Drug and Alcohol Dependence 118 (2011) 341–348

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Caffeine choice prospectively predicts positive subjective effects of caffeine and *d*-amphetamine

Stacey C. Sigmon[a,*], Roland R. Griffiths[b,c]

[a] Department of Psychiatry, University of Vermont College of Medicine, SATC-UHC, Room 1415, Burlington, VT 05401, USA
[b] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224-6823, USA
[c] Department of Neuroscience, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224-6823, USA

ARTICLE INFO

Article history:
Received 15 December 2010
Received in revised form 18 April 2011
Accepted 19 April 2011
Available online 19 May 2011

Keywords:
Psychomotor stimulant
Caffeine
d-Amphetamine
Individual differences
Subjective effects
Reinforcement

ABSTRACT

Background: Individuals vary in their subjective and behavioral response to psychomotor stimulants and these differences may be associated with the likelihood of developing problematic use of these drugs. The present study sought to determine whether individual differences in caffeine choice prospectively predict subjective response to acute doses of caffeine and *d*-amphetamine.
Methods: In Phase 1, Choosers and Nonchoosers of caffeine were identified using 10 independent choice trials in which subjects repeatedly chose between caffeine (200 mg/70 kg) and placebo. Choosers were defined as those who chose caffeine over placebo on ≥7 of the 10 trials; Nonchoosers were those who chose placebo on ≥7 trials. In Phase 2, Choosers and Nonchoosers were compared in their subjective response to caffeine (100, 200, 400 mg/70 kg) and *d*-amphetamine (5, 10, 20 mg/70 kg).
Results: Of the 22 participants completing the study, 11 met criteria for being a caffeine Chooser and 8 were Nonchoosers. In Phase 1, Choosers reported higher ratings of positive (i.e., pleasant) and lower ratings of negative (i.e., unpleasant) effects of caffeine during the sampling sessions. In Phase 2, caffeine Choosers reported more positive subjective effects and fewer negative effects of caffeine and *d*-amphetamine, particularly at the highest doses examined.
Conclusions: Individual differences in caffeine reinforcement predicted subsequent subjective response to both *d*-amphetamine and caffeine. This observation may have clinical utility for identifying individuals who are vulnerable to the reinforcing effects of abused psychomotor stimulants.

1. Introduction

While the abuse potential of psychomotor stimulants has been widely demonstrated (Foltin and Fischman, 1991), it is also the case that not everyone who tries a stimulant will develop abuse or dependence. Of people who use stimulants, such as cocaine or *d*-amphetamine at least once, only a small proportion go on to use them in excessive amounts or to develop problems (de Wit, 1998). Individual variability in subjective and behavioral response to abused stimulants has been especially well-demonstrated (de Wit et al., 1986; Singha et al., 1999; Sofuoglu et al., 2000; Gabbay, 2003).

As with the abused psychomotor stimulants, studies using choice and repeated drug self-administration have shown that the stimulant caffeine can function as a reinforcer in humans (Evans et al., 1994; Griffiths et al., 1989; Hughes et al., 1991, 1992). The average incidence of caffeine reinforcement across studies in normal caffeine users is about 40% (Griffiths et al., 2003; Griffiths and Woodson, 1988; Hughes et al., 1993). Individual differences in the reinforcing effects of caffeine have been shown to covary with individual differences in subjective response to caffeine (Griffiths and Woodson, 1988; Hughes et al., 1993; Stern et al., 1989). For example, in a choice study examining the subjective effects of placebo and caffeine on forced-exposure days prior to choice sessions, participants who chose caffeine over placebo in the choice sessions reported more positive subjective effects of caffeine relative to placebo, including increased alertness, contentedness, energy and liking (Evans and Griffiths, 1992). Those who chose placebo over caffeine reported more negative effects of caffeine relative to placebo, including increased anxiety, mood disturbance and jitteriness.

The purpose of the present study was to more fully investigate the individual differences in the reinforcing effects of caffeine and also evaluate the relationship between these individual differences and the subsequent assessment of caffeine and *d*-amphetamine subjective effects. Of particular interest was whether caffeine Chooser status would prospectively predict subjective response to

* Corresponding author. Tel.: +1 802 656 8714.
E-mail addresses: stacey.sigmon@uvm.edu (S.C. Sigmon), rgriff@jhmi.edu (R.R. Griffiths).

0376-8716/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2011.04.018

d-amphetamine. Prior studies have demonstrated individual differences in the reinforcing and subjective effects of *d*-amphetamine (de Wit et al., 1986; Gabbay, 2003; Sigmon et al., 2003; Uhlenhuth et al., 1981), and a recent study in college students has shown that consumption of caffeinated energy drinks prospectively predicts non-medical use of prescription stimulants (Arria et al., 2010). Identification of caffeine reinforcement as a predictor of *d*-amphetamine response would contribute important new information about individual differences in vulnerability to reinforcement and abuse of classic psychomotor stimulants such as amphetamine and cocaine. Toward this end, in the present study we first used a discrete-trial choice procedure with 10 experimentally-independent choice trials to categorize participants into caffeine Choosers or Nonchoosers. In a subsequent phase, the acute effects of a range of doses of caffeine and *d*-amphetamine were characterized.

2. Methods

2.1. Participants

Participants were recruited through newspaper advertisements and community postings. To be eligible, participants had to be adult volunteers between the ages of 18 and 60 years, report a history of regular or intermittent caffeine use, provide a urine specimen that tested negative for illicit drugs of abuse, be in good health as determined by medical history and vital signs, be fluent in English, and be capable of understanding and complying with the protocol. Females were required to be non-pregnant and non-lactating. Exclusion criteria included: known hypersensitivity or medical contraindication to stimulants; a past or current significant medical or psychiatric condition; current diagnosis of any substance dependence other than nicotine; significant illness in the past 30 days; diastolic blood pressure >90 mmHg or a systolic pressure >140 mmHg; body weight 20% above or below their ideal body weight, as calculated using the Metropolitan Life Insurance index; use of prescription or over-the-counter medications that could interfere with the study. The study was approved by the local institutional review board, and subjects provided written informed consent before participating.

Twenty-two participants (14 females and 8 males) completed the study; 17 were Caucasian, 4 were African American, and 1 was Asian. Participants had a mean (range) age of 32.4 (19–51) years, 15.5 (12–16) years of education, and reported drinking a mean of 2.7 (0–6) standard alcohol drinks per week. Subjects reported consuming 167 (14–410) mg caffeine per day. None reported recent use of illicit drugs, and urine samples for all subjects tested negative for illicit substances.

2.2. Intake screening

Individuals came to the Behavioral Pharmacology Research Unit (BPRU) at the Johns Hopkins University School of Medicine and completed a battery of questionnaires assessing demographic variables and drug use history (i.e., age, gender, ethnicity, education, body weight, cigarettes/day, use of alcohol (number of drinks/day), caffeine (mg/day) and illicit drugs (number of times used/lifetime)). They received a brief medical screening that included measurement of vital signs, urine toxicology, and a medical and psychiatric questionnaire. In order to accurately assess participants' dietary intake before the study, they also were asked to keep a food/medication diary for 7 days, recording the amounts, types and timing of all foods, drinks and medications consumed. Questions about foods without caffeine were included to keep participants blind as to the exact drugs under study.

2.3. Study design

This double-blind, placebo-controlled study was 10–14 weeks in duration (including an initial 1-week caffeine abstinence period). Subjects were informed that its purpose was to examine how commonly-used medications may influence mood and medication preference and that they could receive placebo or a variety of commonly-prescribed or over-the-counter sedatives, stimulants or antihistamines. Dietary restrictions were in place throughout the study to eliminate caffeine from each subject's diet; in addition to restricting caffeinated foods, non-caffeinated foods were also restricted in order to keep subjects blind to the exact drugs under study (e.g., foods containing NutraSweet, oysters, mussels, almonds, coconuts, poppy seeds and all beverages except milk, fruit juice and water). To further facilitate compliance with dietary restrictions, participants provided saliva samples at each study visit and were told that the samples would be analyzed for the various compounds contained in the restricted foods. Two samples were chosen from each participant for caffeine quantification and all were collected a minimum of 2 days after last caffeine exposure. These analyses provided an opportunity to confirm compliance with study dietary restrictions at a point when little or no caffeine should have been ingested. Salivary caffeine concentrations were analyzed by Gas Chromatography-Thermionic Specific Detection (Labstat Inc, Ontario, Canada) using methods previously described (Griffiths and Woodson, 1988; Jacob et al., 1981). The tested saliva samples were collected an average of 3.2 (range 2–6) days following last caffeine exposure and had a median caffeine concentration of 8.4 ng/ml, indicating that subjects were compliant with the caffeine restrictions during the study.

During the week before initiation of drug administration, subjects followed dietary restrictions and reported to the laboratory 3 times (e.g., Monday, Wednesday, Friday) to provide a saliva sample. Participants then began Phase 1, which consisted of 30 experimental sessions over a 6–10 week period depending on subjects' schedules. Participants visited the laboratory 3–5 times per week, during which they provided a saliva sample, completed a pre-capsule Drug Effect Questionnaire (DEQ), and ingested p.o. 2 identical color-coded capsules with water under double-blind conditions. The 30 sessions in Phase 1 were comprised of 10 sequences of 3 sessions (Sample-Sample-Choice) per sequence. Each test sequence began with two "no-choice" drug-sampling days during which participants received 2 different types of color-coded capsules on different days (e.g., red capsules on Monday and green capsules on Tuesday). Participants always received placebo on one sample day and caffeine anhydrous (200 mg/70 kg) on the other sample day, with the order of exposure to caffeine and placebo counterbalanced across trials. After leaving the laboratory, participants completed the DEQ at 1, 2, 4, and 8 h after capsule ingestion, which assessed drug effects and drug liking (described in more detail below). On the subsequent "choice session" day, they were shown their self-report data from the prior two sample days to help them recall specific drug effects associated with each pair of capsules. They then chose to ingest one of the two color-coded capsule pairs. The content of the color-coded capsules was always the same as during the preceding 2 sample sessions (one pair contained placebo and the other 200 mg caffeine anhydrous). After leaving the laboratory, participants again completed the DEQ at 1, 2, 4 and 8 h post-capsule. This 3-day test sequence (2 sample days followed by 1 choice day) was repeated for a total of 10 consecutive test sequences. Each 3-day sequence was experimentally independent (i.e., each sequence involved novel color-codes for the capsules and participants were told that capsule ingredients may or may not change across sequences).

Phase 2 of the study consisted of 7 experimental sessions over a 3- to 4-week period, during which participants reported to the laboratory approximately 2–3 times per week. At each visit, participants provided a saliva sample, completed a pre-capsule DEQ and then ingested p.o. 2 capsules with water under double-blind conditions. These sessions were similar to the drug sampling days of Phase 1 except that there was never an opportunity for choosing between capsules during Phase 2. Phase 2 capsules contained placebo, caffeine anhydrous (100, 200 or 400 mg/70 kg), or *d*-amphetamine sulfate (5, 10 or 20 mg/70 kg), with order of exposure to caffeine and *d*-amphetamine doses and to placebo counter-balanced across subjects and trials in a Latin Square sequence. Capsules were not color-coded but rather were identical across all 7 sessions. After leaving the laboratory, subjects completed the DEQ at 1, 2, 4 and 8 h post-capsule. At least one non-experimental day was scheduled between sessions to eliminate any drug carryover effects. Subjects received approximately $1300 for participating in the study.

2.4. Drug preparation and administration

Size 0, opaque hard gelatin capsules were used throughout the study. Two capsules were used for each instance of drug or placebo administration in both Phase 1 and Phase 2. During Phase 1, caffeine capsules (200 mg/70 kg) were prepared using powdered lactose and caffeine anhydrous (USP). Placebo capsules were prepared using powdered lactose. The color of the caffeine and placebo capsules varied across experimental sessions within and across participants; there were 7 possible colors (e.g., red, yellow, blue) and a total of 28 possible color combinations (including solid-colored capsules and capsules with each half being a different color). During Phase 2, all capsules were blue. Caffeine capsules (100, 200 or 400 mg/70 kg) were prepared using powdered lactose and caffeine anhydrous (USP). *d*-Amphetamine capsules (5, 10 or 20 mg/70 kg) were prepared using powdered lactose and *d*-amphetamine sulfate. Amphetamine doses are expressed as the salt. Identical placebo capsules were prepared using powdered lactose.

2.5. Subjective measures

Participants completed the Drug Effect Questionnaire (DEQ) immediately before and at 1, 2, 4, and 8 h after capsule administration. This questionnaire was designed to assess subjective effects of drugs and included 25 items: Drug Effect, Arousing/Stimulant Effect, Depressant/Sedating Effect, Good Effects, Bad Effects, Liking, Alert/Attentive, Well-Being, Refreshed, Desire To Socialize/Talkativeness, Anxious/Nervous, Happy, Urge To Do Task/Work-Related Activities, Drowsy/Sleepy, Overjoyed, Ability To Concentrate, Energy/Active, Jittery/Shaky, Elated, Lethargy/Fatigued/Tired/Sluggish, Pleased, Muzzy/Foggy/Not Clear-Headed, Satisfied, Self-Confidence and Heart Pounding. Participants rated each item on a 5-point scale from 0 (not at all) to 4 (extremely). An additional 9-point item was included that asked participants to rate their "liking" of the drug effect they were feeling right now, using a scale that ranged from −4 (dislike very much) to +4 (like very much) and which also included the option of rating their liking of drug effect as 0 (neutral or no effect). For the items assessing general drug effects (i.e., Drug Effect, Arousing/Stimulant Effect, Depressant/Sedating Effect, Good