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HUMAN d-*AMPHETAMINE DRUG DISCRIMINATION: METHAMPHETAMINE AND HYDROMORPHONE*

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Standard measures of subjective and discriminative effects of drugs were compared in 5 human volunteers. Subjects responded on a second-order color-tracking procedure, where 30 mg of *d*-amphetamine served as a discriminative stimulus for one response and its absence as the discriminative stimulus for another response. Self-reported subjective effects were assessed concurrently using the single-dose questionnaire, subscales of the Addiction Research Center Inventory, and several analogue rating scales. On different days following discrimination acquisition, varying doses of *d*-amphetamine, methamphetamine, and hydromorphone were administered. In these test sessions, either response was reinforced. Methamphetamine and *d*-amphetamine occasioned dose-related increases in *d*-amphetamine appropriate responding; hydromorphone did not. Methamphetamine and *d*-amphetamine occasioned dose-related increases in reports of the drug received being most like "speed"; hydromorphone occasioned dose-related increases in reports of the drug received being most like "dope." All three drugs occasioned dose-related increases in reports of drug liking, and increases in the morphine-benzedrine group, amphetamine, and benzedrine group scales of the Addiction Research Center Inventory. This experiment demonstrated that although explicit discriminative control of behavior by a drug may covary with drug identification, it does not necessarily covary with other self-reported subjective effects. Thus, the complementary nature of the data provided by drug discrimination and standard subjective-effects measures provides quantitative and qualitative data useful in studying both relatively novel compounds and the behavioral biology of psychoactive drugs in general.

Key words: drug discrimination, subjective reports, *d*-amphetamine, methamphetamine, hydromorphone, rating scales, lever pull, humans

This study compares two types of responding following drug administration. In the first type, one response is reinforced following amphetamine administration, and another is reinforced in its absence. The second type is the self-report following prompts (e.g., "Do you like the drug?"). Clearly, drug administration can be an important determinant of either response. Administration of the training drug will occasion drug-lever responding and may also occasion self-reports of drug liking. There are many reasons to feel that these two types of responses (self-reported drug effects and drug-controlled discriminative responding) are related, but there is also reason to suspect that this relationship is more complex than one might at first assume.

Discriminative stimuli may be either public or private. A tone is an example of a public discriminative stimulus (Pierrel, 1958). Private events serving a discriminative function might include expanding a balloon in the gut or an epinephrine injection (Cook, Davidson, Davis, & Kelleher, 1960). In these latter cases, the presence or absence of the discriminative stimulus is uniquely accessible to the individual (Skinner, 1953). Commonly, behavior is multiply determined, being occasioned by the interaction between public and private events and individual history. Subjective responses are characterized by the imperfection that surrounds our ability to define the stimuli and the history necessary for reliably occasioning the response (Beecher, 1959; Skinner, 1957). Examples of subjective responses include reports of pain, anger, joy, and hunger.

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The many studies on pain and analgesia provide an interesting example of the ways in which discriminative stimuli, public and private events, and subjective responses can interrelate and interact with pharmacological agents. Pain can be produced by electric shock, and analgesia can be measured by how the response to the shock changes. For instance, morphine increases the shock level maintained under a procedure in which the shock level increases at a fixed rate in the absence of lever presses but decreases with each lever press (Dykstra & McMillan, 1977; Weiss & Laties, 1964). This result has been considered to be a measure of the subjective response called analgesia. However, morphine has little effect on the discriminative control of responding by shock presentation that signals the availability or unavailability of food (McMillan & Morse, 1967). Thus, morphine affects the discriminative and subjective effects of electric shock differently. The effects of morphine on the control of behavior by electric shock depend on the contingencies operating in the immediate environment. Two other factors also determine the behavioral responses observed after drug administration: the history of the organism and its biologic background.

Preparedness, the preexisting biological attributes of the stimulus–organism interaction, can be a determinant of what response is most likely to occur following a given stimulus (Seligman, 1970). Thus, subjects may be more prepared to make a certain response than another response following particular drugs. This preparedness may partially determine the likelihood that a compound is abused or avoided, and interacts with the current environment and subject history to determine the individual response. Thus, certain drugs (e.g., stimulants) are likely to occasion reports of drug liking in subjects with a wide variety of histories; other drugs (e.g., opioids) are likely to occasion such reports in subjects with a narrower range of histories (Smith, Semke, & Beecher, 1962), and still other drugs (e.g., neuroleptics) may require very specific and unusual histories to occasion such responses. It is important to note that although preparedness helps to determine the ease with which a response may be shaped, once behavior has been shaped, preparedness plays a much smaller role (Burns & Malone, 1992).

Subject history determines the effectiveness of private events as stimuli for various responses, including those responses that describe the private events. Thus, subject history helps determine how drug-produced private events modulate or set the occasion for responses to various prompts (e.g., "Do you like the drug?"). Much in the same fashion, in the drug discrimination paradigm one response is reinforced following drug administration and another is reinforced in its absence. Thus, subject history determines the response likely to follow drug administration. However, it seems unlikely that the same private events control responding in the same manner across all situations.

The present study examined the relationship among various subjective responses, other self-report measures, and responding controlled by amphetamine as an explicitly arranged discriminative stimulus. Amphetamine was chosen as the training drug because a wide variety of species can be trained to discriminate amphetamine (human, Chait, Uhlenhuth, & Johanson, 1986; Heishman & Henningfield, 1991; rat, D'Mello & Stolerman, 1977; gerbil, Järbe & Kroon, 1980; monkey, de la Garza & Johanson, 1987; pigeon, Järbe, 1982; cat, Kilby & Ellinwood, 1979; mouse, Snoddy & Tessel, 1983). Hydromorphone was chosen as a test drug because there is considerable overlap in the subjective responses to opioids and stimulants in those who abuse these drugs (Martin, Sloan, Sapira, & Jasinski, 1971; McCaul, Stitzer, Bigelow, & Liebson, 1983), but experienced drug abusers can readily identify appropriate doses of each drug as belonging to a distinctly different drug class (Martin et al., 1971; McCaul et al., 1983).

METHOD

Subjects

Five subjects participated in this study. Subjects were males older than 21 years of age with histories of opioid and stimulant abuse who had used drugs during the 14 days preceding recruitment. Subjects were not currently physiologically dependent on opioids or other drugs, as determined by self-report and by observation for withdrawal signs for several days while subjects resided on the Addiction Research Center research ward before beginning the study. Subjects were not currently seeking treatment for their drug abuse, nor had

they been in treatment in the last 6 months. Other than their drug abuse, subjects were in good health, as determined by history, physical examination, routine clinical chemistries, and standardized psychological tests and interviews.

Written informed consent was obtained from all subjects, and subjects were free to leave the study at any point. Subjects were informed that they might receive sedatives, minor tranquilizers, diet pills, stimulants, antidepressants, opioids, or major tranquilizers and that placebo might be administered during the study. Subjects were paid for their participation.

Subjects participated in this study while residing on the residential research ward of the Addiction Research Center. This ward consisted of subjects' bedrooms, a nursing station, study and examination rooms, and a central day room that had various recreational facilities (e.g., television, pool table, crafts, etc.) and a small kitchen and dining area. Nursing staff and physicians were present 24 hr per day.

Apparatus

Experimental sessions were conducted in rooms that housed the subject, the operant conditioning panel, a personal computer, and the physiologic monitoring equipment. A nurse sat in an adjacent room. Control and recording equipment for the operant panels was housed separately. The panels (Micro Lab Services) consisted of three Lindsley levers, above which were white Plexiglas panels that could be transilluminated by colored stimulus lights, and another white Plexiglas panel that was centered and could be illuminated. The panels were controlled by a PDP/8® compatible computer running SKED® software. Heart rate, blood pressure, and oral temperature were collected using an IVAC® Vital Check Model 4000AEE. Pupil diameter was measured using a stationary close-up pupilometer (Marquardt, Martin, & Jasinski, 1967). Subjective-effects measures were collected using an IBM® compatible personal computer.

Procedures

General. Subjects were tested each weekday. Physiologic and subjective-effects measures were collected half an hour before drug administration and then 0.5, 1, 2, and 4 hr after drug administration. In some subjects, measures were collected 6 and 8 hr after drug administration as well. Drug discrimination sessions were conducted 3 hr after drug administration. Between data collection periods, subjects were free to participate in normal activities in the day areas of the research ward. Physiologic measures (heart rate, blood pressure, and oral temperature) were collected both for medical safety purposes and to provide physiologic measures of drug exposures.

Subjective effects. The subjective-effects measures collected before each session were a version of the Addiction Research Center Inventory (ARCI). The ARCI scales included the MBG (morphine-benzedrine group) scale, the PCAG (pentobarbital-chlorpromazine-alcohol group) scale, the LSD scale, the BG (benzedrine group) scale, and the AG (amphetamine group) scale (Martin et al., 1971). These measures of subjective effects were collected again after drug administration; in addition, subjects were given the single-dose questionnaire (Fraser, van Horn, Martin, Wolbach, & Isbell, 1961; Martin & Fraser, 1961) and a series of computerized analogue rating scales that could be resolved into 50 points. Subjects used these scales to rate drug liking, good and bad effects, and drug strength. The single-dose questionnaire consisted of four scales. The first asked subjects if they felt the medicine. The second required subjects to categorize the drug received as most like one of the following: blank, dope, cocaine, marijuana, Valium,® downers, alcohol, speed, LSD, Thorazine,® glue, PCP, tobacco, or other. The third asked subjects to rate, on a 5-point Likert scale, how much they liked the drug (0 = not at all; 4 = an awful lot). The fourth asked subjects to indicate which if any of the following symptoms they experienced: normal, skin itchy, relaxed, coasting, nodding, high, sleepy, drunken, nervous, drive, soap box, turning stomach, pleasant sick, and other.

Drug discrimination. Subjects responded under a second-order color-tracking procedure similar to that used by McMillan (Heishman & Henningfield, 1991; McMillan, Cole-Fullenwider, Hardwick, & Wenger, 1982; McMillan & Wenger, 1983). Under this procedure, a session began when the white light above the center lever was lit. Ten responses on the center lever (fixed-ratio [FR] 10) turned off the center light and lit lights above the two side levers, one with a red light and the other with a green light. Thirty responses on either

lever (FR 30) turned off the lights above the side levers, reset the ratio on the side levers to 30, and relit the light above the center lever to reinstate the starting condition. A Sonalert tone signaling the earning of money credited to the subject's account occurred after 30 completions of the FR 30 component had been completed on the correct lever. Completion of 30 side-lever FR 30 components on the wrong lever ended the session without the Sonalert tone. Responding on the lever under the green light was defined as correct following the administration of 30 mg of *d*-amphetamine, and responding on the lever under the red light was defined as correct following placebo or no drug administration. Position of the red and green lights varied randomly after completion of each center-lever FR 10.

Subjects were trained during their initial three sessions. In the first and third of these sessions, subjects were administered the training dose of *d*-amphetamine (30 mg) and were told:

> This is Drug A; when you receive Drug A, you can earn extra money by responding on the green lever; when you do not get Drug A, you should respond on the red lever to earn extra money.

On the second session subjects were not given any drug and were told: "To earn extra money when you do not get Drug A, respond on the red lever."

Drug discrimination sessions were conducted once each weekday. After discrimination training, several sessions were conducted in which acquisition of the discrimination was examined by the blind administration of the training dose of amphetamine and placebo. Following these test-of-acquisition sessions, test sessions were conducted. Typically, three test sessions were conducted each week, and two sessions with either placebo or the training dose of amphetamine administered were also conducted each week. In test sessions, responding on either lever was considered correct, and the completion of 30 FR 30 units on the lever associated with one color was reinforced.

Pharmacological. Drugs were administered orally in gelatin capsules prepared each day by the Addiction Research Center Pharmacy. Drugs were *d*-amphetamine sulfate (3.75, 7.5, 15, 30, and 45 mg), hydromorphone hydrochloride (1, 2, 4, 6, 8, and 12 mg), and methamphetamine hydrochloride (5, 10, 20, and 30 mg). These doses were chosen based upon previous studies using parenteral administration of these drugs to include doses that produce clear subjective effects as well as those that produce minimal effects (Martin et al., 1971; McCaul et al., 1983). Drug doses were calculated on the basis of the salt.

Data Analysis

Data are presented as follows: Drug-lever appropriate responding was calculated as the percentage of responding on the lever associated with the green light by dividing the number of responses on this lever by the sum of responses on this lever and the red lever and multiplying by 100. Subjective-effects measures use the data collected 0.5, 1, 2, and 4 hr following drug administration. ARCI scales are presented as sums of the change scores. Change scores are calculated by subtracting the predrug value from the postdrug value. These change scores are then summed. Liking is presented as a sum of the postdrug Likert measure. Feel-drug, speed or cocaine identifications, and dope identifications are presented as a percentage of the four postdrug opportunities for endorsement. Correlations were conducted using linear regression.

RESULTS

The discrimination was acquired in the three training sessions, with subjects responding on the green lever following 30 mg *d*-amphetamine and on the red lever following no drug or placebo administration. As shown in Table 1, in the maintenance sessions interspersed among the test sessions that followed training, administration of the training dose of amphetamine occasioned predominantly drug-appropriate responding, whereas placebo administration rarely did so.

Examination of the subject self-reports in Table 1 shows that there were a number of dimensions correlated with the discriminative control of responding. Reports of feeling the drug, the drug being either cocaine or speed, liking the drug, and endorsement of items on the MBG, BG, and AG scales of the ARCI were all increased following administration of *d*-amphetamine. Further examination of subject self-reports in Table 2, sorted according to whether the subject completed the response

Table 1

Self-reports and percentage responding on the green lever following administration of either 30-mg amphetamine sulfate (A) or placebo (P).

	% Green[a]		Feel drug		Stimulant		Liking		MBG		BG		AG	
Subject	A	P	A	P	A	P	A	P	A	P	A	P	A	P
1130	66.7	0.0	33.3	0.0	33.3	0.0	0.00	0.00	0.0	−5.0	−4.3	3.0	2.0	3.5
1153	100.0	0.0	66.7	37.5	66.7	12.5	4.00	1.25	40.7	2.0	12.7	−0.8	17.7	0.8
1665	75.0	25.0	25.0	0.0	12.5	0.0	1.25	0.00	0.5	−1.5	3.0	1.3	1.0	0.3
1971	66.7	0.0	50.0	8.3	33.3	0.0	2.00	1.00	9.7	−4.7	5.7	0.3	4.3	−1.0
1952	75.0	5.1	75.0	41.7	62.5	8.3	4.50	1.67	6.3	−0.3	−0.5	−3.0	3.5	−1.3
M	76.7	6	50.0	17.5	41.7	4.2	2.35	0.78	11.4	−1.9	3.3	−1.53	5.7	−1.0

Note. Reports of feeling drug are given as a percentage of the times, when asked, the subject reported feeling the drug. Stimulant identifications are the percentage of the occasions, when asked, that the subject identified the drug administered as being most like speed or cocaine. Liking is reported as the sum of the results from the Likert scale measure. MBG, BG, and AG scales are reported as the sum of the difference between the postdrug measures and the predrug measure.

[a] Percentage of the total responding on the drug-appropriate lever.

Table 2

Self-reports associated with responding on the lever associated with either the green (G) or the red (R) light following administration of either 30-mg amphetamine sulfate or placebo.

	Feel drug		Stimulant		Liking		MBG		BG		AG	
Subject	G	R	G	R	G	R	G	R	G	R	G	R
1130	50.0	12.5	50.0	12.5	0.00	0.00	−1.5	−2.1	−2.5	−4.1	3.50	−1.1
1153	62.5	45.0	62.5	25.0	3.50	2.00	39.0	10.4	13.0	1.8	17.5	4.2
1665	25.0	0.0	12.5	0.0	1.25	0.00	0.8	−1.8	3.8	−2.0	2.8	−1.5
1871	62.5	12.5	50.0	0.0	2.50	1.00	13.5	−3.0	6.0	1.5	6.0	−0.5
1952	75.0	55.0	62.5	30.0	3.50	3.20	−1.0	5.2	−3.0	−1.0	1.0	1.6
M	55.0	25.0	47.5	13.5	2.15	1.24	10.2	1.8	3.5	−0.8	6.2	0.5

Note. Reports of feeling drug are given as a percentage of the times, when asked, the subject reported feeling the drug. Stimulant identifications are the percentage of the occasions, when asked, that the subject identified the drug administered as being most like speed or cocaine. Liking is reported as the sum of the results from the Likert scale measure. MBG, BG, and AG scales are reported as the sum of the difference between the postdrug measures and the predrug measure.

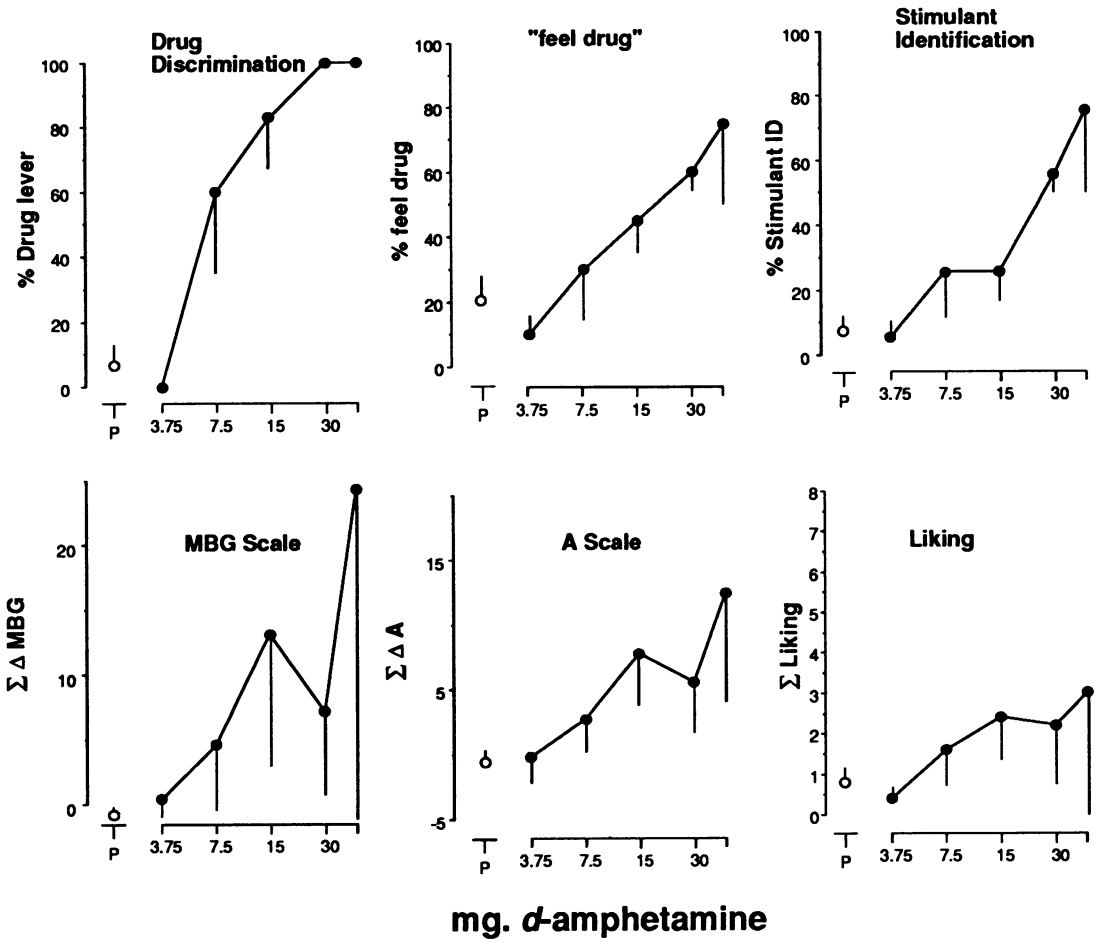

Fig. 1. The effects of different doses of *d*-amphetamine sulfate on various measures are illustrated in this figure. Points represent mean effects across subjects, and bars represent the standard error of the mean. Points above "P" represent the effects of placebo administrations. Drug dose is in milligrams (p.o.) on a logarithmic scale. Measures from top left to bottom right are: Drug discrimination: percentage of the total responding on the drug-appropriate lever. Reports of "feeling drug": percentage of the times, when asked, that the subject reported feeling the drug. Stimulant identifications: percentage of the occasions, when asked, that the subject identified the drug administered as being most like speed or cocaine. MBG scale: sum of the difference between the postdrug measures and the predrug measure. A scale: sum of the difference between the postdrug measures and the predrug measure. Liking: sum of the results from the Likert scale measure.

requirement on the lever associated with the red or green light, shows that similar changes were associated with responding on the lever associated with the green light. In all subjects, reports of feeling the drug and the drug being either cocaine or speed were more likely after amphetamine administration or in association with green-lever responding. Similarly increased reports of drug liking were more likely in the 4 subjects who reported any drug liking. Increased AG scale scores were more likely in all subjects in association with responding on the lever associated with the green light and in 4 of 5 subjects following amphetamine administration. Conversely, increased MBG scale scores were more likely in 4 of 5 subjects in association with responding on the green lever and in all subjects following amphetamine administration. Increased BG scale scores were more likely in 4 of 5 subjects after administration of amphetamine or in association with responding on the lever associated with the green light.

As shown in Figure 1, when different doses of *d*-amphetamine were tested, there was a dose-related increase in drug-appropriate re-

Table 3

Self-reports and percentage of responding on the green lever following administration of various doses of methamphetamine.

Subject	Dose (mg)	% Green[a]	Feel drug	Stimulant	Liking	MBG	BG	AG
1153	10	—[b]	100	100	4	61	19	25
	20	100	75	75	4	47	17	21
	30	100	75	75	5	44	12	18
1665	5	0	25	0	1	−1	−4	−3
	10	100	25	25	1	1	0	−2
	20	0	25	0	1	6	2	3
	30	—	0	0	0	−1	−2	−2
1871	5	—	0	0	0	−3	−1	0
	10	0	0	0	0	−15	−5	−2
	20	100	50	50	3	−4	1	2
	30	—	0	0	0	5	3	0
M	5	0	13	0	1	−2	−3	−2
	10	50	42	42	2	16	5	7
	20	67	50	42	3	16	7	9
	30	100	25	25	2	16	4	5

Note. Reports of feeling drug are given as a percentage of the times, when asked, that the subject reported feeling the drug. Stimulant identifications are the percentage of the occasions, when asked, that the subject identified the drug administered as being most like speed or cocaine. Liking is reported as the sum of the results from the Likert scale measure. MBG, BG, and AG scales are reported as the sum of the difference between the postdrug measures and the predrug measure.

[a] Percentage of total responding on the drug-appropriate lever.

[b] Data missing.

sponding. This dose-related increase was apparent in both the grouped data and the individual-subject data. Similarly, dose-related increases in feeling the drug and the drug administered being most like speed or cocaine were observed (Figure 1). Interestingly, the one point inconsistent with dose-related increases in drug-appropriate responding (Subject 1952 producing only partial amphetamine lever responding at 15 mg) was also associated with no speed or cocaine identifications, but was associated with reports of feeling the drug.

Although administration of different doses of *d*-amphetamine produced less robust effects on the MBG, BG, and AG scales of the ARCI than the measures discussed above, *d*-amphetamine did produce small dose-related increases on all these scales for the grouped data (Figure 1). However, this was not the case for each individual. Ratings of drug liking increased as a direct function *d*-amphetamine dose (Figure 1). This increase was related to dose both in the group data and in the individual-subject data, except for 1 subject (1130) for whom no increase was seen.

In each subject, certain doses of methamphetamine occasioned drug-appropriate responding (Table 3). This responding tended to be associated with increased reports of feeling the drug, the drug being most like speed or cocaine, liking the drug, and increased MBG, BG, and AG scale scores.

With one exception (2 mg hydromorphone in Subject 1871), administration of hydromorphone resulted in responding completely on the red lever (Figure 2). Administration of hydromorphone resulted in increased reports of feeling the drug, identifications of the drug administered being most like dope, drug liking, and increased MBG, BG, and AG scale scores (Figure 2). Administration of hydromorphone was not associated with identifications of the drug administered being most like a stimulant (with one exception: Subject 1871 at 2 mg hydromorphone).

The relationship between increased MBG scale scores and drug liking was explored through regression analysis. Likert scale ratings of drug liking were regressed on MBG scale scores; the analysis explained 10.8% of the variance; when subject was added as a factor, 23.7% of the variance could be explained. Two factors may limit the variance explained by the regression: (a) between-sub-

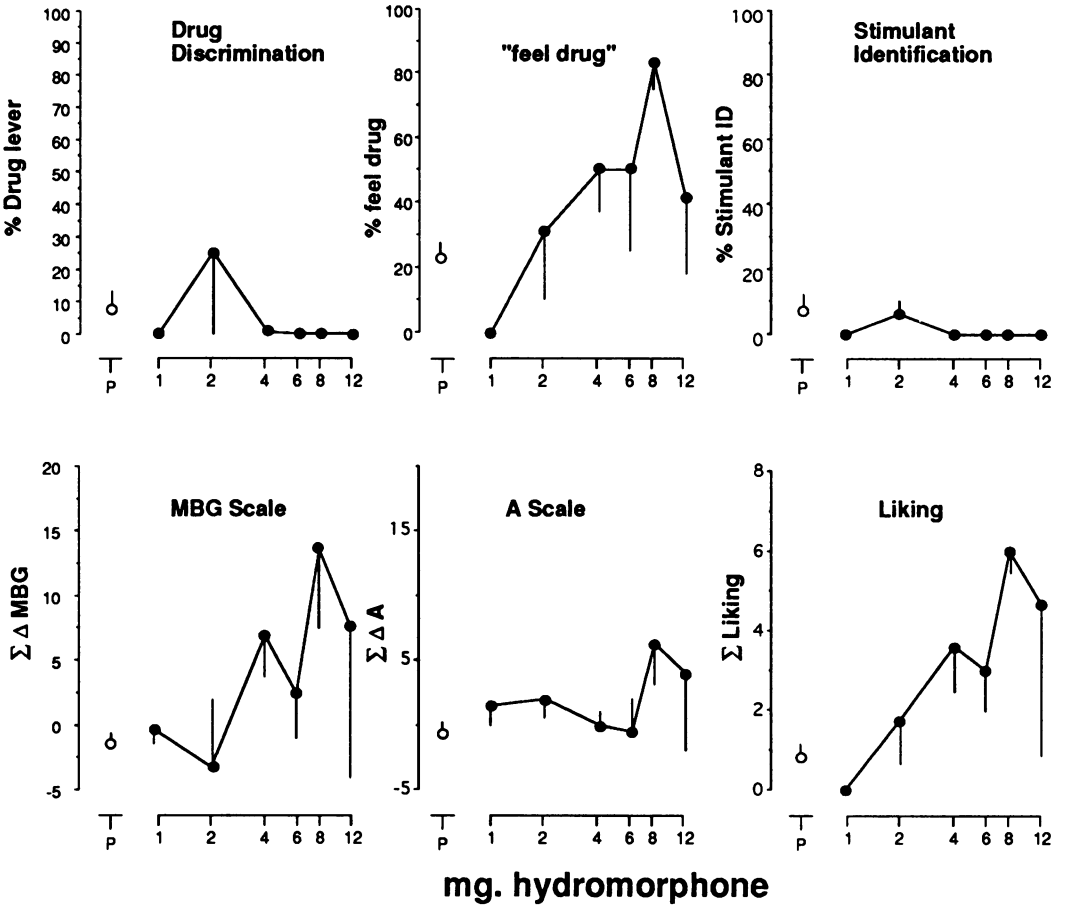

Fig. 2. The effects of different doses of hydromorphone on various measures are illustrated in this figure. Points represent mean effects, and bars represent the standard error of the mean. Points above "P" represent the effects of placebo administrations. Drug dose is in milligrams (p.o.) on a logarithmic scale. Measures are the same as in Figure 1.

jects differences, possibly in differences in baseline MBG scales, and (b) the restricted range of liking rates available from using the Likert scale data. To address these two concerns, analogue ratings of drug liking ranging from 0 to 50 were regressed on change in the MBG scale from baseline. This regression accounted for 27% of the variance; when subject was added as a factor, the regression accounted for 38.6% of the variance. Although this appears to be an impressive level of explained variance, other variables in this experiment are more highly intercorrelated. For example, if the relationship between drug identifications as a stimulant and responding on the green lever is examined, one finds that in the 76 sessions for which these data are available, 40 had red-lever responding and no reports of the drug being a stimulant, 30 had green-lever responding and reports of the drug being a stimulant, 2 had green-lever responding with no reports of the drug being a stimulant, and 4 had red-lever responding with reports of the drug being a stimulant. If these data are subjected to regression analysis, they account for 70.3% of the variance. Thus this type of data is capable of robust explanatory power. When individual-subject data for the relationship of MBG change scores and analogue ratings of drug liking are examined, it becomes clear that there are substantial intersubject differences in these relationships: 1665, 3.0%; 1871, 10.4%; 1130, 21.8%; 1153, 47.0%; and 1952, 68.9%.

DISCUSSION

In this study, subjects with histories of stimulant and opioid abuse responded differen-

tially to the presence or absence of *d*-amphetamine in a two-lever tracking procedure. This replicates previous studies in which similarly trained humans with or without histories of drug abuse (as well as other species) respond differentially to the presence or absence of *d*-amphetamine administration (Chait et al., 1986; de la Garza & Johanson, 1987; D'Mello & Stolerman, 1977; Heishman & Henningfield, 1991; Järbe, 1982; Järbe & Kroon, 1980; Kilby & Ellinwood, 1979; Snoddy & Tessel, 1983). In this study, drug-appropriate responding was dose dependent, with the probability of responding on the drug-appropriate lever increasing as the dose of *d*-amphetamine increased. This dose-dependent generalization is consistent with the results of previous studies (Chait, Uhlenhuth, & Johanson, 1985; Heishman & Henningfield, 1991; Järbe & Kroon, 1980; Schechter & Cook, 1975; Stolerman & D'Mello, 1981). In rats discriminating between the presence or absence of the effects of *d*-amphetamine, methamphetamine at appropriate doses has occasioned drug-appropriate responding (Kuhn, Appel, & Greenberg, 1974), as was the case in this study. Although methamphetamine has not been similarly studied in humans previously, other related psychomotor stimulants, such as phenmetrazine and methylphenidate, can occasion drug-appropriate responding (Chait et al., 1986; Heishman & Henningfield, 1991).

In this study, hydromorphone did not occasion *d*-amphetamine-appropriate responding. In studies of nonhumans, the opioid fentanyl did not occasion *d*-amphetamine-appropriate responding (Colpaert, Kuyps, Niemegeers, & Janssen, 1976), nor did other pharmacologically distinct agents, such as the sedative phenobarbital (Harris & Balster, 1970). In humans, the anxiolytic diazepam did not occasion *d*-amphetamine-appropriate responding (Chait et al., 1985; Heishman & Henningfield, 1991). Conversely, subjects discriminating between a morphine-like opioid and vehicle did not reliably make training drug-appropriate responses following *d*-amphetamine administration (Colpaert, Niemegeers, & Janssen, 1975; Shannon & Holtzman, 1976).

In this experiment, subjects were instructed to make one response in the presence of Drug A and another response in its absence. This instructional set offers advantages over other instructional sets, such as "make this response after Drug A and this response after Drug B," when Drug A is an active drug and Drug B is a placebo. The present instructional set seems more consistent with the discrimination learned by nonhumans (i.e., that they learn to discriminate the presence vs. the absence of a drug's effects; Overton, Merkle, & Hayes, 1983). Further, the present instructional set might reduce possible confusion that could result when the drug administered is neither the training drug nor the placebo. The extent to which different instructions (Drug A vs. not Drug A; Drug A vs. Drug B; or "Your task is to respond on either the right or left lever in order to obtain tokens that can be exchanged for cash") produce similar or distinctly different results in human drug discrimination requires empirical investigation.

Administration of *d*-amphetamine, methamphetamine, and hydromorphone occasioned dose-dependent changes in self-reports. For instance, certain doses of *d*-amphetamine and methamphetamine occasioned reports of the drug received being most like speed, whereas certain doses of hydromorphone led to reports of the drug received being most like dope. Administration of increasing doses of all three drugs was associated with reports of drug liking, endorsement of items on the MBG, BG, and AG scales of the ARCI, reports of feeling the drug, and decreasing reports of the drug being most like a blank. These results are consistent with the results of previous studies in similar populations, when these drugs were given parenterally (Martin et al., 1971; McCaul et al., 1983). Thus, neither the route of administration nor the procedure under which the drugs were administered appears to affect substantially the self-reports collected in this experiment.

The object or event occasioning a self-report can in certain cases be quite clear and accessible (e.g., a red light). In other cases, the object or event occasioning a self-report can still be clear, but at the same time relatively inaccessible (e.g., tachycardia). In still other cases, the object or event occasioning a self-report is neither clear nor accessible (e.g., pleasure or pain). Subjective responses are self-reports of this last kind occasioned by poorly defined private stimuli that are also controlled by the interaction of these stimuli with other stimuli. These other stimuli may be either public or private and are at least partially determined by the individual's peculiar history. Drug discrimination responding and some classes of verbal self-re-

ports have less between-subjects variability than do subjective-effects measures, because as these "objective" responses were shaped the reinforcement contingencies were clearer and likely to be applied more discerningly than can typically be the case with subjective responses; this is especially true of drug discrimination procedures in which much of the shaping of the response occurs in the laboratory. At the same time, the type of information gathered with these "objective" measures is not always relevant to the question of major interest. For instance, many times we are less interested in the question of whether the drug is an opiate than whether the compound relieves pain or is likely to be abused. Consequently, subjective responses have been of great interest in the study of the effects of psychotropic drugs.

In this experiment, responding on the drug-appropriate lever was closely correlated with self-reports of the administration of a stimulant drug. Both of these responses are occasioned by a clearly defined but relatively inaccessible stimulus. Further, the clearly defined stimulus, amphetamine administration, is the same for both responses: responding appropriate to Drug A and identification of the drug as being like speed. Thus, the degree of covariation between the two responses is hardly surprising.

In contrast, responding on the drug-appropriate lever was not well correlated with some other self-report measures. For instance, reports of drug liking were occasioned after both *d*-amphetamine and hydromorphone administration, whereas drug-lever responding was occasioned only following *d*-amphetamine administration. Reports of drug liking are probably complexly controlled by both the private events produced by the drug and the subject's past history (i.e., the subject's assessment of how likely his own behavior is to be maintained by the drug). Thus, unlike reports of the drug administered being most like speed, reports of drug liking are occasioned by a variety of drugs, because, in part, these subjects' behavior has been reinforced by the consumption of a wide variety of drugs in the past.

Similarly, true–false responses to prompts such as "my thoughts come more easily than usual" or "I feel a pleasant emptiness" that make up the various subscales of the ARCI have been complexly and imprecisely shaped and, like most verbal behavior, are multiply determined (Skinner, 1957) and controlled by both public and private events. Their multidetermined nature and dependence upon varied individual history make responses such as endorsement of items on the ARCI unlikely to be controlled in the same one-to-one manner by drug administration as is reporting speed. On the other hand, this complex control is what makes such responses what they are, and in part define their usefulness.

Drug-produced subjective effects are frequently assumed to mediate drug-produced reinforcement. In nonhuman animals, these subjective effects have been presumed to be measured by the discriminative effects of the drug. As was demonstrated in this experiment, the self-report that was most correlated with the differential control of responding was the report of the drug administered being most like speed. Although drug identification in this case is clearly controlled by drug-produced private events, these are not typically assumed to be the ones mediating drug-produced reinforcement. Rather, subjective effects such as drug liking have been assumed to mediate drug-produced reinforcement. However, such an assumption may be as flawed (Lamb et al., 1991) as the assumption that all or most relevant drug-produced subjective effects are measured with a drug discrimination paradigm, or that drug-produced discriminative and reinforcing effects are necessarily causally or directly related. Rather, the reinforcing and discriminative effects and the verbal reports resulting from drug administration are all complexly determined by the interactions between the current environment, past history, and the biology of the organism. Thus, the intercorrelations among these different drug effects are a function of these variables, and should be manipulable. The experimental manipulation of these interrelationships will be an interesting area for future investigation.

In summary, because of the well-controlled and specific history provided to nonhuman animals used in drug discrimination assays, these procedures with nonhuman animals can serve as highly specific and useful pharmacologic assays. This and other experiments (e.g., Chait et al., 1986; Preston, Bigelow, Bickel, & Liebson, 1987) indicate that when similar histories are provided to humans, similarly quantitative and drug-class-specific data are obtained. Thus, these procedures have great cross-species va-

lidity and are useful tools in the experimental analysis of the relationship between the behavioral and biologic effects of drugs. In addition to providing valuable pharmacological assays, the control of human behavior by drug administration provides an interesting approach for studying the relationship between self-reports occasioned by private events, how these reports can be altered by environmental contingencies, and how they relate to other types of ongoing behavior.

REFERENCES

Beecher, H. K. (1959). *Measurement of subjective responses: Quantitative effects of drugs.* New York: Oxford University Press.

Burns, J. D., & Malone, J. C. (1992). The influence of preparedness on autoshaping, schedule performance, and choice. *Journal of the Experimental Analysis of Behavior, 58,* 399–413.

Chait, L. D., Uhlenhuth, E. H., & Johanson, C. E. (1985). The discriminative stimulus and subjective effects of *d*-amphetamine in humans. *Pyschopharmacology, 86,* 307–312.

Chait, L. D., Uhlenhuth, E. H., & Johanson, C. E. (1986). The discriminative stimulus and subjective effects of *d*-amphetamine, phenmetrazine and fenfluramine in humans. *Pyschopharmacology, 89,* 301–306.

Colpaert, F. C., Kuyps, M. D., Niemegeers, C. J. E., & Janssen, P. A. (1976). Discriminative stimulus properties of a low *d,l*-amphetamine dose. *Archives Internationales de Pharmacodynamie et de Thérapie, 223,* 34–42.

Colpaert, F. C., Niemegeers, C. J. E., & Janssen, P. A. (1975). The narcotic cue: Evidence for the specificity of the stimulus properties of narcotic drugs. *Archives Internationales de Pharmacodynamie et de Thérapie, 218,* 268–276.

Cook, L., Davidson, A., Davis, D. J., & Kelleher, R. T. (1960). Epinephrine, norepinephrine, and acetylcholine as conditioned stimuli for avoidance behavior. *Science, 131,* 990–991.

de la Graza, R., & Johanson, C. E. (1987). Discriminative stimulus properties of intragastrically administered *d*-amphetamine and pentobarbital in rhesus monkeys. *Journal of Pharmacology and Experimental Therapeutics, 243,* 955–962.

D'Mello, G. D., & Stolerman, I. P. (1977). Comparisons of the discriminative stimulus properties of cocaine and amphetamine in rats. *British Journal of Pharmacology, 61,* 415–422.

Dykstra, L. A., & McMillan, D. E. (1977). Electric shock titration: Effects of morphine, methadone, pentazocine, nalorphine, naloxone, diazepam and amphetamine. *Journal of Pharmacology and Experimental Therapeutics, 202,* 660–669.

Fraser, H. F., van Horn, G. D., Martin, W. R., Wolbach, A. B., & Isbell, H. (1961). Methods for evaluating addiction liability. (A) "attitude" of opiate addicts toward opiate-like drugs, (B) a short-term "direct" addiction test. *Journal of Pharmacology and Experimental Therapeutics, 133,* 371–387.

Harris, R. T., & Balster, R. L. (1970). An analysis of psychological dependence. In R. T. Harris, W. M. McIssac, & C. R. Schuster (Eds.), *Advances in mental science II: Drug dependence* (pp. 214–226). Austin: University of Texas Press.

Heishman, S. J., & Henningfield, J. E. (1991). Discriminative stimulus effects of *d*-amphetamine, methylphenidate, and diazepam in humans. *Psychopharmacology, 103,* 436–442.

Järbe, T. U. C. (1982). Discriminative stimulus properties of *d*-ampheramine in pigeons. *Pharmacology Biochemistry and Behavior, 17,* 671–675.

Järbe, T. U. C., & Kroon, E. R. (1980). Discriminative properties of *d*-amphetamine in gerbils: Tests for drug generalization and antagonism. *General Pharmacology, 11,* 153–156.

Kilbey, M. M., & Ellinwood, E. H. (1979). Discriminative stimulus properties of psychomotor stimulants in the cat. *Psychopharmacology, 63,* 151–153.

Kuhn, D. M., Appel, J. B., & Greenberg, I. (1974). An analysis of some discriminative properties of *d*-amphetamine. *Psychopharmacologia, 39,* 57–66.

Lamb, R. J., Preston, K. L., Schindler, C. W., Meisch, R. A., Davis, F., Katz, J. L., Henningfield, J. E., & Goldberg, S. R. (1991). The reinforcing and subjective effects of morphine in post-addicts: A dose-response study. *Journal of Pharmacology and Experimental Therapeutics, 259,* 1165–1173.

Marquardt, W. G., Martin, W. R., & Jasinski, D. R. (1967). The use of the Polaroid CU camera in pupillography. *International Journal of Addiction, 2,* 301–304.

Martin, W. R., & Fraser, H. F. (1961). A comparative study of physiological and subjective effects of heroin and morphine administered intravenously in postaddicts. *Journal of Pharmacology and Experimental Therapeutics, 133,* 388–399.

Martin, W. R., Sloan, J. W., Sapira, J. D., & Jasinski, D. R. (1971). Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clinical Pharmacology and Therapeutics, 12,* 245–258.

McCaul, M. E., Stitzer, M. L., Bigelow, G. E., & Liebson, I. A. (1983). Intravenous hydromorphone: Effects in opiate-free and methadone maintenance subjects. In L. Harris (Ed.), *Problems of drug dependence 1982. Proceedings of the 4th annual scientific meeting, the Committee on Problems of Drug Dependence, Inc.* (National Institute on Drug Abuse Research Monograph No. 43, pp. 238–244). Washington, DC: U.S. Government Printing Office.

McMillan, D. E., Cole-Fullenwider, D. A., Hardwick, W. C., & Wenger, G. R. (1982). Phencyclidine discrimination in the pigeon using color tracking under second-order schedules. *Journal of the Experimental Analysis of Behavior, 37,* 143–147.

McMillan, D. E., & Morse, W. H. (1967). Schedules using noxious stimuli. II: Low intensity electric shock as a discriminative stimulus. *Journal of the Experimental Analysis of Behavior, 10,* 109–118.

McMillan, D. E., & Wenger, G. R. (1983). Effects of barbiturates and other sedative hypnotics in pigeons trained to discriminate phencyclidine from saline. *Journal of the Experimental Analysis of Behavior, 40,* 133–142.

Overton, D. A., Merkle, D. A., & Hayes, M. L. (1983). Are "no-drug" cues discriminated during drug-dis-

crimination training. *Animal Learning & Behavior, 11,* 295–301.

Pierrel, R. (1958). A generalization gradient for auditory intensity in the rat. *Journal of the Experimental Analysis of Behavior, 1,* 303–313.

Preston, K. L., Bigelow, G. E., Bickel, W., & Liebson, I. A. (1987). Three-choice drug discrimination in opioid-dependent humans: Hydromorphone, naloxone and saline. *Journal of Pharmacology and Experimental Therapeutics, 243,* 1002–1009.

Schechter, M. D., & Cook, P. G. (1975). Dopaminergic mediation of the interoceptive cue produced by *d*-amphetamine in rats. *Psychopharmacologia (Berlin), 42,* 185–193.

Seligman, M. E. P. (1970). On the generality of the laws of learning. *Psychological Review, 77*(5), 406–418.

Shannon, H. E., & Holtzman, S. G. (1976). Evaluation of the discriminative effects of morphine in the rat. *Journal of Pharmacology and Experimental Therapeutics, 198,* 54–65.

Skinner, B. F. (1953). *Science and human behavior.* New York: The Free Press.

Skinner, B. F. (1957). *Verbal behavior.* Englewood Cliffs, NJ: Prentice-Hall.

Smith, G. M., Semke, C. W., & Beecher, H. K. (1962). Objective evidence of mental effects of heroin, morphine and placebo in normal subjects. *Journal of Pharmacology and Experimental Therapeutics, 136,* 53–58.

Snoddy, A. M., & Tessel, R. E. (1983). Nisoxetine and amphetamine share discriminative stimulus properties in mice. *Pharmacology Biochemistry and Behavior, 19,* 205–210.

Stolerman, I. P., & D'Mello, G. D. (1981). Role of training conditions in discrimination of central nervous stimulants by rats. *Psychopharmacology, 73,* 295–303.

Weiss, B., & Laties, V. G. (1964). Analgesic effects in monkeys of morphine, nalorphine, and a benzomorphan narcotic antagonist. *Journal of Pharmacology and Experimental Therapeutics, 143,* 169–173.