulus properties of morphine and ethanol *Psychopharmacologia* **44** 209–214 1975
44 Winter, J C Drug-induced stimulus control In *Contemporary Research in Behavioral Pharmacology* vol 1 edited by T Thompson and P B Dews New York Academic Press 1977
45 Witkin J M , L A Dykstra and R B Carter Acute tolerance to the discriminative stimulus properties of morphine *Pharmacol Biochem Behav* **17** 223–228 1982
46 Woods, J H , S Herling, R J Valentino, D W Hein and E H Coale Jr Narcotic drug discriminations by rhesus monkeys and pigeons In *Problems of Drug Dependence 1979 Proceedings of the 41st Annual Scientific Meeting The Committee on Problems of Drug Dependence Inc* edited by L S Harris NIDA Research Monograph 27 Washington DC U S Government Printing Office, 1980, pp 128–134