Pharmacology Biochemistry and Behavior, Vol. 64, No. 2, pp. 319–326, 1999

0091-3057/99/$–see front matter

PII S0091-3057(99)00084-2

Effects of Training Dose on the Relationship Between Discriminative-Stimulus and Self-Reported Drug Effects of *d*-Amphetamine in Humans

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KOLLINS, S. H. AND C. R. RUSH. *The effects of training dose on the relationship between discriminative-stimulus and self-reported drug effects of* d-*amphetamine in humans.* PHARMACOL BIOCHEM BEHAV—**64**(2) 319–326, 1999.—The aim of the present experiment was to examine the relationship between the discriminative-stimulus and self-reported effects of drugs in humans. To accomplish this aim, nine healthy adult volunteers (four females, five males) were trained to discriminate between placebo and 10 mg *d*-amphetamine (low-dose group) or 20 mg *d*-amphetamine (high-dose group). After acquiring the placebo-amphetamine discrimination, a range of doses of *d*-amphetamine (1.25–20 mg) was tested to determine if they shared discriminative stimulus effects with the training dose. Participants in the low-dose group exhibited a significant leftward shift in the dose–response function for discrimination performance, which is concordant with previous preclinical and human drug discrimination studies that assessed the effects of training dose. Consistent with the drug discrimination findings, participants in the low-dose group exhibited a significant leftward shift in the dose–response function for several self-reported drug effects (e.g., Like the Drug and Stimulated). However, several other self-reported drug effect items were not significantly influenced by training condition (e.g., Anxious/Nervous and Bad Effects). These results suggest that the discriminative-stimulus and self-reported drug effects of *d*-amphetamine overlap, but are not isomorphic. Furthermore, these results illustrate that behavioral history significantly influences subsequent drug effects in humans. © 1999 Elsevier Science Inc.

d-Amphetamine Stimulants Humans Drug discrimination Subjective effects

THE discriminative-stimulus and self-reported effects (i.e., subjective effects) of drugs in humans are thought to be related (16,20). Drugs that substitute for the training drug in drug-discrimination procedures generally produce a similar constellation of self-reported effects. By contrast, drugs that do not substitute for the training drug generally produce a different constellation of self-reported drug effects. For example, in a previous study conducted in our laboratory, nondrug-abusing adults were trained to discriminate between 20 mg *d*-amphetamine and placebo (18). *d*-Amphetamine (2.5–20 mg) and methylphenidate (5–40 mg) increased drug-appropriate responding as a function of dose. The two highest doses of *d*-amphetamine and methylphenidate occasioned ⩾75% drug-appropriate responding. *d*-Amphetamine and methylphenidate produced a similar pattern of self-reported effects in that both drugs dose dependently increased ratings of Alert-energetic, Vigorous, Elated, Good effects and Like the Drug. Triazolam, a benzodiazepine hypnotic, by contrast, occasioned low levels of *d*-amphetamine–appropriate responding and produced a distinct profile of self-reported drug effects (i.e., increased ratings of Drowsy, Sleepy, and Tired). A similar relationship between the discriminative-stimulus and self-reported effects of drugs has been observed with compounds from other pharmacologic classes including opioids and sedative/hypnotics [e.g., (12,19)].

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Although the discriminative-stimulus and the self-reported effects of drugs overlap, it is important to emphasize that they are not interdependent. There are several instances in which the discriminative-stimulus and self-reported effects of drugs have been shown to dissociate [e.g., (5,18)]. For example, in the previous study conducted in our laboratory that was described above, buproprion (50–400 mg), an antidepressant, occasioned less than 40% *d*-amphetamine-appropriate responding (18). Interestingly, bupropion, like *d*-amphetamine and methylphenidate, dose dependently increased participant ratings of Alert-energetic, Vigorous, Elated, and Good effects. In another study, nondrug-abusing adults were trained to discriminate between 10 mg *d*-amphetamine and placebo (5). High doses of phenylpropanolamine and mazindol, two commonly prescribed anoretics, occasioned ⩾80% *d*-amphetamine responding. *d*-Amphetamine and phenylpropanolamine produced a similar pattern of self reported drug effects. Mazindol, on the other hand, produced relatively few self-reported drug effects. Thus, some drugs produce similar self-reported drug effects, but different discriminative-stimulus effects (18). By contrast, some drugs produce similar discriminative-stimulus effects, but different self-reported drug effects (5).

The aim of the present experiment was to further examine the relationship between the discriminative-stimulus and self-reported effects of drugs in humans. To accomplish this aim, we trained separate groups of participants to discriminate between *d*-amphetamine (10 or 20 mg) and placebo. Training dose has previously been shown to influence subsequent drug-discrimination performance in nonhuman animals trained to discriminate between a stimulant and vehicle (4,6,8,11,13, 21–24). To the best of our knowledge, there are only two published human drug-discrimination studies that have prospectively manipulated training dose, and measured subsequent discrimination performance and self-reported drug effects (14,15). For example, in one study, separate groups of participants were trained to discriminate between placebo and either 10 or 30 μg/kg nicotine. The nicotine drug-discrimination dose–response function was shifted leftward in the low- vs. high-dose group. Similar group differences were observed on participant ratings of Head Rush and Urge to Smoke. In the second study, however, when discrimination performance was maintained at progressively lower training doses of hydromorphone (20–3.5 mg), self-reported drug effects decreased significantly (15). Whether a similar relationship between the discriminative-stimulus and self-reported drug effects would be observed with compounds other than nicotine or opioids is unknown.

METHODS

Participants

Nine healthy (four females, five males), nondrug-abusing, paid volunteers who were recruited through newspaper ads, flyers, and word of mouth, completed this study. Volunteers were paid $10/session to participate in this experiment, and earned performance-based payment as outlined below.

The nine participants ranged in age from 21 to 50 years (mean = 31) and in weight from 53 to 102 kg (mean = 70). Participants reported consuming 0 to 20 alcohol-containing beverages per week (mean = 3.4), 0 to 340 mg caffeine/day (mean = 126), and had completed 12 to 19 years of education (mean = 16). One subject reported smoking six tobacco cigarettes/day. Participants completed questionnaires assessing drug use, medical and psychiatric history, were interviewed by a psychiatrist, and provided written informed consent before participating. Individuals with current or past histories of serious psychiatric disorder (i.e., Axis I of the Diagnostic and Statistical Manual of Mental Disorders), except nicotine dependence, were excluded (2). All participants were in good health and were free from contraindications to stimulant medications. Drug urine analyses conducted during screening were negative for amphetamines, benzodiazepines, barbiturates, cocaine, and opioids. In the female participants, urine pregnancy tests before and periodically during study participation were negative. The experimental protocol and the informed consent document were approved by the Institutional Review Board of the University of Mississippi Medical Center.

Once all screening measures had been completed, participants were randomly assigned to one of two separate training dose conditions. The low-dose group received 10 mg *d*-amphetamine as a training dose, while the high-dose group received 20 mg *d*-amphetamine as a training dose.

General Procedures

Participants enrolled as outpatients at the Laboratory of Human Behavioral Pharmacology at the University of Mississippi Medical Center each morning Monday through Friday for between 16 and 28 experimental sessions (mean = 21). Prior to participation, volunteers were informed that they would receive various drugs that could include placebo, various sedatives, muscle relaxants and anxiolytics, stimulants and weight-loss medications, antidepressants, and antihistamines. Participants were told that the purpose of the study was to see if they could tell the difference between various drugs and to see how these drugs affect mood and behavior. Other than receiving this general information, participants were unaware of the type of drug administered. Participants were given no instructions regarding what they were supposed to do or what outcomes might be expected. On each experimental session day, participants arrived at the laboratory between 0715 and 0900 h and provided a urine sample that was screened on a random, unannounced basis for drug use outside the laboratory. Participants also provided an expired air specimen that was assayed for the presence of alcohol by means of a handheld Alco-Sensor (Intoximeters, Inc., St. Louis, MO). All urine and expired air specimens were negative, and indicated that participants had complied with our requests.

On all experimental-session days, heart rate and blood pressure were recorded, and participants completed the Addiction Research Center Inventory (ARCI) and a Drug-Effect Questionnaire before drug administration. Subjects ingested four capsules then left the laboratory. Participants were provided with five sets of questionnaires (ARCI, Drug-Effect Questionnaire and Drug-Identification Questionnaire) and instructed to complete one set 1, 2, 4, 6, and 8 h after drug administration. Participants reported to the laboratory approximately 24 h after drug administration to turn in their completed forms from the previous day and to complete the drug-discrimination task described below. Experimental sessions were generally conducted on Monday–Thursday. On Friday, participants reported to the laboratory, turned in their completed forms from the previous session, and completed the drug-discrimination task.

Experimental Phases

Medical safety session. Prior to participation in the experimental phases, all participants completed a single medical-

safety session to ensure that they could tolerate the effects of the highest *d*-amphetamine dose to be tested. On this day, participants reported to the laboratory at approximately 0800 h. Before drug administration, heart rate and blood pressure were recorded, and subjects completed a computerized version of the ARCI, a Drug-Effect Questionnaire, and a Circular Lights Task. Participants then ingested four capsules that contained a total of 20 mg *d*-amphetamine (i.e., 5 mg/capsule). Participants remained at laboratory for approximately 6.5 h. The cardiovascular effects of 20 mg *d*-amphetamine were recorded 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 h after drug administration. Participants that exhibited a clinically significant cardiovascular response to 20 mg *d*-amphetamine were excluded from further research participation. No participants were excluded on the basis of this criterion. The ARCI, Drug-Effect Questionnaire and Circular Lights Task were completed 1, 2, 3, 4, 5, and 6 h after administration of 20 mg *d*-amphetamine. Approximately 6 h after drug administration participants completed an End-of-Day Questionnaire.

Sampling phase. All participants completed two sampling sessions to acquaint them with the effects of the training dose of *d*-amphetamine and the daily procedures. During both of these sessions, participants ingested four identical capsules that contained a total of 10 mg (low-dose group) or 20 mg (high-dose group) *d*-amphetamine. *d*-Amphetamine was identified by a unique letter code (e.g., DRUG A) for each participant, but participants were not explicitly informed of the capsules' content. During both sampling sessions, volunteers were instructed to pay close attention to how DRUG A made them feel, because in future sessions, they would not be told whether they received DRUG A and that they could earn extra money by correctly identifying when they had received DRUG A. Participants were further instructed that they could also earn extra money by correctly identifying when they did not receive DRUG A (i.e., NOT DRUG A). Participants also completed a paper-and-pencil version of the ARCI and Drug-Effect Questionnaire during the sampling sessions.

Test-of-acquisition phase. After the sampling phase, a test-of-acquisition phase was conducted to determine if participants could discriminate between the training dose of *d*-amphetamine (i.e., 10 or 20 mg *d*-amphetamine) and placebo. On test-of-acquisition days, participants ingested four capsules under double-blind conditions, but were not told whether the capsules were DRUG A (i.e., *d*-amphetamine) or NOT DRUG A (i.e., placebo). Participants were not explicitly instructed that they would be attempting to acquire a drug–placebo discrimination. Participants were provided with questionnaires and instructed to complete them 1, 2, 4, 6, and 8 h after drug administration and then allowed to leave the laboratory. Participants reported to the laboratory approximately 24 h after drug administration and turned in their completed forms from the previous session, and then completed the drug-discrimination task. After completing the drug-discrimination task, participants opened an envelope that told them whether they had received DRUG A (i.e., *d*-amphetamine) or NOT DRUG A (i.e., placebo) the previous session. Subjects were thus provided feedback regarding the accuracy of their response. The criterion for having acquired the discrimination was ≥80% drug-appropriate responding on four consecutive sessions. Subjects who did not reach this criterion in 12 sessions were excluded from further research participation. Two subjects in the low-dose group and one subject in the high-dose group failed to acquire the discrimination. Data from these subjects were not included in subsequent analyses.

Test-of-novel doses. After the test-of-acquisition phase, participants completed a test-of-novel-doses phase to determine if other doses of *d*-amphetamine shared discriminative-stimulus effects with the training dose. The test-of-novel-doses phase consisted of 6 test days. During this phase, participants were instructed that there would be days on which they would not be given any feedback concerning the accuracy of their drug discrimination performance, and on these days they would be credited with the total amount of money earned on both response options (i.e., the DRUG A option and the NOT DRUG A option). Thus, these test days were identical to test-of-acquisition days except that participants did not receive any feedback concerning their drug discrimination performance and that they received the total amount of money earned on both response options. Participants were not told the purpose of these test days, nor did they know when the test days were scheduled until after they opened the sealed envelope.

To ensure that participants maintained the original *d*-amphetamine–placebo discrimination throughout the test-of-novel-doses phase, test-of-acquisition days were randomly interspersed among the test days. These test-of-acquisition days were identical to those in the test-of-acquisition phase. If a participant responded incorrectly on a test-of-acquisition day, additional test-of-acquisition days were scheduled. These additional test-of-acquisition days continued until the participant correctly identified both training conditions once (i.e., either 10 mg or 20 mg *d*-amphetamine and placebo). If participants were unable to correctly identify both training conditions within six additional sessions, they were excluded from further research participation. No participants were excluded based on this criterion.

On test days during the test-of-novel-doses phase, participants received placebo, 1.25, 2.5, 5, 10, or 20 mg *d*-amphetamine. Each dose was administered one time. Thus, the training conditions (i.e., placebo and *d*-amphetamine) for each group were administered once to each participant under test conditions. The order of drug administration was quasi-random in that an active dose of drug was never administered on more than three consecutive sessions.

Dependent Measures

Drug-discrimination task. In this procedure, the participant distributed 100 points between two options (e.g., DRUG A or NOT DRUG A). Points allocated to the correct option were exchangeable for money at the rate of $0.05 per point. Thus, participants were able to earn a maximum of $5.00 per session on this task. The dependent measure in this procedure was percentage of points allocated to the DRUG A (i.e., percent *d*-amphetamine-appropriate responding).

Subject rated drug effects. Participants completed three paper-and-pencil questionnaires. The first questionnaire was the short form of the ARCI. The ARCI consisted of 49 true–false questions, and contained five major subscales: Morphine-Benzedrine Group (MBG; a measure of euphoria); Pentobarbital, Chlorpromazine, Alcohol Group (PCAG; a measure of sedation); Lysergic Acid Diethylamide (LSD; a measure of dysphoria); and benzedrine group (BG) and Amphetamine (A) scales (empirically derived amphetamine sensitive scales) (9,10). The second questionnaire was a Drug-Effect Questionnaire that consisted of 11 items. Participants rated each item on a five-point scale (0 = "Not at all," 1 = "Quite a bit," 2 = "A little bit," 3 = "Moderately," and 4 = "Extremely"). The items rated were: How much can you FEEL THE DRUG

right now? How much do you LIKE THE EFFECT of the drug right now? How much is the drug STIMULATING you right now? How much does the drug make you feel like TALKING/SOCIALIZING right now? How much is the drug making you feel NERVOUS/ANXIOUS right now? Do you feel any BAD EFFECTS of the drug right now? Do you feel any GOOD EFFECTS of the drug right now? How much is the drug IMPAIRING YOUR PERFORMANCE right now? How much is the drug IMPROVING YOUR PERFORMANCE right now? How much is the drug making you feel TIRED/SLEEPY right now? and How HUNGRY are you right now? The third questionnaire was a two-item Drug-Identification questionnaire. The first item asked participants which drug do you think you received today: DRUG A or NOT DRUG A. The second item on this questionnaire asked participants how confident were they about their selection. Data from the first item of this questionnaire were not analyzed statistically because there were no monetary contingencies involved. Participants completed the ARCI and the Drug-Effect Questionnaire before drug administration, and were instructed to complete the ARCI, Drug-Effect Questionnaire and Drug-Identification Questionnaire 1, 2, 4, 6, and 8 h after drug administration.

Drug Administration

All drug conditions were administered in a double-blind fashion. During each experimental session, participants orally ingested four capsules with approximately 150 ml water. Doses were prepared by encapsulating commercially available *d*-amphetamine in a size 00 capsule. *d*-amphetamine capsules contained 1.25, 2.5, or 5 mg (Dexedrine, SmithKline Beecham Pharmaceuticals, Philadelphia). The remainder of all capsules were filled with lactose. Placebo capsules contained only lactose. Dose was manipulated by administering the appropriate number of drug- and placebo-containing capsules (e.g., 10 mg dose = two 5-mg capsules plus two placebo capsules).

Drug administration procedures were designed to ensure that participants swallowed the capsules and did not open them in their mouths and taste the contents (1). To accomplish this, the research assistant (a) watched the participant to ensure that he or she swallowed the capsules and did not remove them from his or her mouth, (b) conducted a brief oral examination to ensure that the participant was not hiding the capsules under her or his tongue, and (c) spoke with the participant to determine if he or she had anything in his or her mouth.

Data Analysis

Statistical analyses of group data were conducted with analysis of variance (ANOVA) (SuperANOVA, Abacus Concepts, Inc., Berkeley, CA) to examine drug effects on the drug-discrimination task, self-reported drug-effect questionnaires and cardiovascular measures. For all statistical analyses, effects were considered significant for $p \leq 0.05$. For repeated-measure ANOVAs, Greenhouse-Geisser adjusted *p*-values were used.

Drug-effect questionnaire performance and cardiovascular data from the medical safety session were analyzed with a two-factor mixed-model ANOVA. Factors for these analyses were Training Condition and Time (predrug, 1, 2, 3, 4, 5, and 6 h after drug administration for behavioral measures; predrug, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, and 6 h after drug administration for cardiovascular measures). Training condition was a between-subject factor, while time was a within-subject factor. Data from the End-of-Day questionnaire were analyzed with one-factor ANOVA with training condition as the factor.

Drug-discrimination data collected during the test-of-acquisition phase were averaged across all exposures to placebo and 10 or 20 mg *d*-amphetamine on the four sessions that subjects met the discrimination criteria. Drug-discrimination data were then analyzed by two-factor mixed-model ANOVA with training condition (10 or 20 mg *d*-amphetamine) and drug (placebo and 10 or 20 mg *d*-amphetamine) as the factors. Training condition was a between-subject factor, while drug was a within-subject factor. Data from the self-reported drug-effect questionnaires collected during the test-of-acquisition phase were analyzed by three-factor mixed-model ANOVA with training condition (10 or 20 mg *d*-amphetamine), drug (placebo and 10 or 20 mg *d*-amphetamine), and time (predrug, and 1, 2, 4, 6, and 8 h after drug) as the factors. Training condition was a between-subject factor, while drug and time were within-subject factors.

Drug-discrimination data collected during the test-of-novel doses phase were analyzed with a two-factor mixed-model ANOVA with training condition (10 or 20 mg *d*-amphetamine) and dose (placebo, 1.25, 2.5, 5, 10, and 20 mg *d*-amphetamine) as factors. Training condition was a between-subject factor, while dose was a within-subject factor. For the Drug-Effect Questionnaire, Drug-Identification Questionnaire, and ARCI, peak effect (i.e., the maximum subject-rated effect observed after drug administration) was determined for each of the individual subjects and analyzed in a similar fashion.

RESULTS

Behavioral and Physiological Effects During the Medical-Safety Session

Subject ratings of "Feel the Drug" on the Drug-Effect Questionnaire changed as a function of time ($p = 0.01$), but the low- and high-dose groups did not differ significantly in this regard. There were no significant effects on the other items on the Drug-Effect Questionnaire. There were no statistically significant effects on any of the ARCI scales. There were no statistically significant differences between the low- and high-dose groups on any of the items on the End-of-Day Questionnaire. Performance on the circular-lights task improved as a function of time ($p = 0.01$), but the low- and high-dose groups did not differ in this regard. Heart rate, systolic pressure, and diastolic pressure changed as a function of time (*p*-values < 0.003), but the low- and high-dose groups did not differ significantly on these measures.

Discrimination and Self-Reported Drug Effects During the Test-of-Acquisition Phase

Drug-discrimination performance. The four subjects in the low-dose group met the discrimination criterion in 8, 4, 5, and 4 (mean = 5.3) sessions. During the four sessions in which these subjects met the criterion, mean percent drug-appropriate responding was 80, 100, 100, and 100 (mean = 95) for the individual participants when 10 mg *d*-amphetamine was administered, and 10, 10, 10, and 0 (mean = 8) when placebo was administered. The five subjects in the high-dose group met the discrimination criterion in 4, 4, 6, 6, and 4 (mean = 4.8) sessions. During the four sessions in which these subjects met the criterion, mean percent drug-appropriate responding was 100, 90, 100, 100, and 100 (mean = 98) for the individual

participants when 20 mg *d*-amphetamine was administered, and 0, 0, 0, 0 and 0 (mean = 0) when placebo was administered.

During the four sessions in which the subjects met the criterion, placebo occasioned significantly more drug-appropriate responding in the low- vs. the high-dose group ($p = 0.01$). There were no other statistically significant differences between the groups.

ARCI, drug-effect questionnaire, and drug-identification questionnaire. There were no statistically significant effects on any of the ARCI scales during the test-of-acquisition phase. Significant effects were observed on two items from the Drug-Effect Questionnaire during the test-of-acquisition phase: subject ratings of "Feel the Drug" and "Feel like Talking or Socializing." Figure 1 shows time–action functions for the training dose of *d*-amphetamine and placebo in the low- and high-dose groups. Relative to placebo, *d*-amphetamine increased ratings of "Feel the Drug" as an orderly function of time in both the low- and high-dose groups. However, drug effects were larger in magnitude, peaked later, and abated more slowly in the high-dose vs. the low-dose group (i.e., interaction of dose, time, and training condition, $p < 0.02$). Relative to placebo, *d*-amphetamine also increased ratings of "Feel Like Talking or Socializing" as an orderly function of time in both groups (i.e., interaction of dose and time, $p < 0.03$). However, the magnitude of the drug effect and the time-action function of *d*-amphetamine did not differ significantly across the groups (i.e., main effect of training condition, $p > 0.42$; interaction of dose, time, and training condition, $p > 0.34$).

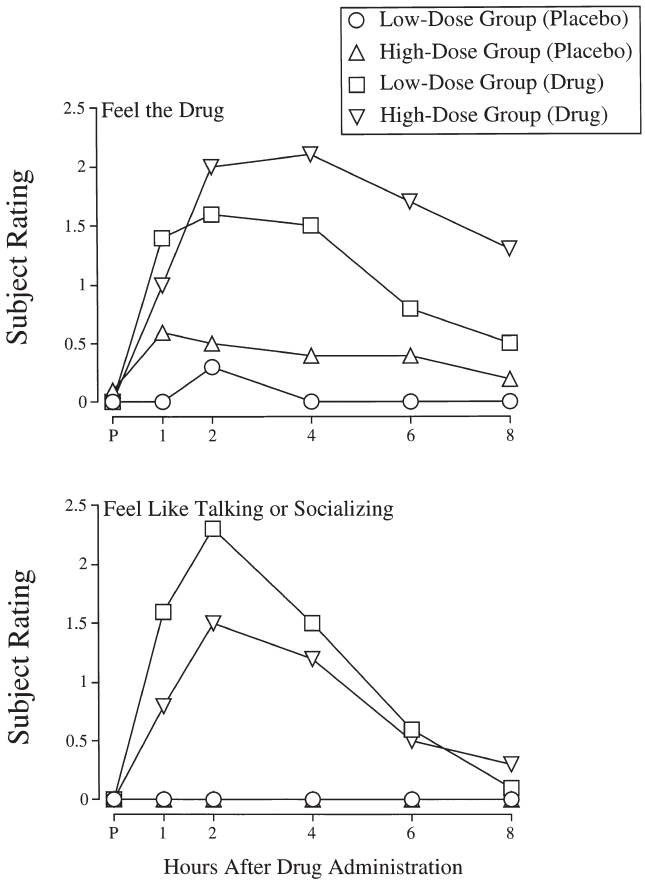

FIG. 1. Time course functions for *d*-amphetamine (10 and 20 mg) and placebo for the two items from the Drug-Effect Questionnaire that were significantly affected during the test-of-acquisition phase: subject ratings of "Feel the Drug" and "Feel Like Talking or Socializing." X-axes: time after drug administration in hours; P indicates predrug. Data points show means of four subjects for the low-dose group and five subjects for the high-dose group averaged across the four sessions during which the subjects met the discrimination criteria. Error bars are omitted for clarity.

Subject ratings of confidence on the Drug-Identification Questionnaire were not affected to a statistically significant degree by the administration of *d*-amphetamine.

Discrimination and Subject-Rated Effects During the Test-of-Novel Doses Phase

Drug discrimination performance. Accurate discrimination performance was maintained on the test-of-acquisition sessions that were interspersed among the test sessions in the test-of-novel doses phase. During these sessions, on average placebo occasioned 25 percent (range = 17–33) drug-appropriate responding on in the low-dose group (Fig. 2, circles above ND) and 0% drug-appropriate responding in the high-dose group (Fig. 2, squares above ND). *d*-Amphetamine (10 mg) on average occasioned 86% (range = 67–100) drug-appropriate responding in the low-dose group (Fig. 2, circles above D). *d*-Amphetamine (20 mg) on average occasioned 95% (range = 75–100) drug-appropriate responding in the high-dose group (Fig. 2, squares above D). During these test-of-acquisition sessions, placebo occasioned significantly more drug-appropriate responding in the low-dose group vs. the high-dose group. By contrast, the training dose of *d*-amphetamine occasioned significantly less drug-appropriate responding in the low-dose group vs. the high-dose group (i.e., interaction of training condition and dose, $p < 0.002$).

Figure 2 also shows that *d*-amphetamine increased drug-appropriate responding as an orderly function of dose in both the low- and high-dose groups (i.e., main effect of dose, $p < 0.001$). However, the *d*-amphetamine dose–response function was shifted significantly leftward in the low- vs. high-dose group (i.e., main effect of training condition, $p < 0.02$). The interaction of training condition and dose did not attain statistical significance. *d*-Amphetamine (0, 1.25, 2.5, 5, 10 and 20 mg) on average occasioned 12.5, 0, 45, 50, 100, and 100% drug-appropriate responding, respectively, in the low-dose group. *d*-Amphetamine (0, 1.25, 2.5, 5, 10, and 20 mg) on average occasioned 0, 0, 0, 0, 70, and 100% drug-appropriate responding, respectively, in the high-dose group.

ARCI, drug-effect questionnaire and drug-identification questionnaire. Three subscales from the ARCI were significantly affected by dose: A, BG and MBG (p-values < 0.04). Scores on these scales generally increased as a function of *d*-amphetamine dose in both the low- and high-dose groups. There were no statistically significant differences between the groups (i.e., main effect of training condition, p-values > 0.15; interaction of training condition and dose, p-values > 0.09) on these scales.

Eight items from the Drug-Effect Questionnaire were significantly affected by dose: Anxious/Nervous, Bad Effects, Feel the Drug, Good Effects, Improved Performance, Like the Drug, Stimulated, and Feel Like Talking or Socializing (p-values < 0.03). *d*-Amphetamine generally increased these ratings as an orderly function of dose in both groups. The *d*-amphetamine dose–response function was shifted significantly leftward in the low-dose group vs. the high-dose group

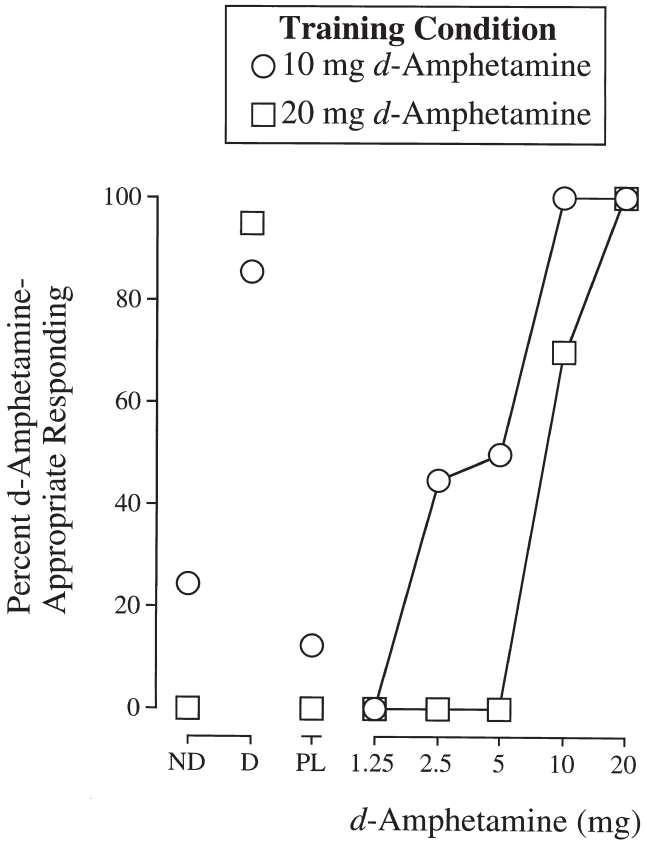

FIG. 2. Dose effects for *d*-amphetamine for percentage drug-appropriate responding on the point distribution procedure for the low-dose (circles) and the high-dose group. X-axes: dose in mg. Data points above "ND" indicate placebo values from the additional test-of-acquisition sessions that were interspersed among "test." Data points above "D" indicate *d*-amphetamine (10 or 20 mg) values from the additional test-of-acquisition sessions that were interspersed among "test." Data points above "PL" designate values from the placebo "test" session. Y-axes: percent drug-appropriate responding. Data points show means of four subjects for the low-dose group and five subjects for the high-dose group. Error bars are omitted for clarity.

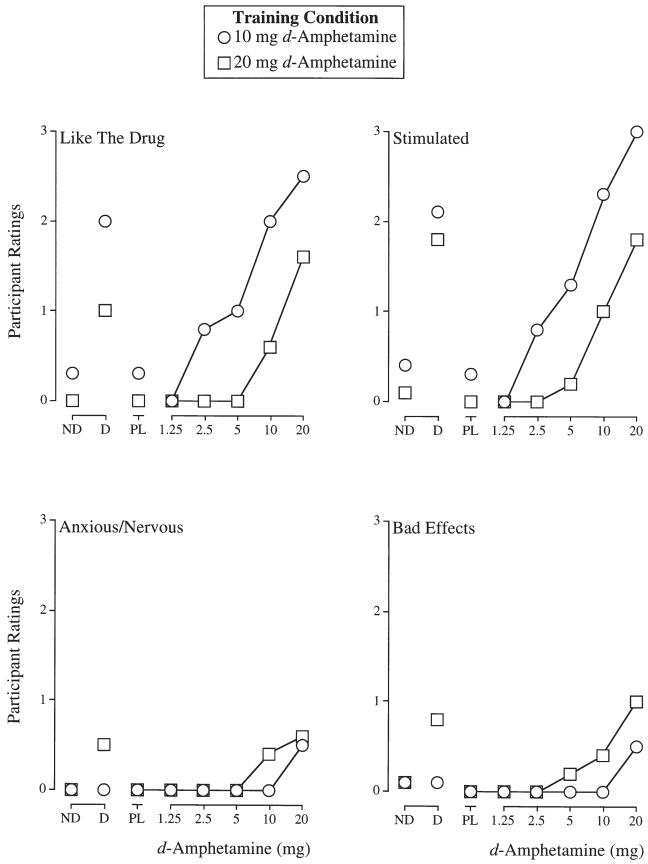

FIG. 3. Peak dose effects for *d*-amphetamine for subject ratings of Like the Drug, Stimulated, Anxious/Nervous, and Bad Effects from the Drug-Effect Questionnaire from the test-of-novel-doses phase. Other details are the same as in Fig. 2.

on four of these items: Improved Performance, Like the Drug, Stimulated, and Feel Like Talking or Socializing (main effect of training condition, p-values < 0.05). By contrast, training condition did not significantly influence subject ratings of Anxious/Nervous, Bad Effects, Feel the Drug, and Good Effects (i.e., effect of training condition, p-values > 0.10; interaction of training condition and dose, p-values > 0.45). Figure 3 shows *d*-amphetamine dose–response functions for four of these items: Like the Drug, Stimulated, Anxious/Nervous and Bad Effects. There were no significant effects on subject ratings of confidence on the Drug-Identification Questionnaire.

DISCUSSION

In the present experiment, separate groups of participants were trained to discriminate between placebo and a low (10 mg) or high dose (20 mg) of *d*-amphetamine. For those participants trained to discriminate between placebo and 10 mg *d*-amphetamine, testing a range of doses of *d*-amphetamine 1.25–20 mg) resulted in a significant leftward shift of the drug-discrimination dose–response function relative to those participants trained to discriminate between placebo and 20 mg *d*-amphetamine. These findings are concordant with other human drug-discrimination studies that assessed the effects of training dose on subsequent drug-discrimination performance (14,15,17). For example, as noted above, in one previous study separate groups of participants were trained to discriminate between placebo and 10 or 30 μg/kg nicotine (14). The nicotine drug-discrimination dose–response function was shifted leftward in the low- vs. high-dose group.

The findings of the present study are also concordant with preclinical drug-discrimination studies that examined the influence of training dose (4,6,8,11,21–24). In these studies, when a range of doses of the training drug are tested, the dose–response function is shifted leftward as animals are trained to discriminate lower drug doses. Interestingly, preclinical studies suggest that manipulating training dose also alters the substitution profile of other compounds [e.g., (3,7,24)]. For example, norepinephrine uptake blockers like tomoxetine and nisoxetine dose dependently increased cocaine-appropriate responding, and the highest dose of each compound produced $> 80\%$ cocaine-appropriate responding, in rats trained to discriminate between vehicle and 3 mg/kg cocaine (24). By contrast, norepinephrine uptake blockers do not occasion significant levels of drug-appropriate responding in rats trained to discriminate between vehicle and 10 mg/kg cocaine (3,7). Future human–drug discrimination studies

should determine if manipulating training dose alters the substitution profile of other drugs.

A significant leftward shift in the dose–response function was also observed with several subject-related drug-effect items in the low-dose vs. the high-dose group. The demonstration of a covariation between the discriminative-stimulus and self-reported effects of drugs after the explicit reinforcement of discrimination performance, but not self-reported drug effects, suggests a functional relationship between the discriminative-stimulus and self-reported effects of drugs. The present findings are concordant with the results of two previously published reports that examined self-reported drug effects after experimentally manipulating discrimination performance (14,17). In the first study, as noted above, separate groups of participants were trained to discriminate between placebo and 10 or 30 μg/kg nicotine (14). The nicotine drug-discrimination dose–response function was shifted leftward in the low- vs. high-dose group. Similar shifts were observed on participant ratings of Head Rush and Urge to Smoke. In the second study, participants were trained to discriminate between placebo and progressively lower doses of diazepam or buspirone (17). The drug-discrimination dose–response functions for diazepam and buspirone were shifted leftward in a low-dose generalization vs. a low-dose training phase. A similar leftward shift was observed for subject ratings of Drug Strength. The results of the present experiment extend previous findings of a possible functional relationship between the discriminative-stimulus and self-reported drug effects of drugs to another compound, *d*-amphetamine.

Although the results of present experiment suggest a possible functional relationship between the discriminative-stimulus and self-reported drug effects of drugs, it is important to note that a significant shift of the dose–response function between the low- vs. high-dose group was observed on only half of the subject-rated items. Despite significant differences between the two groups in terms of discrimination performance, participant ratings of Anxious/Nervous, Bad Effects, Feel the Drug, and Good Effects did not differ significantly as a function of training condition. Similarly, training condition did not significantly influence the self-reported drug effects of *d*-amphetamine as measured by the ARCI. Such discordance between discriminative stimulus and self-reported drug effects has been noted previously. In one recent study, individuals were trained to discriminate progressively lower doses (20–3.5 mg) of the opioid agonist hydromorphone from placebo (15). Although discrimination performance was maintained (75–98% correct drug identifications), physiological and self-reported drug effects generally did not differ from placebo at the lowest training doses.

It is possible that the small size of the training groups in the present study may have limited the statistical power necessary to detect significant main effects for some of the self-reported drug-effect items (e.g., Feel the Drug) The main effect of training condition that was detected for some, but not all, of the self-reported drug-effect items possibly reflects the variable nature of self-reported drug effects in general. Such variability is probably due to the fact that human research participants bring to the laboratory extensive, but diverse, behavioral histories regarding their verbal responses to environmental stimuli. By contrast, research participants probably have limited experience with the behavioral responses typically employed in human drug-discrimination experiments. Moreover, human research participants in drug-discrimination experiments are trained extensively regarding the drug effects before testing is initiated, and thus they are provided with a common behavioral history. Consequently, the human drug-discrimination paradigm may be better suited than self-reported drug-effect questionnaires to study the complex relationship between behavioral history and drug responses.

The differences between the low- and high-dose groups described above appear to be due to the training history of the participants rather than a preexisting difference between the groups (e.g., self-reported drug use). During the medical safety session, prior to any discrimination training, participants in the low- and high-dose groups did not differ significantly from one another in terms of their behavioral and physiological responses to 20 mg *d*-amphetamine. Although several measures (e.g., participant ratings of Feel the Drug, heart rate and blood pressure) showed significant main effects of time, the effects of 20 mg *d*-amphetamine did not differ significantly across the two groups. These results suggest that the participants in both groups were similar with respect to their responses to 20 mg *d*-amphetamine, and that the group differences that emerged during the test-of-novel-doses phase were related to the discrimination training history. Such results further highlight the significant influence that behavioral history exerts on subsequent drug effects.

In summary, in this study we demonstrated that training dose significantly influences the dose–response function for the discriminative-stimulus effects of *d*-amphetamine, as well as some self-reported drug effects. However, manipulating discrimination performance did not significantly alter all of the self-reported drug effects of *d*-amphetamine. Thus, the discriminative-stimulus and self-reported drug effects of *d*-amphetamine overlap, but they are not isomorphic. Future research is needed to better define the relationship between the discriminative-stimulus and self-reported effects of drugs.

ACKNOWLEDGEMENTS

This research was supported by funds provided by the University of Mississippi Medical Center School of Medicine and the Department of Psychiatry and Human Behavior, and by the National Institute on Drug Abuse Grant DA 10325 (C.R.R.). The authors are grateful to Richard L. Ogletree Jr., Pharm.D. for preparing the medications, and Catherine A. Hayes for expert technical assistance. Finally, the authors are grateful to Peggy J. Pazzaglia, MD for her expert medical assistance.

REFERENCES

1. Abreu, M. E.; Griffiths, R. R.: Drug tasting may confound human drug discrimination studies. Psychopharmacology (Berlin) 125:255–257; 1996.
2. American Psychiatric Association.: Diagnostic and statistical manual for mental disorders, 4th ed. Washington, DC: American Psychiatric Press; 1994.
3. Broadbent, J.; Michael, E. K.; Riddle, E. E.; Appel, J. B.: Involvement of dopamine uptake in the discriminative stimulus effects of cocaine. Behav. Pharmacol. 2:187–197; 1991.
4. Broadbent, J.; Michael, E. K.; Appel, J. B.: Generalization of cocaine to the isomers of 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine: Effects of training dose. Drug Dev. Res. 16:433–450; 1989.
5. Chait, L. D.; Uhlenhuth, E. H.; Johanson, C. E.: The discrimina-

tive stimulus and subjective effects of phenylpropanolamine, mazindol, and *d*-amphetamine in humans. Pharmacol. Biochem. Behav. 24:1665–1672; 1986.
6. Colpaert, F. C.; Janssen, P. A.: Factors regulating drug cue sensitivity: Limits of discriminability and the role of a progressively decreasing training dose in a cocaine-saline discrimination. Neuropharmacology 21:1187–1194; 1982.
7. Cunningham, K. A.; Callahan, P. M.: Monoamine reuptake inhibitors enhance the discriminative state induced by cocaine in the rat. Psychopharmacology (Berlin) 104:177–180; 1991.
8. De Vry, J.; Slangen, J. L.: Effects of chlordiazepoxide training dose on the mixed agonist-antagonist properties of benzodiazepine receptor antagonist RO 15-1788, in a drug discrimination procedure. Psychopharmacology (Berlin) 88:177–183; 1986.
9. Jasinski, D. R.: Assessment of the abuse potential of morphine-like drugs (methods used in man). In: Martin, W. R., ed. Drug addiction I. New York: Springer Verlag; 1977:197–258.
10. Martin, W. R.; Sloan, J. W.; Sapira, J. D.; Jasinski, D. R.: Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin. Pharmacol. Ther. 12:245–258; 1971.
11. Mumford, G. K.; Holtzman, S. G.: Qualitative differences in the discriminative stimulus effects of low and high doses of caffeine in the rat. J. Pharmacol. Exp. Ther. 258:857–865; 1991.
12. Oliveto, A. H.; Bickel, W. K.; Kamien, J. B.; Hughes, J. R.; Higgins, S. T.: Effects of diazepam and hydromorphone in triazolam-trained humans under a novel-response drug discrimination procedure. Psychopharmacology (Berlin) 114:417–423; 1994.
13. Overton, D. A.: Applications and limitations of the drug discrimination method for the study of drug abuse. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abused drugs. New York: Springer Verlag; 1989:291–340.
14. Perkins, K. A.; D'Amico, D.; Sanders, M.; Grobe, J. E.; Wilson, A; Stiller, R. L.: Influence of training dose on nicotine discrimination in humans. Psychopharmacology (Berlin) 126:132–139; 1996.
15. Preston, K. E.; Bigelow, G. E.: Opioid discrimination in humans: Discriminative and subjective effects of progressively lower training dose. Behav. Pharmacol. 9:533–543; 1998.
16. Preston, K. L.; Bigelow, G. E.: Subjective and discriminative effects of drugs. Behav. Pharmacol. 2:293–313; 1991.
17. Rush, C. R.; Critchfield, T. S.; Troisi, J. R., III; Griffiths, R. R.: Discriminative stimulus effects of diazepam and buspirone in normal volunteers. J. Exp. Anal. Behav. 63:277–294; 1995.
18. Rush, C. R.; Kollins, S. H.; Pazzaglia, P. J.: Discriminative stimulus and self reported drug effects of methylphenidate, buproprion, and triazolam in *d*-amphetamine-trained humans. Exp. Clin. Psychopharmacol. 6:32–44; 1998.
19. Rush, C. R.; Madakisira, S.; Goldman, N. H.; Woolverton, W. L.; Rowlett, J. K.: Discriminative stimulus effects of zolpidem in pentobarbital-trained subjects: Comparison with triazolam and caffeine in humans. J. Pharmacol. Exp. Ther. 280:174–188; 1997.
20. Schuster, C. R.; Fiscman, M. W.; Johanson, C. E.: Internal stimulus control and the subjective effects of drugs. In: Johanson, C. E.; Thompson, T., eds. Behavioral pharmacology of human drug dependence. Research monograph 37. Rockville, MD: National Institute on Drug Abuse. Public Health Service: Alcohol, Drug Abuse and mental Health Administration. U.S. Department of Health and Human Services; 1981:116–129.
21. Stolerman, I. P.; D'Mello, G. D.: Role of training conditions in discrimination of central nervous system stimulants by rats. Psychopharmacology (Berlin) 73:295–303; 1981.
22. Stolerman, I. P.; Garcha, H. S.; Pratt, J. A.; Kumar, R.: Role of training dose in discrimination of nicotine and related compounds by rats. Psychopharmacology (Berlin) 84:413–419; 1984.
23. Tang, A. H.; Franklin, S. R.: The discriminative stimulus effects of diazepam in rats at two training doses. J. Pharmacol. Exp. Ther. 258:926–931; 1991.
24. Terry, P.; Witkin, J. M.; Katz, J. L.: Pharmacological characterization of the novel discriminative stimulus effects of a low dose of cocaine. J. Pharmacol. Exp. Ther. 270:1041–1048; 1994.