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Drug Preference and Mood in Humans: Repeated Assessment of *d*-Amphetamine

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JOHANSON, C. E., AND E. H. UHLENHUTH. *Drug preference and mood in humans: Repeated assessment of* d-*amphetamine*. PHARMAC. BIOCHEM. BEHAV. **14**(2) 159–163, 1981.—Ten normal human volunteers participated in 3 identical choice experiments comparing 5 mg *d*-amphetamine and placebo. Each experiment consisted of 9 sessions. During the first 4 sessions of each experiment, subjects received alternatively drug or placebo. During the next 5 sessions, they were given a choice between amphetamine and placebo. Subjective effects were assessed using the Profile of Mood States (POMS) before drug was taken and 1, 3 and 6 hrs later. Subjects chose amphetamine an average of 4.0, 3.2 and 2.1 times out of 5 during each of the three experiments, in that order. Compared to placebo, amphetamine produced changes in mood as measured by the POMS including increased Vigor, Elation, Arousal and Positive Mood. Mood changes produced by amphetamine were similar across all three experiments despite the decrease in drug preference, suggesting the independence of these two measures. The results are discussed in terms of developing methods for predicting the abuse potential of psychotropic drugs.

Amphetamine Drug preference Subjective effects POMS Humans Abuse liability

IN humans, studies designed to assess the abuse potential of psychotropic drugs have measured their physiological and subjective effects in drug-experienced subjects [6, 14, 15, 16]. The extent to which the pharmacological profile of an unknown compound is similar to the profile of known drugs of abuse is viewed as an indication of its abuse potential [3]. On the other hand, in animal studies, experimenters have attempted to study abuse potential by viewing the drugs as reinforcers and allowing animals an opportunity to voluntarily ingest or inject them [10,19]. In these studies, the degree to which drug-seeking behavior is generated and maintained by a compound is viewed as an indication of its abuse potential [9,21]. Although both approaches have yielded surprisingly similar results [5,20] there have been few studies designed to establish the concordance between these two types of measures.

In this context, the present study is part of a series of studies designed to measure simultaneously the reinforcing properties of drugs in a group of humans as well as their subjective effects. Previous studies have shown that subjects given a choice between amphetamine and placebo prefer the drug [11]. The subjective effects produced by the drug as measured by the Profile of Mood States included increases on the Vigor and Arousal subscales. In the present study, the preference for amphetamine and its subjective effects were studied repeatedly over a more extended time period to determine their reliability.

METHOD

Subjects

The subjects in these experiments were 10 normal human volunteers (8 males and 2 females) between the ages of 21 and 32. They were recruited using advertisements in the local student newspaper, notices posted on the University campus, and word-of-mouth referral. Prior to acceptance, each subject was given a brief interview during which: (1) the nature of the experiments was explained in detail, (2) a psychological evaluation was conducted and (3) a drug history was taken. Subjects were accepted if they were considered normal on the basis of this interview and a subsequent physical examination which included ECG, blood chemistry screen, complete blood count, differential and routine urinalysis. Most subjects had some experience with psychotropic drugs but none had a history of any type of drug abuse or dependence.

Subjects signed a consent form prior to participation which outlined the study in detail and indicated the possible side effects of any drug they might be given. They were informed that they would not be told what drug they ingested at the time, except that it would be either a psychomotor stimulant, minor tranquilizer or placebo, and the dose would be within the daily therapeutic range. Each subject also agreed not to take other drugs except their normal amounts of coffee and cigarettes 12 hours before and 6 hours after

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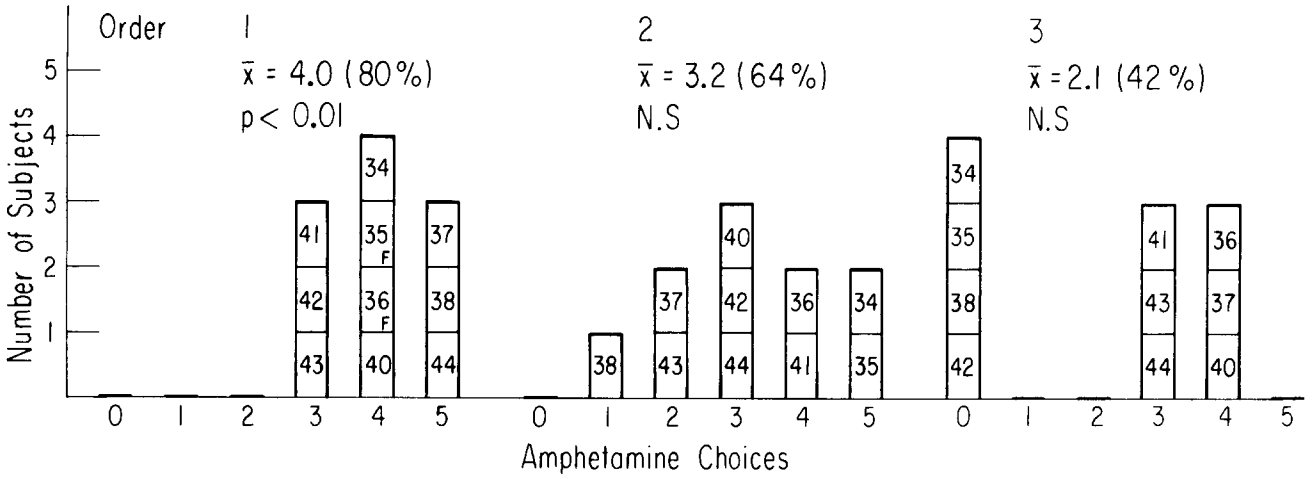

FIG. 1. The number of subjects (ordinate) who chose 5 mg *d*-amphetamine 0 to 5 times (abscissa) during each of 3 identical sequential experiments. The same 10 subjects participated in each experiment. The individual subject numbers are included within the histogram. The "F" by subject numbers 35 and 36 indicate that these subjects were females. The mean number and percent drug choices are also shown. Significance levels were determined using a two-tailed *t*-test.

receiving drug. Except for the actual drug ingested, subjects were completely informed of all other procedural details as outlined below.

Contact between subjects was minimal. Each subject began participation as soon as his/her recruitment procedures were completed with no regard to the schedules of other subjects. During any one week only an average of 3 or 4 subjects participated. Contact was further minimized since the individual schedules of each subject determined at what exact time between 9 and 11 a.m. and which three days of the week between Monday and Friday they reported to the laboratory. The entire experiment was conducted over a 6 month period.

Procedure

Each subject participated in 3 identical choice experiments, i.e., the same experiment was replicated 3 times. In each experiment, subjects were first exposed to 5 mg *d*-amphetamine and placebo, then were given a choice between capsules containing these two compounds. An experiment consisted of 3 sessions per week over a 3-week period, resulting in a total of 9 sessions. Sessions were conducted Monday through Friday and each subject was free to participate on any three of these days. During the first 4 sessions, the subject reported to the experimental room between 9 and 11 a.m. for approximately 5 min. At this time, he/she filled out a mood form (see below) and received a colored capsule (i.e., drug or placebo) for immediate ingestion. Half of the subjects received drug during sessions 1 and 3 and placebo during sessions 2 and 4. The order was reversed for the other half. For each subject, drug and placebo capsules were consistently colored in order to facilitate identification. The capsule colors associated with amphetamine and placebo were assigned randomly across subjects to avoid the influence of color preference. Each subject was instructed during the initial four sessions to note the color of the capsule and to try to associate characteristic effects with each of the 2 capsule colors. After ingesting the capsule, the subjects were free to leave. They took three additional mood forms with them which they were to fill out 1, 3 and 6 hours later.

During the last five sessions, the procedure was identical in every respect, except that the subjects were given a choice of which of the two colored capsules they would ingest, i.e., they were given a choice between drug and placebo.

The next two 3-week experiments were identical to the first one (i.e., subjects were given forced exposure to 5 mg *d*-amphetamine and placebo, then allowed to choose between capsules containing these two compounds), except that for each subject the colors of both the capsules were changed for each new experiment, i.e., subjects were never exposed to any color more than once. No indication was given that the experiments would be the same. The instructions were worded, however, in such a way that this possibility was not precluded.

The deviation of the mean number of amphetamine choices from the number expected by chance (2.5) in each experiment was tested by a single sample *t*-test. The difference between experiments in the mean number of amphetamine choices was tested by one-way (experiment) analysis of variance with repeated measures. A two-tailed confidence level of $p<0.05$ was employed to reject the null hypothesis.

Subjective Effects

The scale used to assess mood was an experimental version of the Profile of Mood States (POMS; [17]), which has been shown to be sensitive to the effects of psychotropic drugs [11,12]. The scale consists of 72 adjectives used commonly to describe momentary mood states. Subjects indicated how they felt at the moment in relation to each of the 72 adjectives on a 5-point scale from "not at all" (0) to "extremely" (4). There are 8 clusters (subscales) of items which have been separated empirically using factor analysis (Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness and Elation). The value of each subscale is determined by adding the numbers checked for each adjective in the cluster and dividing the total by the number of adjectives. Two additional subscales, Arousal and Positive Mood, were derived from other subscales: Arousal = (Anxiety+Vigor)

−(Fatigue+Confusion); Positive Mood=Elation−Depression.

For each experiment the 10 POMS scores were averaged across drug sessions and across placebo sessions for each subject at each of the 4 time periods. A three-way analysis of variance within subjects (drug×hour×experiment) was performed separately for each POMS factor. If a significant ($p<0.05$) drug×hour interaction was found, the effect was further evaluated by *post hoc* contrasts to determine the specific hours when significant differences between drug and placebo occurred. (Because of the exploratory nature of this work, a relatively powerful *post hoc* test, Fisher's LSD [4,23] was employed for contrasting cell means. The drawback to this procedure is that because of the non-independence of the individual tests performed, the overall probability of at least one Type I error is greater than that set for each comparison taken separately. In the current study, a 0.05 significance level was considered the maximum acceptable. In most of the actual cases, a much smaller probability was computed.)

Drug Preparation

Five mg *d*-amphetamine tablets were placed in opaque gelatin capsules (size 00), which then were filled with dextrose powder. Placebo capsules were identical in size and contained dextrose powder alone.

RESULTS

Figure 1 shows the number of times out of a possible 5 that 5 mg *d*-amphetamine was chosen by each of the 10 subjects. In the first experiment, 7 subjects chose drug 4 or 5 times and no subjects chose it less than 3 times with an overall mean of 4.0 (80%) drug choices. In the second experiment, the overall mean number of drug choices decreased to 3.2 (64%) and 3 subjects chose drug only 1 or 2 times. In the last experiment, the mean number of drug choices was only 2.1 (42%), and 4 subjects chose placebo on all 5 choice sessions. The mean number of drug choices was significantly ($p<0.01$) different from chance expectation in the first experiment, but not in the second and third experiments. The mean number of drug choices differed significantly ($p<0.05$) among the three experiments. *Post hoc* contrasts among all possible pairs of cell means indicated that the means of the first and third experiments differed significantly ($p<0.01$). The mean of the second experiment differed significantly from neither the first nor the third experiment.

Although there was a decrease in overall mean drug choice across the three experiments, there was considerable subject variability as shown in Fig. 1. For instance, in Experiment 3, 6 subjects showed a decrease in drug choices and 4 stayed the same compared to Experiment 1. Subjects varied also in terms of the number of weeks elapsing between each of the experiments. Between Experiments 1 and 2, 8 subjects took no break, 1 took off one week and 1 (No. 38) was gone 6 weeks. Between Experiments 2 and 3, the number of weeks elapsing varied between 0 and 2 and averaged 0.7 weeks. Individual differences in time between experiments were not systematically related to the preference results.

Figure 2 shows the 4 POMS factors for which there was a significant drug×hour interaction ($p<0.05$). Compared to placebo, drug produced significant increases in the mean scores for Vigor, Elation, Arousal, and Positive Mood. Analysis of contrasts at each hour revealed that these differences were greatest 3 hours following drug and had not disappeared even after 6 hours. Furthermore, scores during placebo sessions changed as the day progressed. At hour 6 compared to hour 0, scores were increased for Fatigue and were decreased for Vigor, Elation, Arousal and Positive Mood.

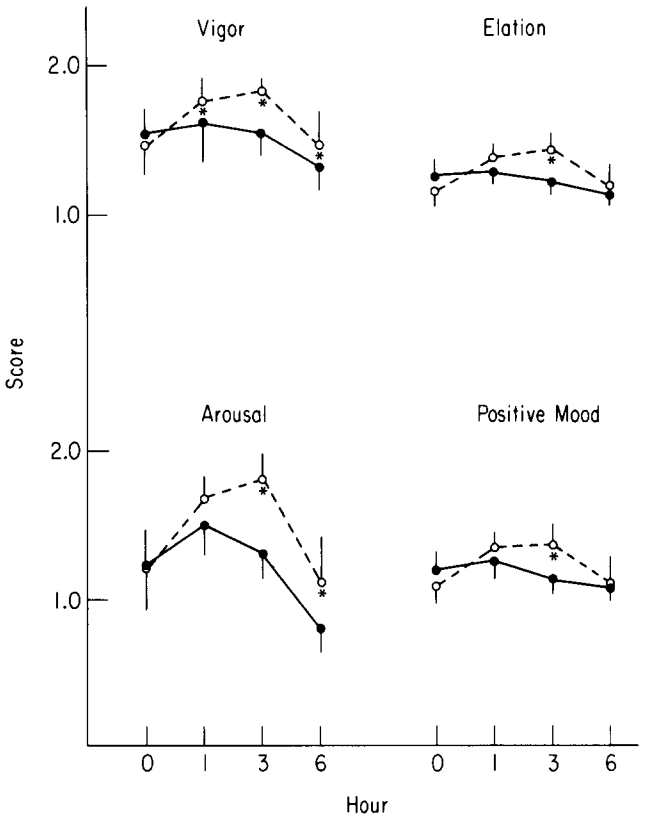

FIG. 2. The effects of amphetamine (open circles) and placebo (closed circles) at 0, 1, 3 and 6 hrs after ingestion on the scores of 4 subscales of the POMS. Each point represents the mean (± SE) of 3 average scores for each of 10 subjects. Each of the average scores was the mean of all drug or placebo exposures for that subject during a given experiment. Significance levels were determined using a three-way (drug×hour×experiment) analysis of variance. Subscales which did not show a significant drug×hour interaction ($p<0.05$) are not shown. The asterisks (*) indicate a significant difference ($p<0.05$) between drug and placebo at that hour specifically as revealed by *post hoc* analyses.

There were no significant 3-way interactions, indicating that amphetamine produced similar changes in mean subjective effects across all experiments despite a change in mean drug preference. This similarity can be seen more clearly in Fig. 3 where the 4 POMS factors during amphetamine sessions are shown separately for each experiment.

DISCUSSION

A previous study demonstrated that 5 mg *d*-amphetamine was chosen over placebo an average of 4 out of 5 times [11]. This pronounced preference was correlated with typical amphetamine-like subjective effects [2, 7, 15, 16]. In the present study, similar results were found during the initial 3-week experiment, i.e., a preference for amphetamine correlated with increased Vigor, Elation, Arousal and Positive Mood scores on the POMS. On the other hand, during the two replications of the initial experiment, the number of

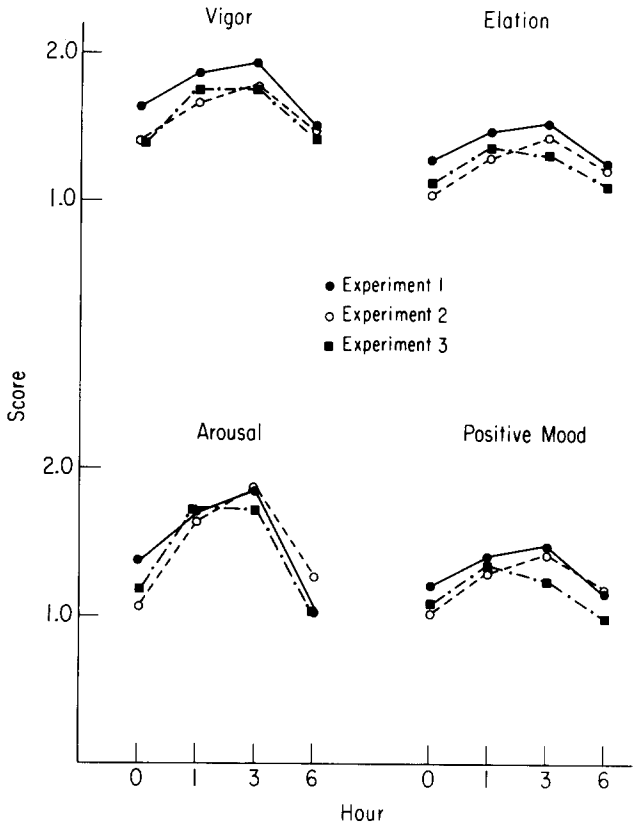

FIG. 3. The effects of amphetamine at 0, 1, 3 and 6 hrs after drug ingestion on the scores of 4 subscales of the POMS shown separately for each experiment. Each point represents the mean of 10 subjects during sessions when drug was ingested. These means were determined as described for Fig. 2.

choices for amphetamine decreased and during the last replication, placebo was chosen on an average more than drug. The decrease in preference was not associated with changes in mean subjective effects (cf. Fig. 3). Amphetamine still produced increases in Vigor, Elation, Arousal and Positive Mood compared to placebo even though overall preference changed from drug to placebo.

The present results are puzzling for two reasons. First, given the results of previous studies and the fact that amphetamine is a known drug of abuse, it is surprising that the reinforcing properties of amphetamine progressively declined. It is well known that tolerance to many of the effects of the amphetamines occurs over relatively short time periods in many species [1, 4, 13, 22, 23]. If this had occurred in the present study, amphetamine may have been chosen if higher doses had been made available. However, although some subjects took breaks between experiments, this was not correlated with preference. The change in preference also may have been due to disruptive effects of the drug becoming predominant. While an increase in Arousal, for instance, initially may have been associated with increased reinforcer efficacy, perhaps due to its novelty, extended exposure to this effect of the drug may alter the reinforcing properties. Such a change may account for the fact that while many people try amphetamines, relatively few go on to become abusers. Likewise, in studies of the natural history of amphetamine abuse, it has been documented that after continuous use the originally euphoric qualities of the drug experience are changed to feelings of irritability and paranoia [18]. Interestingly, even individuals (including animals) administering large quantities of amphetamine to themselves, voluntarily abstain from consumption for periods of days [8,13].

The second puzzling aspect of the present study is the similarity in the mean subjective effects produced by amphetamine over all three experiments despite the change in overall preference. However, it is important to note that the subjective effects reported are for the group as a whole. Whether individual initial levels or changes in subjective effects are related to choice must await future analyses. Many studies in humans designed to assess the abuse potential of drugs use measures of subjective effects. These studies assume that if the subjective effects of an unknown drug are similar to those of a known drug of abuse, it too has abuse potential. The results of the present study indicate that subjective effects may not always predict the reinforcing properties of a drug.

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