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RAPID COMMUNICATION

A Three-Choice Haloperidol-Saline-Cocaine Drug Discrimination Task in Rats

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GAUVIN, D. V., K. L. GOULDEN AND F. A. HOLLOWAY. *A three-choice haloperidol-saline-cocaine drug discrimination task in rats.* PHARMACOL BIOCHEM BEHAV **49**(1) 223–227, 1994.—This study was conducted to test whether rats could be trained and successfully maintain a three-choice drug discrimination task using 0.1 mg/kg haloperidol (SC, 2-h pretreatment), saline (IP or SC, 2 h and 15 min pretreatment), and 10 mg/kg cocaine (IP, 15-min pretreatment) as training stimuli. Six male Sprague–Dawley rats achieved criterion performance for stimulus control by these training stimuli under a fixed-ratio-5 schedule of food reinforced lever-press responding in an average of 164 training sessions. Dose–response functions for cocaine and haloperidol demonstrated both quantitative and qualitative specificity of the training stimuli. The data also are presented along a single pharmacological continuum (agonist-antagonist) that we hypothesize to represent a parallel subjective or interoceptive stimulus continuum associated with the drug injections. Based on the previous multidimensional model of drug stimuli dimensionality (3), this specific stimulus dimension is characterized as an unidimensional bipolar continuum represented by the hypothetical states of hedonia or euphoria on one end (cocaine) and anhedonia or depression on the opponent end (haloperidol), with a neutral (saline) centroid region. We propose that this specific three-choice drug discrimination task in rats may function as an animal analog of the subjective states associated with cocaine abuse and the subsequent withdrawal or, crash, in humans (7,8,21).

Cocaine Haloperidol Haldol® Rats Drug discrimination Cocaine withdrawal

OUR laboratory has proposed a set of experiments designed to examine the subjective effects of cocaine and acute cocaine withdrawal in the rat using a three-choice drug discrimination task with saline, haloperidol, and cocaine as training stimuli. We believed that this specific drug discrimination task would be sensitive to the hypothesized neurochemical substrates attributed to high dose cocaine bouts and the cocaine withdrawal syndrome previously described by Dackis and Gold (7,8). Koob and Bloom (21) have postulated a dynamic opponent process between dopamine increases produced by cocaine administration as the neurochemical process of the cocaine-induced euphoria, and dopamine depletion as the neurochemical mechanism of depression or anhedonia associated with cocaine withdrawal [cf., (7,8)]. This hypothesis was based on previous work demonstrating a simple infraadditive interaction correlated with the neurochemical changes induced by both haloperidol and cocaine administered alone or in combination (4). Similar reciprocal behavioral interactions have been reported between haloperidol and cocaine treatments by Epstein and Altshuler (11). We hypothesized that the three-choice discrimination task would mimic, in theory, the within systems approach described by Koob and Bloom (21) and would involve the complex neurochemical interactions described by Bhattacharyya et al. (4).

The long-term treatment with haloperidol during the training of the proposed three-choice drug discrimination task could, in theory, alter the opposing drug stimulus (cocaine), due to the earlier reports that demonstrated dopaminergic supersensitivity after chronic haloperidol treatments (5,6,17, 23,25,28,31). However, there appears to be no clear agreement

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as to the exact neurochemical nature of the behavioral changes seen after chronic APD treatment. And contrary to the earlier reports of supersensitivity, many recent studies using more sophisticated techniques have shown no significant dopaminergic sensitivity changes due to chronic haloperidol treatment of up to 1 year (1,10,20,26).

The purpose of the present report was to demonstrate empirically that a) rats could be trained in a three-choice saline, haloperidol, cocaine drug discrimination task, and b) that, once trained, rats would not demonstrate a significant supersensitivity to the cocaine stimulus (defined as a significant reduction in the threshold dose of cocaine (ED_{50}) when compared to our previous two-choice cocaine-saline drug discrimination task using a FR10 schedule of reinforcement (13).

METHOD

Prefatory Note

The specific parameters used in this study were based on two previous groups of rats that we attempted to train in a similar three-choice drug discrimination task. The specific drug doses, pretreatment times, scheduling parameters, and schedule of reinforcement were based on the results of those unpublished studies.

Subjects

Six male Sprague–Dawley rats (Sasco, Inc., Omaha, NE) were individually housed between daily experimental sessions in separate suspended wire cages located in an AAALAC-accredited colony room under the direct supervision of the University of Oklahoma Health Sciences Center Department of Animal Resources. Each subject was initially maintained at approximately 85% of its free-feeding weight by restricted access to food, supplemental to that earned in the experimental session; water was continuously available in the home cage. Basal body weights were allowed to increase approximately 10 g per month to allow for normal growth. Environmental factors in the colony room were maintained as follows: lights on from 0530 to 1730 h, temperature 20–22°, and relative humidity 60%.

Apparatus

Experimental sessions were conducted in standard operant chambers (Model 8000, Lafayette Instruments, Lafayette, IN), equipped with three simple rodent levers (SRL-003, BRS-LVE, Beltsville, MD) laterally mounted equidistant from each other across one wall 6 cm from the grid flooring. Three stimulus lamps (Model 80221, Lafayette Instruments, Lafayette, IN) were mounted centrally over each lever 9.2 cm above the grid floor. A pellet dispenser and protruding food pellet cup were mounted on the opposite steel panel wall. Each chamber was housed in a sound-attenuating cubicle (Model 80015, Lafayette Instruments). Continuous white noise and exhaust fans masked extraneous sounds. Experimental contingencies and data collection were controlled by a set of Commodore 64C microcomputer systems (American Neuroscience Research Foundation, Oklahoma City, OK).

Procedure

Three-choice drug discrimination training. The illumination of the house light and three response-lever lights signaled the beginning of the experimental session. The subjects were trained to the food pellet dispenser and to operate any of the three levers by the method of successive approximation. Each response was reinforced (FR1) by delivery of one 45 mg food pellet. Once this initial lever-press response had been demonstrated, drug discrimination training began.

Prior to the commencement of training, a drug/saline (stimulus) presentation schedule was created for each rat such that over a 30-day period each rat would be maintained on a training-stimulus presentation ratio of 1 : 1 : 1 to ensure: a) each of the discriminative stimuli was presented equally often, and b) the training condition varied across animals each day. These procedures were designed to reduce the probability of a response bias and to ensure that the only predictive cue available to the subject (in locating the correct lever) was the drug or saline injection. Each rat received two intraperitoneal injections prior to a training session on alternating sides of the abdomen. On saline (SAL) training days, each rat received an injection of SAL (1 ml/kg) 1 h, and again 15 min prior to the session. On cocaine (COC) training days, each rat received a SAL injection 2 h before and a 10 mg/kg COC injection 15 min before the training session. On haloperidol (HDL) training days, each rat received 0.1 mg/kg HDL 2 h before and a 1 ml/kg SAL injection 15 min before the training session. This specific injection schedule was maintained to ensure that the specific time of handling and subsequent injection could not be used as a functional stimulus to solve the discrimination task. HDL training sessions were always followed by a day off to ensure that no acute or carryover effects of the haloperidol injection were present for the next training session. Administration of one of these latter injections (hereafter referred to as training stimuli) determined the appropriate lever to select and obtain food. Training sessions lasted for 20 min or until 50 reinforcements with food delivery, whichever occurred first. The number of responses required for food delivery was raised across successive sessions until five consecutive responses (FR5) were required. Once the contingencies for reinforcement were raised above the initial FR1 requirement, responses on any stimulus-inappropriate lever reset the ratio requirement on the stimulus-appropriate lever. Training sessions were conducted 5 to 7 days per week, and continued until each rat met the criteria of emitting fewer than 10 responses prior to the first reinforcer delivery and of emitting at least 90% of the total session responses on the stimulus-appropriate lever for 3 consecutive days. Each rat was then required to meet these criteria for six more consecutive sessions in a double alternation sequence (i.e., HDL-HDL-SAL-SAL-COC-COC).

Discrimination testing. When discriminative control was established, dose–response test sessions were conducted. Test sessions were identical to training sessions except that during test sessions, five consecutive responses on any lever produced food. Training and test sessions were alternated throughout the week, ensuring that three separate training stimuli were presented between each test day. A typical week's sequence was: train COC, train HDL, day off, train SAL, test, train HDL, day off, train SAL, train COC, test, etc. If a rat did not meet the criteria for stimulus control during a training session, further testing was postponed until the criteria for HDL-SAL-COC training days were achieved. Drug dose–response functions for both HDL and COC were generated by testing each of a selected dose of the training drug only once per subject in a pseudorandom order.

Drugs

Cocaine hydrochloride was purchased from Sigma Chemical Corporation (St. Louis, MO). Haldol® brand of haloperi-

dol as the lactate with 1.8 mg methylparaben, 0.2 mg propylparaben, and lactic acid for pH adjustment to 3.0–3.6 (5 mg/ml vials, McNeil Pharmaceutical, Spring House, PA) and normal sterile saline were purchased from the pharmacy of the Oklahoma Memorial Hospital (Oklahoma City, OK). All doses of cocaine were dissolved and Haldol were diluted in saline and expressed in mg/kg as the salt. Each drug was prepared daily in a photographic darkroom and stored in a light-impermeable bottle (amber serum bottles, wrapped in aluminum foil and black tape) to prevent oxidation by light.

Data Analysis

The data are presented as the percentage of the total number of responses emitted during the session that were distributed on the designated stimulus injection-appropriate lever. A test drug dose was considered to produce discriminative effects similar to those of the training stimuli if at least 90% of the total session responses were emitted on the specific drug-appropriate lever. This laboratory has adopted the view that intermediate levels of stimulus-appropriate responding (10–90%) represent an accurate behavioral measure of the relative qualitative and quantitative similarities between the test condition and the training stimulus conditions (15,19).

The mean cocaine ED_{50} was calculated by averaging the linear regression analysis (least squares procedure) of the individual dose response functions. The cocaine ED_{50} from the present study was compared to the cocaine ED_{50} of our previous cocaine vs. saline (two-choice) drug discrimination task (12). This comparison was made in an attempt to assess a) the relative contamination of the response choice measure by anchoring (13) the discrimination against a haloperidol stimulus and, b) the alteration of the cocaine cue resulting from the chronic administration of haloperidol over the training course of the study. If supersensitivity to cocaine occurs as a result of chronic weekly injections of haloperidol, we would suspect a significant shift to the left in the cocaine dose-response function (and a resulting lower ED_{50}) when compared to our previous cocaine vs. saline drug discrimination task in which rats were never exposed to HDL.

The rates of responding, expressed in responses per second, were also recorded and were used as another behavioral measure of drug action which appears to be independent of the response choice measure.

RESULTS

The criteria for stimulus control by the three training stimuli was achieved in an average of 164 training sessions (range 160 to 170 sessions) for all six rats. Due to the nature of the training stimuli and the requisite day off after HDL training days, the total training period spanned approximately 7 months.

The rates of responding during the sequence of the six consecutive training sessions scheduled in a double-alternation sequence (i.e., COC-COC-SAL-SAL-HDL-HDL), and used as the training criteria for stimulus control, were extremely stable and were not significantly different from each other (COC−0.63 ± 0.06; HDL−0.58 ± 0.05; SAL−0.60 ± 0.07).

Figure 1 shows the stimulus generalization functions for the percentage of total session responses emitted on the cocaine-appropriate (panel A) and haloperidol-appropriate (panel B) levers plotted as a function of test dose. Additionally, the percentage of total session responses emitted on all three levers during test sessions conducted with the full spectrum of test doses of both training drugs (including saline) is plotted on a hypothetical single continuum (lower panel). Each drug produced a graded increase in the percentage of total session responses emitted on the stimulus-appropriate lever. No responses were emitted on the HDL-appropriate lever during any test session conducted with various doses of cocaine, and vice versa, suggesting each rat was able to maintain pharmacological or quantitative specificity of lower test doses from the training dose. The ability to plot the three stimulus functions along a single continuum with a resulting neutral (default-lever responding) centroid region suggests that each rat was able to maintain qualitative specificity between the three training stimuli.

Most importantly, the ED_{50} for the response choice measure of the discrimination task using the 10 mg/kg cocaine training stimulus in the present study was 3.24 mg/kg (SE = 0.23). The ED_{50} for a similar 10 mg/kg cocaine stimulus, trained in a more typical two-choice cocaine vs. saline discrimination task in this laboratory (using similar procedures), was 3.44 mg/kg (SE = 0.45). These two ED_{50}s were not significantly different (*t*-test, independent groups).

DISCUSSION

The results of this study demonstrate that rats can be trained to maintain a three-choice drug discrimination task using haloperidol, saline, and cocaine. This discrimination did not seem to be based on the response class elements associated with the rates of responding, because these rates were not significantly different across drug stimulus training conditions that engendered significant differences in the response choice measure. We also believe these data support our hypothesis that this particular three-choice drug discrimination task provides a behavioral assay for the measurement of the physical domain of competing pharmacological stimuli. The interoceptive stimuli induced by the drug injections correspond to a hypothesized unitary subjective dimension (3) best categorized as a single continuum bounded on one end by euphoria or hedonia (cocaine) and anhedonia or depression on the opponent end (haloperidol), with a neutral centroid (as depicted in Fig. 1, lower panel). This particular subjective continuum is based on the within systems hypothesis of cocaine euphoria and the resulting dysphoria rebound first proposed by Koob and Bloom [(21), described in the introductory paragraphs] and appears to operate through an opponent process (9,29,30). The dynamic unidimensionality of the proposed subjective attributes of these specific drug stimuli is similar to the affective and pharmacological continuum previously described by Gauvin and Holloway (14) and first proposed by Little, Nutt, and Taylor (22) and Nutt (24) for the affective attributes engendered by the benzodiazepine-β-carboline spectrum. This multidimensional scaling approach (27) was first delineated by Barry and Krimmer (3) to explain the qualitative and quantitative relationships between dimensions of drug stimuli, in general.

We have previously proposed an index that appears to differentiate between opponent and orthogonal dimensions of subjective states (13). Opponent unidimensionality (180°) of subjective states would be characterized by: a) symmetrical blockade of the individual properties of one drug by the concomitant administration of the second drug. This relationship has been previously demonstrated for the psychomotor stimulants and APDs (2,4,5,7,8,11,18,21), b) the ability to induce the opponent process that competes with, or neutralizes, the direct effect of the affective or subjective state induced by the

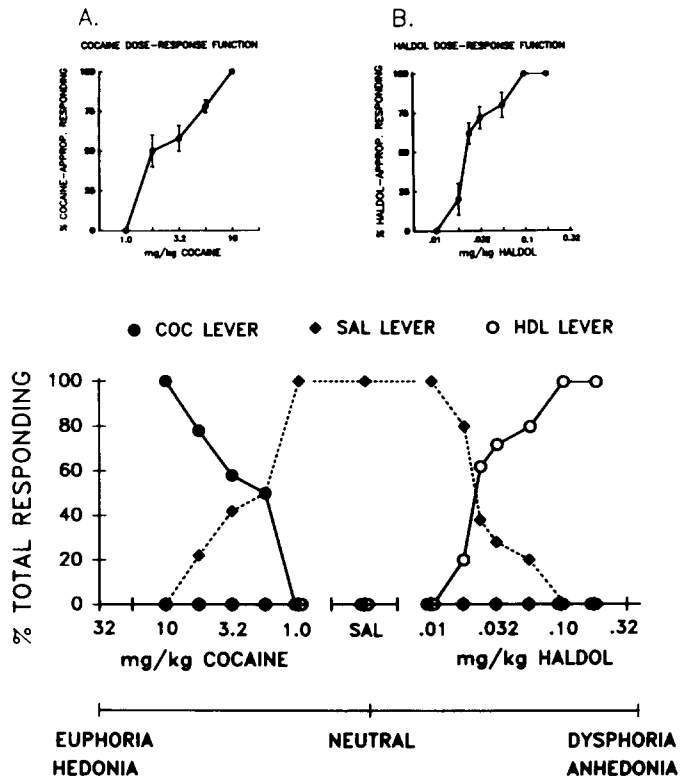

FIG. 1. Upper panels: the percentage of total session response emitted on the cocaine-appropriate lever (panel A) and the haldol-appropriate lever (panel B) during test sessions are plotted against various logarithmic doses of each of the two training drugs. Lower panel: the percentage of total session responses emitted on any of the three stimulus-appropriate levers are plotted against various logarithmic doses of the training drugs plotted on a theoretical single pharmacological continuum (agonist-antagonist) which corresponds to a unidimensional affective metric space best categorized as shown. Each point on all graphs reflects the group average (±SEM, top panels only) percentage of total session responses emitted during a 20-min test session. Each point is the result of a single test in each of six trained animals.

drug stimulus; this adaptation has been demonstrated by acute pretreatments with large doses of both psychomotor stimulants and APDs in a two-choice drug discrimination task (2,18), and c) represents a simple scalar or mathematical summation of drug effects. These reciprocal relationships do not exist between other drug stimulus dimensions such as those that might be produced as a result of training other three-choice drug discrimination tasks (i.e., cocaine-saline-morphine) which would represent a vector (trigonometric) addition of stimulus dimensions sensitive to both intensity and direction. With reference to the Barry and Krimmer (3) model of drug dimensions, these latter relationships between nonopponent dimensions would be represented as vector continua of some degree of orthogonality (i.e., not 180°), such as two dimensions emanating from the neutral centroid by acute or obtuse angles. This type of interaction would produce a combined drug effect that would be dependent upon both quantity and direction of the continua. Operationally, these types of drug interactions would produce drug mixtures that would not produce saline- or default-appropriate responding, but rather some level of responding on each of the two functioning drug levers. This pattern of responding has been reported by Gauvin and Young (16) during drug interaction (mixture) tests between morphine and amphetamine by pigeons trained in a three-choice morphine-saline-amphetamine drug discrimination task.

One of the most important results of the present study was the lack of development of supersensitivity to the cocaine training stimulus over the course of chronic (once weekly) injections of haloperidol. The cocaine ED_{50} for the response choice measure of the present three-choice drug discrimination, in which the cocaine stimulus was anchored (13) against a 0.1 mg/kg haloperidol stimulus, was not significantly different from the cocaine ED_{50} for the same measure in our previous two-choice cocaine-saline drug discrimination task. This apparent lack of contamination of the response choice measure for cocaine by chronic exposure to haloperidol is fully supported by a number of previous reports that have also failed to show supersensitivity to other dopamine agonists after up to 1 year of chronic treatment with dopamine antagonists (APDs) (1,10,20,26). This apparent lack of development of behavioral supersensitivity to the discriminative stimulus

effects of cocaine (as measured by the drug discrimination task) by the concomitant weekly injections of haloperidol in the present study also may suggest that dopamine mechanisms may contribute to, or even initiate, the multidimensional aspects of the subjective or interoceptive stimulus attributes of cocaine, but that these dopaminergic mechanisms are not the only or most critical substrate engendering the discriminative response in the rat. In other words, dopaminergic mechanisms may be a necessary but not a sufficient mechanism for the expression of the multidimensional stimulus attributes of cocaine. It must be remembered that the existing literature supports the view that the drug discriminative response is a reliable behavioral correlate of drug action but this correlation is not equal to 1.0; drug stimulus generalization is a behavioral correlate of stimulus similarity, not identity of effects.

We believe the specific behavioral assay described in this study provides a sensitive measure of the dynamic process between competing or opponent stimuli elicited by this particular pair of competing agonist-antagonist drug stimuli. We also believe that the proposed model may provide a sensitive assay for the assessment of the subjective effects of cocaine and acute cocaine-withdrawal in the rat.

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