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Bias of Morphine Generalization to Cyclazocine by Drug History[1]

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PAULE, M G AND G R WENGER *Bias of morphine generalization to cyclazocine by drug history* PHARMACOL BIOCHEM BEHAV **24**(3) 479–483, 1986 —Pigeons trained to discriminate morphine from saline under a color tracking procedure received cumulative doses of cyclazocine after various regimens of daily morphine or saline administration Cyclazocine generalization curves were obtained after zero, one, two, or six completely drug-free days In four or five animals, cyclazocine produced more response generalization to morphine after six drug free days than after no drug free days In two animals the cyclazocine dose-effect generalization curves were generally shifted to the left with increased time from last drug exposure Morphine response generalization to cyclazocine was also related to the degree of stimulus control evident in the non-drug (saline) condition during early portions of the subjects' experimental histories The less stimulus control evident in the non-drug (saline) condition (i e , the more morphine-appropriate responses made after saline injections and the greater variability of such responding), the more likely it was to obtain morphine-appropriate responding after cyclazocine administration

Drug discrimination Bias Drug history Color tracking Morphine Cyclazocine Key peck Pigeons

IT has been well documented that drugs can act as discriminative stimuli to control responding and the study of drug discrimination is currently popular among behavioral pharmacologists It has been suggested [1] that drugs be classified according to their discriminable effects and recent reports have emerged that use the discriminative stimulus properties of drugs to define drug classes [11] Most drug discrimination studies have focused primarily on the ability of drugs to control behavior Recently, however, investigators [2,9] have explored the ability of environmental factors to "bias" responding that is under the discriminative control of a drug In these studies, the schedules of reinforcement were altered to produce biases either toward or away from drug-appropriate responding

In rats trained to discriminate the narcotic analgesic fentanyl from saline (using a typical two-lever, food-reinforcement procedure) and biased toward drug-appropriate responding (i e , with the reinforcement schedules arranged to make responding on the drug appropriate key more likely), the dose-response curves for stimulus generalization of fentanyl were shifted to the left of those obtained under non-biased conditions Similarly, in animals biased toward saline-appropriate responding (i e away from drug-appropriate responding), the dose-response curves for fentanyl generalization were shifted to the right of those obtained under non-biased conditions [2]

Pigeons trained to discriminate phencyclidine from saline under a color tracking procedure [8] were similarly biased to respond either toward or away from responding in a drug-appropriate fashion [9] Evidence has been provided [9] that under drug-biased schedules, subjects responded in a drug-appropriate fashion when given drugs that produced saline-appropriate responding under non-biased schedules Likewise, under saline-biased schedules subjects responded in a saline-appropriate fashion when given certain doses of drugs that produced drug-appropriate responding under non-biased schedules

In the present experiment, pigeons responded under a procedure which required them to track the location of a particular key color depending upon whether they had received injections of 5 0 mg/kg morphine (red keys) or saline (green keys) In drug generalization tests in these animals, morphine (a prototypic narcotic agonist) was found to generalize, albeit inconsistently, to various doses of cyclazocine (a narcotic mixed agonist-antagonist) It had been shown previously in rats that the degree of morphine generalization to cyclazocine is dependent upon the training dose of morphine (the lower the training dose, the more generalization to

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cyclazocine [4,6]), and that, in pigeons trained to discriminate 10 0 mg/kg morphine from saline, morphine does not generalize to cyclazocine [5] Thus, the observation that morphine generalized to cyclazocine in our animals trained with 5 0 mg/kg morphine was not surprising The inconsistency of this generalization in our studies, however, was of interest to us and in light of the recent findings concerning response bias, the present experiment was designed to examine some factors thought to be contributing to the variability of our findings In pigeons that had a long history of morphine versus saline discrimination training [10], morphine generalization to cyclazocine was studied after a variety of recent drug histories (0 to 6 completely drug-free days) Additionally, the relationship between stimulus control over responding during the early experimental history of the subjects and later morphine generalization to cyclazocine was examined

METHOD

Subjects

The same 5 male white Carneaux pigeons used in previous experiments [10] were used The birds were maintained at approximately 80% of their free-feeding weights (500 to 570 grams) 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 in a sound and light-attenuating chest (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-d c 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 A TRS-80 Model III (Radio Shack) computer located in an adjacent room controlled the schedule and recorded the data

Procedure

The schedule used in the present experiments is the same as that described previously [10] where details of training can be found In brief, subjects were required to peck the center key once when it was illuminated with a white light (observing response) A response on the center key extinguished the center key light and illuminated the two side keys, one with a red and the other with a green light Five responses on either side key [fixed ratio 5 (FR5)] extinguished both side keys, reset the response requirements back to five, and reilluminated the white center key Grain (8-sec access) was presented only after 15 FR5's had been completed on the correct side key Pecks on the green keys were defined as correct if saline had been administered before the session and pecks on the red keys were correct if morphine had been administered before the session This schedule is referred to as fixed ratio 15 (fixed-ratio 5) or FR15 (FR5) according to the terminology of Kelleher [7] for second-order schedules Position of the green and red colors on the side keys varied randomly after each observing response Pecks on the incorrect key counted down the FR5 requirement but did not

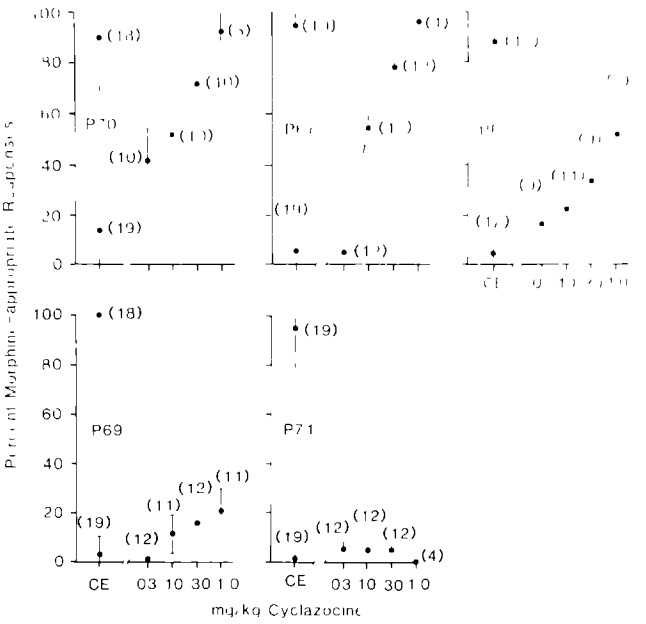

FIG 1 Control data from subjects during their early experimental history where upper points above CE represent data obtained after the administration of the 5 0 mg/kg morphine training doses and lower points above CE represent data obtained after the administration of the saline training doses All points above CE are means (±SD) of (n) observations Cyclazocine dose response curves are means (±SE) representing (n) observations Where deviations were smaller than the size of the data point, error bars were omitted

decrease the number of FR5's necessary for reinforcer (food) delivery Daily sessions (once per day, Monday through Friday) terminated after 15 presentations of grain or after 3600 sec

For the first four days of the week, in a mixed order, subjects were given control injections of saline, saline acidified with lactic acid, or 5 0 mg/kg morphine intramuscularly before the session Data obtained from Monday through Thursday sessions were used to determine baseline control of responding by vehicle or morphine On Fridays, cumulative dose-response curves [12] were obtained for response generalization from the morphine training dose to other doses of morphine and cyclazocine The session was started 15 minutes after subjects had been injected and placed into the chamber The session was interrupted after the first delivery of food, the subject was given a second injection and the procedure was repeated This continued until a dose was reached that drastically supressed responding (no food obtained within 600 sec)

Morphine sulfate (Mallinckrodt, St Louis, MO) was dissolved in 0 9% saline *d-l*-Cyclazocine (Sterling-Winthrop Research Institute, Rensselaer, NY) was dissolved in 0 9% saline and acidified to approximately pH 5 0 with lactic acid All injection volumes were 1 ml/kg and doses for morphine refer to the sulfate salt

Only those discrimination data obtained prior to the first food delivery of a session were used These were plotted as percentages of responses made on the morphine-appropriate (red) key The rates of responding on the side keys were also determined

Two aspects of drug discrimination responding were examined in these experiments First, the effects of recent

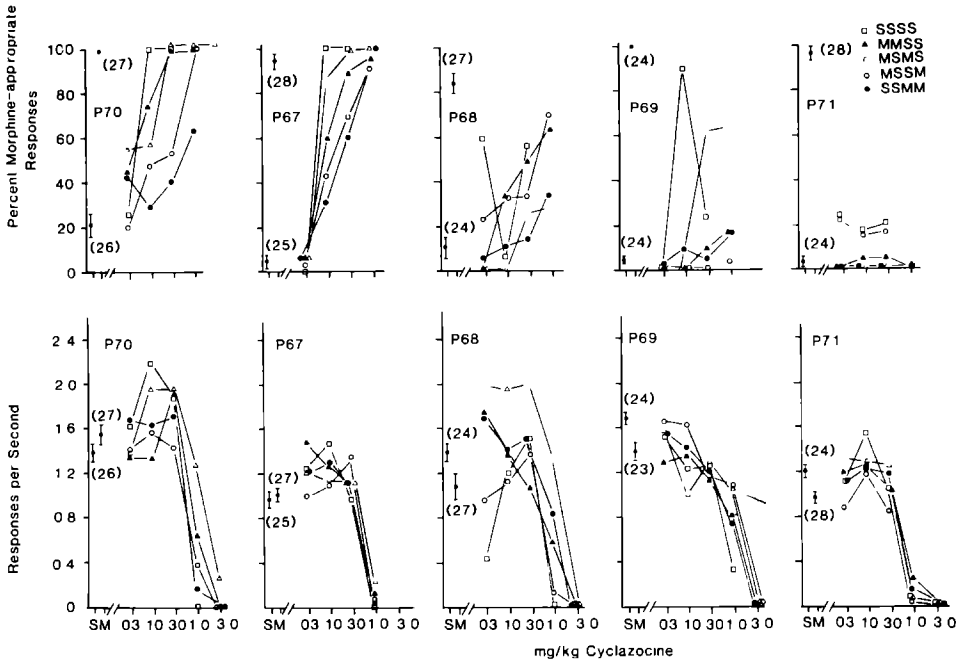

FIG 2 The effects of recent drug history on morphine generalization to cumulative doses of cyclazocine Points above S (saline) and M (morphine) represent averages (±S E) for (n) Monday through Thursday control sessions Upper panels represent percent responses made to the red (morphine-appropriate) keys and lower panels represent side-key response rates after various doses of cyclazocine after various recent drug histories Points represent mean values for an average of 2 determinations Monday through Thursday treatment schedules are indicated by the sequences (S or M) in the upper right panel

drug history on morphine generalization to cyclazocine were studied The order of weekly Monday through Thursday morphine (M) or Saline (S) treatments was arranged to be either S-S-M-M, M-S-S-M, M-S-M-S, M-M-S-S or S-S-S-S Cumulative cyclazocine dose-response curves were then determined for individual animals after each pretreatment schedule Generally, one to two such determinations were made for each subject The purpose of these experiments was to determine whether morphine generalization to cyclazocine could be "biased" by the recent drug history of the subject

The second set of data was analyzed to determine whether the degree of drug stimulus control over responding early in the subject's experimental history could be predictive of later morphine generalization to cyclazocine Here stimulus control over responding (variability of correct responding) in individual subjects was determined by the variability of mean percent morphine-appropriate responding after morphine or saline

RESULTS

Figure 1 shows data (points above CE) from control days for individual subjects during their early experimental history, i e , the first 10 weeks after beginning the establishment of the morphine (5 0 mg/kg) versus saline discrimination [10] In this figure, the cyclazocine generalization dose-response curves have been averaged without regard to recent drug history The data in Fig 1 show that P-69 and P-71 do not generalize morphine to cyclazocine (i e , few, if any, red-key responses were made after any dose of cyclazocine) Conversely, P-70 and P-67 generalize morphine to cyclazocine completely (i e , responses after the higher doses of cyclazocine—0 03 or 1.0 mg/kg—were often indistinguishable from those noted after training doses of morphine) Subject P-68 was intermediate between that of subjects P-69, P-71, and P-67, P-70, and exhibited intermediate (e g , 52 percent) morphine-appropriate responses after 1 mg/kg cyclazocine There appeared to be some correlation of degree of morphine generalization to cyclazocine with variability of saline responding Those animals not generalizing morphine to cyclazocine (P-69 and P-71) very rarely responded on the morphine-appropriate key after saline injections Those animals completely generalizing morphine to cyclazocine (P-70 and P-67) made more responses on the morphine-appropriate key after saline than did animals P-69 and P-71

The effects of recent drug history on morphine generalization to cumulative doses of cyclazocine can be seen in Fig 2 (upper panels) In all five subjects, multiple points from the cyclazocine dose-response curve obtained after six drug free days (S-S-S-S) fell to the left or above the cyclazocine dose-response curve obtained after no drug-free days (S-S-M-M or M-S-S-M) For subjects P-67 and P-70, the cyclazocine dose-effect curves were generally shifted to the left as a function of the number of days since drug (cyclazocine or morphine) was last administered Thus, as the time since last drug administration increased, the likelihood of these two subjects responding in a morphine-appropriate fashion after cumulative doses of cyclazocine increased For the other three subjects, this relationship was not as striking It was, however, evident that considerable morphine-appropriate responding occurred in two (P-68 and P-69) of

these three animals after six drug free days when low doses (0 03 or 0 10 mg/kg) of cyclazocine were administered In contrast, much less morphine-appropriate responding occurred when the same doses were given after no drug free days That such shifts in the generalization curves were not related to changes in response rates can also be seen in Fig 2 (lower panels) where it is seen that recent drug history had no systematic effect on this parameter in any subject

DISCUSSION

These experiments demonstrate that in pigeons trained to discriminate morphine from saline, the recent drug history of some subjects may profoundly influence their generalization from morphine to cyclazocine The longer the time since the training drug (morphine) or the test drug (cyclazocine) was administered, the more likely some subjects were to generalize morphine to the narcotic agonist-antagonist cyclazocine Animals whose behavior was under strong stimulus control in the non-drug condition, e g , after saline injections (evidenced by a low percentage of morphine-appropriate responses and small variability of such responding) were the least likely (biased) to respond in a morphine-appropriate fashion after cumulative doses of cyclazocine

As all subjects received essentially the same training during the development of the morphine versus saline discrimination, it would appear that the tendency to develop a bias towards or away from morphine-appropriate responding after cumulative doses of cyclazocine is inherent in each individual subject The observation that subjects could be further biased towards morphine-appropriate responding after cumulative doses of cyclazocine by increasing the time since their last exposure to drug is similar to those noted previously after manipulation of other independent variables in drug discrimination studies [2, 4, 6, 9] The time-related bias noted in the present study may also explain the individual sensitivity noted by others to vary considerably in rats trained to discriminate 10 mg/kg cocaine from saline [3] These authors interpreted their findings of a shifting "threshold dose" in generalization studies as supportive of the existence of a "phasically operating factor " It is possible that this "phasically operating factor" may be related to the drug history of their subjects

If tolerance is defined simply as the shift of a dose-response curve to the right, then procedures involving manipulations of the schedules of reinforcement can also cause tolerance development It is in this definition of tolerance where problems arise For this discussion, tolerance will refer to a drug-induced shift to the right in a dose-response curve Bias shall refer to a shift (to either the right or left) in a dose-response curve by any manipulations of the experimental situation including drug treatment It is likely that more than one factor can contribute to an observed bias in specific instances

Our observation of biased responding, evident after various recent drug histories, is similar to those of Witkin [13] These authors noted a shift to the right in their morphine generalization dose-response curves after the administration of a large dose of the training drug (morphine) The dose given was 10 times that of the morphine training dose and it was administered 1 day prior to the assessment of tolerance development Those authors showed that this "tolerance" had disappeared five days after drug administration and the schedule of drug administrations during that study did not appear likely to bias their results

In studies of drug discriminations where the schedules of reinforcement were altered to bias drug-appropriate responding [2,9], drug administrations were ordered such that the effects of tolerance development, if any, should not have systematically influenced their findings In the present experiment, both bias and tolerance may have been involved in the alteration of the cyclazocine generalization dose-response curves A drug-administration-schedule bias may have resulted from the long training history (44+ weeks) of our subjects [10] during which the morphine training dose was given on alternate sessions or for two consecutive sessions, but at least every third session A certain level of tolerance to the morphine discriminative stimulus may also have developed as it was generally administered 2 to 3 times weekly It is also possible that residual morphine may have interacted with cyclazocine when morphine was given on the one or two days prior to the determination of cyclazocine dose-response curves However, it is unlikely that tolerance development to the morphine-like discriminative stimulus properties of cyclazocine accounted for much of the results of the present experiment because (1) no tolerance was noted for the response rate suppression of cyclazocine, (2) only training doses of morphine (5 0 mg/kg) were used throughout the experiment, not doses 10 times larger as reported for tolerance development in other pigeons trained to discriminate morphine from saline [13], and (3) the order of morphine training dose presentation served to minimize the influence of tolerance development

Thus, drug history may profoundly influence (bias) a subject's generalization from morphine to cyclazocine It may be that this phenomenon is a general one in drug discrimination studies that may occur for other drug classes, i e , non-opiates, or even other opiates In such cases, it will be important to consider such "bias" when interpreting drug discrimination data

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