A PROCEDURE FOR STUDYING THE WITHIN-SESSION ONSET OF HUMAN DRUG DISCRIMINATION

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The purpose of the present study was to develop a procedure for measuring the within-session onset of human drug discrimination. During daily sessions, under double-blind conditions, caffeine-abstinent adults ingested a letter-coded capsule containing 178 mg caffeine or placebo. Trials were presented at 30-s intervals, beginning immediately after drug ingestion and continuing for 60 min. On each trial, subjects could guess which of their two letter-coded drugs they had received by pressing a left button (for one drug) or right button (for the other drug); subjects could also press a center "no guess" button instead of guessing. Each trial ended after one button press. After each session, subjects were told which drug they had received. Subjects always earned one point (worth \$0.10 per point) for each correct guess. Subjects lost either 0, 1, or 10 points for each incorrect guess; the point-loss contingencies were varied in random order across sessions. Discrimination earnings accumulated across all sessions. The point-loss contingencies decreased random responding and delayed the discrimination time course. Overall, this procedure provided an orderly and relatively continuous measure of the within-session onset of drug discrimination and should have a range of applications in understanding the human behavioral pharmacology of drugs.

Key words: drug discrimination, stimulus control, time course, onset, punishment, caffeine, behavioral pharmacology, button press, humans

Drug discrimination procedures, which have been widely used to investigate the behavioral and pharmacological effects of drugs in non-humans (Samele, Shine, & Stolerman, 1992), have been recently adapted for use with humans (Kamien, Bickel, Hughes, Higgins, & Smith, 1993; Preston, 1991). Although relatively few studies have been conducted, drug discrimination procedures have already been used successfully to classify drugs with regard to their pharmacological mechanisms of action in humans (Preston & Bigelow, 1991), to investigate the abuse liability of compounds (Preston, 1991), and to examine the limits of human behavioral sensitivity to drugs (Griffiths, Evans, Heishman, Preston, Sannerud, Wolf, & Woodson, 1990; Silverman & Griffiths, 1992).

Although drug discrimination methods have been useful in characterizing the time course of onset of drug effects in nonhuman animals

(e.g., Ator, 1990; Stolerman & Garcha, 1989), few analogous studies have been reported for humans. One previous study provided some information on the time course of onset of presumed discriminative-stimulus effects 15 min after oral administration of caffeine or placebo by asking human subjects which of the two drugs they received (Silverman & Griffiths, 1992). However, because this study did not arrange reinforcement contingencies for responding throughout the time course, the variables controlling the early session responding were unclear. To our knowledge, the only drug discrimination study to provide explicit reinforcement contingencies for discriminative responding immediately after drug discrimination in humans was one involving a discrimination between smoking marijuana versus placebo cigarettes (Chait et al., 1988). The immediate onset of correct discrimination responding in combination with the observation that subjects reported taste and harshness as cues for the discrimination make unclear the extent to which responding was controlled by the central effects of marijuana. Thus, the relevance of that study to the development of methods useful in characterizing time course of onset of drug effects is uncertain.

The purpose of the present study was to develop a sensitive and relatively continuous measure of the time course of the onset of discriminative-stimulus effects of drugs in hu-

This work was supported in part by US Public Health Service Research Grant R01DA03890 (National Institute on Drug Abuse). The authors thank Gregory A. Bigelow for his assistance in analyzing and graphing the data and John Yingling for developing the computer software for the discrimination program. Send reprint requests to Roland R. Griffiths, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Behavioral Biology Research Center, 5510 Nathan Shock Dr., Suite 3000, Baltimore, Maryland 21224.

mans. The procedure had three key features: (a) Subjects could make repeated reinforceable discrimination responses, beginning immediately after drug administration. (b) Subjects always had an option of not making the discrimination response by making a "no guess" response instead. (c) Point-loss contingencies were imposed for incorrect responding, thereby reducing the frequency of early session random (or biased) responding. Using this procedure, the present study characterized the time course of a caffeine versus placebo discrimination in adult volunteers. In addition, the study manipulated the magnitude of the point-loss contingencies for incorrect responding to assess the effects of that element of the procedure and to assess the sensitivity of discrimination time course to environmental influences.

METHOD

Subjects

Four healthy adults were recruited to participate in the study through advertisements in newspapers and on bulletin boards. The research protocol was approved by the Institutional Review Board for Human Research, and subjects gave their informed consent before beginning the study. Subjects were considered for the study if they were healthy, had no previous diagnoses of any serious psychiatric condition, were not pregnant, had a high school diploma, were employed or in school, consumed at least 50 mg of caffeine per day, and were not currently using illicit drugs. Monthly urine samples were collected and analyzed for illicit drug use and for pregnancy (women only); no instance of either was detected.

Subjects participated in an initial interview and physical examination before beginning the study. Standardized self-rated psychometric inventories indicated that all subjects were within the normal limits (± 2 SD) on various dimensions of personality (i.e., the Neuroticism, Extroversion, Openness Personality Inventory; Costa & McCrae, 1985) and anxiety (State-Trait Anxiety Inventory; Spielberger, Gorsuch, & Lushene, 1970). Medical histories and brief physical examinations indicated that all subjects were in good health, with no medical contraindications to normal caffeine consumption.

Two subjects never acquired a reliable caffeine versus placebo discrimination. This pa-

per describes the results for the 2 subjects who did acquire the discrimination. Subjects SM and RH weighed 60 and 82 kg, respectively; their ages were 31 and 27 years, respectively; and their mean self-reported caffeine consumption (estimated from a questionnaire given before beginning the study) was 252 and 156 mg per day, respectively. Caffeine intake was calculated as described previously (Silverman & Griffiths, 1992). SM was female, and RH was male. SM had participated in a previous caffeine versus placebo discrimination study (Silverman & Griffiths, 1992).

Setting

Subjects reported to a room with experimental stations that were separated by room partitions. Each station was equipped with a large cushioned chair and a microcomputer keyboard and monitor.

General Procedures

Daily procedures. Experimental sessions were conducted daily (Monday through Friday). Each subject had a fixed scheduled time to report to the laboratory and was required to report within ± 30 min of that time. All scheduled times were between 6:00 a.m. and 11:00 a.m. Sessions lasted for approximately 75 min. After reporting to the laboratory, the subject was seated in his or her experimental station where all of the session activities were conducted. First, the subject completed a self-report questionnaire (see below) and provided a saliva sample. Then the subject ingested a capsule. For the 60 min that followed, the subject performed the drug discrimination task. Before leaving the laboratory, the subject again completed the self-report questionnaire.

Instructions. Each subject was told that the purpose of the study was to examine the behavioral and mood effects of compounds normally found in foods and beverages that are ingested as a part of the daily diet (including chlorogenic acids, aspartame, diterpenes, caffeine, tannin, sugar, theobromine, and theophylline). The subject was told that throughout the study, he or she would receive only two of the compounds listed above or one of the compounds and an inactive placebo, but was not told specifically which two drugs would be received. Instead, the two drugs were identified by letter codes (e.g., A and B) that were unique for each subject.

Dietary restrictions. Except for caffeine received as part of the daily protocol, all outside sources of caffeine intake were restricted, including coffee, tea, soda, chocolate, and caffeine-containing over-the-counter and prescription medications. To keep subjects blind to the exact drugs under study, they were not told directly to eliminate caffeine from their diets. Instead, the following dietary restrictions were imposed, which, if followed, would eliminate virtually all dietary and medicinal sources of caffeine. The only beverages allowed were milk, fruit juices, water, and a specified list of caffeine-free sodas and drinks (e.g., lemonade); chocolate products were prohibited. To divert attention from caffeine, food items without caffeine were also restricted, including all foods containing saccharin or aspartame. Finally, the subjects were asked not to take any medications, except for oral contraceptives, acetaminophen, or ibuprofen. Subjects were also asked to inform the investigators if they took any medications.

Cigarette smoking was allowed except during experimental sessions. Moderate alcohol use was allowed up to 10 hr before experimental sessions, but use of illicit drugs was prohibited. Finally, subjects were instructed to eat either no breakfast at all or a light and consistent (i.e., the same content every morning) breakfast on mornings before sessions.

To facilitate compliance with the dietary restrictions, saliva samples (5 mL each) were collected before capsule administration every weekday and on a random basis on weekends to determine if the dietary restrictions were being followed. At least one sample per phase (see below for description of phases) per subject was analyzed using gas chromatography methods (similar to Jacob, Wilson, & Benowitz, 1981, but using 5-methylcotinine as the internal standard).

Capsule preparation and administration procedures. Caffeine and placebo capsules with identical appearances (Size 0, opaque hard gelatin capsules) were prepared from combinations of caffeine anhydrous (USP) and powdered lactose. At approximately the same time each weekday morning before 11:00 a.m., subjects ingested one capsule under staff supervision and double-blind conditions. Each capsule was taken with 150 mL of water. Drug administration procedures were designed to ensure that subjects swallowed the capsules

without tasting the contents. To accomplish this, the research assistant poured the capsule into the subject's mouth from a clear plastic cup and watched the subject to ensure that the capsule was not removed from the mouth or bitten. To minimize possible development of physical dependence on caffeine, caffeine was never administered on more than 3 consecutive days.

Self-report questionnaires. Immediately before and 60 min after ingesting the capsule at the beginning of each session, subjects completed a 49-item version of the Addiction Research Center Inventory (ARCI) and a 17-item caffeine questionnaire described previously (Silverman & Griffiths, 1992).

Weekend and holiday procedures. Before each weekend or holiday, subjects were given one capsule to take at home for each day that they would not report to the research unit. Each weekend or holiday capsule contained placebo (unknown to the subject). Other details of weekend and holiday procedures, including dietary restrictions and collection of saliva samples, were the same as previously reported (Silverman & Griffiths, 1992).

Payments to subjects. Subjects were paid for their participation in the study. Each subject earned a base pay of \$4 per session for completing each session, paid at the end of each week, and a bonus of \$4 per session for completing the experiment and complying with all the requirements of the study. In addition, subjects earned money for correctly identifying the compound administered each weekday session, as described below.

Initial Caffeine Versus Placebo Discrimination Training Phase

Both subjects participated in an initial caffeine versus placebo discrimination training phase to establish the discrimination prior to entering the experimental phase of the study. During each session, each subject ingested one capsule containing either caffeine or placebo. The sequence of caffeine and placebo capsules across days was randomized with the restriction (unknown to the subject) that neither compound be administered on more than three consecutive sessions. At 30-s intervals, beginning immediately after drug ingestion and continuing for 60 min, drug discrimination trials were scheduled in which the subject could guess which of the two letter-coded drugs he or she

had received. At the beginning of each trial, the computer screen in front of the subject displayed the question "Which drug did you receive today?" Below the question were three choices, horizontally arranged, that corresponded to three buttons: On the left and right of the screen were drug letters (e.g., Drug A and Drug B, respectively; drug letters differed across subjects) that corresponded to the two compounds; "no guess" appeared in the center. Point counters were displayed below the Drug A and Drug B labels. To guess, the subject could press one of three buttons on a rectangular metal box. The left and right buttons corresponded to caffeine and placebo; the button (left or right) associated with caffeine was varied across subjects. Subjects could press the center button if they did not want to guess on a particular trial. Each press on the left button incremented the Drug A point counter by 1 and decremented the Drug B point counter by 1. Similarly, each press on the right button incremented the Drug B point counter by 1 and decremented the Drug A point counter by 1. Presses on the center button did not alter either point counter. Each point earned correctly was worth \$0.10. The discrimination trial ended when the subject pressed one of the three buttons or when 30 s elapsed. The drug discrimination task ended after the subject completed 120 discrimination trials.

After completing the 120 discrimination trials, the subject completed the two paper-and-pencil questionnaires described above. The subject also answered an additional questionnaire item on which he or she guessed which letter-coded drug had been received that session. No consequences were provided for these end-of-session guesses. Then, under staff supervision, the subject opened a sealed envelope that contained the letter of the drug administered at the beginning of the session (i.e., the "correct" drug). The subject earned or lost money based on the total number of points associated with the correct drug (i.e., the number of points accumulated on the correct drug's point counter $\times$ \$0.10). If a positive number of points had been accumulated on the correct drug's point counter, the subject earned money for that session. If a negative number of points had been accumulated on the correct drug's point counter, the subject lost money for that session. The earnings for each session accu-

mulated across all of the discrimination sessions of the experiment.

The caffeine dose for Subject RH was initially 320 mg and was reduced to 178 mg after he responded correctly on five consecutive sessions. Subject SM started discrimination training at 178 mg caffeine, due to her previous history of discrimination training (see above). The initial discrimination training phase was extended in blocks of 10 sessions until the subject responded correctly (based on the final paper-and-pencil guess of each session) with the caffeine dose at 178 mg on 10 of 10 consecutive sessions.

Experimental Phase

The experimental phase was conducted to compare the effects of three different point-loss contingencies for incorrect responses on the caffeine versus placebo discrimination. This phase was identical to the initial discrimination phase except that presses on the left or the right buttons resulted in point losses of one of three values from the point counter of the other drug: -0 points (the -0 point-loss contingency), -1 point (the -1 point-loss contingency), or -10 points (the -10 point-loss contingency). Only one point-loss contingency was in effect on a given day. The -1 point-loss contingency condition was identical to the initial training condition described above, in that each press on the left button incremented the Drug A point counter by 1 and decremented the Drug B point counter by 1; similarly, each press on the right button incremented the Drug B point counter by 1 and decremented the Drug A point counter by 1. During sessions in which the -0 point-loss contingency was in effect, each press on the left button incremented the Drug A point counter by 1 but did not affect the Drug B point counter; each press on the right button incremented the Drug B point counter by 1 but did not affect the Drug A point counter. Under the -10 point-loss contingency, each press on the left button incremented the Drug A point counter by 1 and decremented the Drug B point counter by 10; each press on the right button incremented the Drug B point counter by 1 and decremented the Drug A point counter by 10. The three point-loss contingencies were scheduled in random order in blocks of six sessions, with the restrictions that each contingency occur

twice in each block, once when placebo was administered and once when caffeine was administered. Subjects were told at the beginning of each session which point-loss contingency was in effect for that session.

Data Analysis

The effects of the point-loss contingencies on the within-session time course of the caffeine versus placebo discrimination were analyzed for individual subjects using data from all 120 trials of all of the sessions conducted during the experimental phase. For each subject's data, repeated measures analyses of variance (ANOVAs) were calculated for each of the three discrimination measures (percentage guesses, percentage correct, and percentage incorrect) with three factors for each analysis: Drug (caffeine and placebo), Point-Loss Contingency (-0 , -1 , and -10 points), and Discrimination Trial (120 trials per session). The "guesses" measure included both Drug A and Drug B guesses (i.e., both correct and incorrect guesses). For purposes of graphic presentation, data were collapsed across the two drug conditions and across all sessions of the experimental phase; critical differences were calculated with Tukey's Honestly Significant Difference Test.

Ratings on the self-report questionnaires were analyzed for each individual subject using data from the 60-min time point for all sessions of the experimental phase. For each subject's data, repeated measures ANOVAs were calculated with two factors: Drug (caffeine vs. placebo) and Point-Loss Contingency (-0 , -1 , and -10 points).

For all statistical tests, effects were considered to be significant for $p \leq .05$. For repeated measure ANOVAs, Huynh-Feldt (Huynh & Feldt, 1976) corrected p values are reported.

RESULTS

Amount of Guessing

The top row of Figure 1 shows that the number of discrimination trials on which each subject guessed (i.e., pressed the Drug A or Drug B button, as opposed to pressing the "no guess" button or not guessing at all) decreased as the magnitude of the point-loss contingency increased. Both subjects guessed on almost all trials during sessions in which the -0 point-

loss contingency was in effect. Subjects rarely failed to press one of the three buttons on trials (0.1% of trials for SM and 1.0% of trials for RH) during the entire experimental phase.

Accuracy of Guessing

The bottom row of Figure 1 shows that, based on the trials on which subjects guessed, the point-loss contingencies tended to improve the overall discrimination accuracy. This effect of the point-loss contingencies was more apparent in SM. During the majority of sessions under both the -1 and -10 point-loss contingencies, 100% of SM's guesses were correct. In contrast, under the -0 point-loss contingency, 100% of her guesses were correct in only three sessions. RH showed a similar pattern, particularly late in the study (e.g., during the last 20 sessions); however, he showed more overlap in percentage correct under the -1 and -0 point-loss contingencies.

Discrimination Time Course

Figure 2 shows the within-session time course of the discrimination for each of the 2 subjects averaged across all sessions in the experimental phase. The top row of Figure 2 shows the percentage of sessions in which each subject guessed at the indicated time point within the 60-min session. Guessing tended to increase progressively across the session. In both subjects, these increases were delayed by increases in the magnitude of the point-loss contingency. The middle row shows the percentage of sessions in which each subject was correct at the indicated time point. Correct responding tended to increase across the session. In both subjects, these increases were delayed by increases in the magnitude of the point-loss contingencies. The bottom row shows the percentage of sessions in which each subject was incorrect at the indicated time point. The within-session pattern of incorrect responding was variable across subjects. Incorrect responding was generally a decreasing function of the magnitude of the point-loss contingency. Under the -0 point-loss contingency, early in sessions (e.g., within 15 min after drug ingestion) subjects tended to emit similar amounts of correct and incorrect responses, suggesting random responding. The random pattern of responding early in the sessions was suppressed by the point-loss contingencies.

Fig. 1. The number of trials on which subjects guessed (top row) and the percentage of guesses that were correct (bottom row) for each of 2 subjects. Each column represents data for a different subject. y axes: number of caffeine versus placebo discrimination trials (120 total) on which subjects guessed by pressing either the Drug A or Drug B button (top row), and the percentage of guesses that were correct (bottom row); x axes: consecutive sessions. Data are presented for the three point-loss contingencies: -0 (thin line), -1 (open circles), and -10 (solid circles).

Earnings Under the Discrimination Task

Figure 3 shows that subjects earned money under all three point-loss contingencies. Mean discrimination earnings per session decreased as the magnitude of the point-loss contingency increased.

Self-Reported Effects

Caffeine produced a profile of self-reported mood effects similar to that reported in a recent caffeine versus placebo discrimination study

(Silverman & Griffiths, 1992). For example, in both subjects, relative to placebo, caffeine significantly increased ratings of "alert," "desire to talk to people," "energy/active," and "anxious/nervous" and decreased ratings of "foggy/hazy/not clear headed" and "sleepy." The point-loss contingencies had no consistent effect on self-reports of mood and did not interact with the drug conditions (i.e., there were no consistent main effects of the Point-Loss Contingency and no consistent Drug $\times$ Point-Loss Contingency interactions).

Fig. 2. Within-session time course of the caffeine versus placebo discrimination for each of 2 subjects. Each column represents data for a different subject. Percentages are based on all sessions of the experimental phase. The top row shows the percentage of sessions in which each subject guessed at the indicated time point within the 60-min session. The middle and bottom rows show the percentage of sessions in which each subject was correct and incorrect, respectively, at the indicated time point within the 60-min session. Data are presented for the three point-loss contingencies: -0 (thin line), -1 (open circles), and -10 (solid circles). CD brackets indicate the critical difference within the panel. The difference between any two data points within a panel is statistically significant if it exceeds the CD ($p < .05$).

Salivary Caffeine Concentrations

Analyses of the saliva samples collected during the initial discrimination training and experimental phases in the mornings before capsule administration indicated that subjects generally complied with the dietary restrictions. The mean salivary caffeine concentrations for all of the samples analyzed for both subjects were $0.00 \mu\text{g/mL}$ and ranged between $0.00 \mu\text{g/mL}$ and $0.02 \mu\text{g/mL}$.

DISCUSSION

The present study describes a novel drug discrimination procedure that provided orderly data on the within-session onset of caffeine versus placebo discrimination in 2 adult

human subjects. Repeated discrimination trials, beginning immediately after drug administration and occurring at 30-s intervals, provided a relatively continuous measure of discrimination onset. Point-loss contingencies for incorrect responding in combination with a "no guess" option altered the discrimination time course.

Without point-loss contingencies, subjects made guesses that appeared to be random (i.e., not under the control of the caffeine and placebo discriminative stimuli). The point-loss contingencies decreased that early-session random guessing. In addition, the -10 point-loss contingency delayed the discrimination time course, relative to the time courses under both the -0 and -1 point-loss contingencies.

Fig. 3. Mean discrimination earnings per session for each of 2 subjects. y axis: dollars. Data are presented for the three point-loss contingencies: -0 (open bars), -1 (striped bars), and -10 (shaded bars). Brackets show +1 SEM.

The potential of point-loss contingencies to reduce random responding (i.e., responding not under the discriminative stimulus control of the drugs) suggests that the point-loss contingency may be a useful addition to existing drug discrimination procedures, even when the discrimination time course is not the focus of investigation. Previous drug discrimination procedures that have allowed repeated guesses within a session (e.g., when subjects are allowed to respond repeatedly for several minutes, and each correct discrimination response earns a monetary reinforcer) have had the result that subjects respond at high constant rates, even when varying doses of the training drug are substituted for the training dose or when test drugs are substituted for the training drug (e.g., Bickel, Bigelow, Preston, & Liebson, 1989; Preston, Bigelow, Bickel, & Liebson, 1987, 1989). Without point-loss contingencies of the type used in this study, subjects can maximize their earnings by responding as frequently as possible. Utilization of a point-loss contingency for incorrect responding should diminish the differential reinforcement for high-rate responding that is not under the discriminative control of drugs and thereby produce greater control of responding by the drug stimuli.

These results show that the onset of drug discrimination can be modulated by environmental events. The results demonstrate that the discrimination time course is not a static property of a drug and thus extend the range of findings that show that drugs do not have invariant behavioral effects.

Variations on the present procedures should have a wide range of research applications. For example, a sensitive measure of onset would be useful in characterizing absorption or distribution differences in a series of chemically related compounds or in investigating manipulations that alter absorption or distribution characteristics. Further, because the mechanism underlying the within-session onset of drug effects is probably cumulating drug levels, these procedures may provide information analogous to a within-session cumulative dose-effect curve. Thus, the time course, like cumulative dose-effect curves, may prove to be a particularly sensitive baseline for efficiently evaluating the effects of various pharmacological (e.g., drug interactions, tolerance) and behavioral (e.g., instructions, reinforcement contingencies) factors on the discriminative-stimulus effects of drugs.

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