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The Discriminative Stimulus and Subjective Effects of Phenylpropanolamine, Mazindol and *d*-Amphetamine in Humans

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CHAIT, L. D., E. H. UHLENHUTH AND C. E. JOHANSON. *The discriminative stimulus and subjective effects of phenylpropanolamine, mazindol and d-amphetamine in humans.* PHARMACOL BIOCHEM BEHAV 24(6) 1665–1672, 1986.—The discriminative stimulus (DS) and subjective effects of two anorectic drugs, phenylpropanolamine (PPA) and mazindol (MAZ), were studied in a group of normal, healthy adults trained to discriminate between placebo and 10 mg *d*-amphetamine (AMP). Of 20 subjects who underwent discrimination training, 12 (discriminators) reliably learned the AMP-placebo discrimination. Each discriminator was tested with two doses of PPA (25 and 75 mg) and two doses of MAZ (0.5 and 2.0 mg) to determine whether the DS effects of these drugs would substitute for those of AMP. The high dose of each drug produced primarily (~80%) drug-appropriate responding, whereas the low dose of each drug resulted in primarily placebo-appropriate responding. The subjective effects of PPA were a biphasic function of dose, with 25 mg producing mild sedative-like effects and 75 mg producing stimulant-like effects similar to, but weaker than, those obtained with AMP. MAZ, on the other hand, produced only a few changes in mood (increased anxiety, decreased hunger). Thus, although both PPA and MAZ substituted for AMP in terms of discrimination responding, only PPA produced AMP-like subjective effects. These results provide evidence for a dissociation between the subjective effects (as measured by self-report questionnaires) and the DS effects of drugs in humans.

Humans Drug discrimination Stimulus effects Subjective effects Mood Stimulants
Anorectics Amphetamine Phenylpropanolamine Mazindol

ALTHOUGH the drug discrimination paradigm has been widely accepted as a useful tool for studying the CNS properties of drugs in laboratory animals [7,8], until recently there has been little effort directed towards developing an analogous procedure for studying the discriminative stimulus (DS) properties of drugs directly in humans [3]. At present, the underlying basis for drug discrimination responding (i.e., the particular effects of drugs that come to control differential responding) is poorly understood, and drug discrimination studies with humans could greatly enhance our understanding of the process [21].

We have developed a general experimental paradigm for studying the DS properties of drugs in human subjects. The procedure is analogous to those commonly used in the animal laboratory, but as well allows for the concurrent measurement of subjective drug effects by more traditional means (written questionnaires). To date, we have been primarily interested in studying the DS and subjective effects of anorectic drugs in subjects trained to discriminate *d*-amphetamine (AMP) from placebo [5,6]. The present study examines the effects of two additional anorectics, phenylpropanolamine (PPA) and mazindol (MAZ).

PPA is a commonly used, over-the-counter appetite suppressant, structurally related to amphetamine. Human studies have shown little evidence of CNS stimulation after therapeutic doses (25–75 mg) of PPA [26], and reliable subjective effects have not been reported after PPA, even with doses as high as 80 mg [20,25]. Drug discrimination studies in laboratory animals have produced mixed results. In studies with both pigeons and rhesus monkeys trained to discriminate AMP from saline, 25 to 50% of the animals made primarily saline-appropriate responses after PPA, up to doses that produced non-specific behavioral effects [24,28]. In rats, PPA produced intermediate levels of AMP-appropriate responding [17].

MAZ is an imidazoisoindole compound structurally unrelated to amphetamine. The subjective effects of MAZ have not been thoroughly studied in humans but the drug appar-

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ently does not produce amphetamine-like stimulant or euphoric effects [4, 9, 11, 12]. However, in both pigeons and rhesus monkeys trained to discriminate AMP from vehicle, MAZ substituted for AMP [24,28], indicating that MAZ and AMP possess similar DS properties.

In general, drugs that possess similar DS properties (as determined from drug discrimination studies in laboratory animals) also produce similar subjective effects in humans [1,21]. Although the subjective effects of PPA and MAZ have not been systematically studied, neither drug appears to produce a profile of subjective effects like that of AMP. Therefore, the observation that each of these drugs can substitute for AMP in at least some species of laboratory animals represents an apparent exception to the above generalization. The present study was designed to help resolve these disparate results by concurrently measuring the DS and subjective effects of PPA and MAZ in humans trained to discriminate AMP from placebo.

METHOD

Subjects

Eight males and twelve females participated in the study. They were selected from a group of healthy adults, aged 21–35, recruited from the local university community via newspaper or bulletin board advertisements. Prior to participation potential subjects underwent a physical examination and psychiatric interview. Volunteers with histories of drug abuse or dependence, or significant psychiatric or other medical disorders were not accepted. Subjects were paid a base wage at the end of each phase of the study. Informed consent was obtained.

General Procedure

Subjects were told that their job was to learn to discriminate between two different drugs, "Drug A" and "Drug B," based on the effects produced by each. They were told that they could receive either appetite suppressants, sedatives or placebos. They were further informed that Drug A and Drug B would be different types. Subjects were not told that they would be learning to discriminate an active drug from placebo. Subjects were given no other information as to what specific drugs they might receive, or what types of effects to expect or use as "cues."

Subjects reported to the laboratory between 9 and 11 a.m. three days per week throughout the 8-week study. They were allowed to come in on any three weekdays of their choice. Upon arrival, subjects completed three subjective effects questionnaires (see below). After filling these out (which took about 5 min) subjects received a capsule which they ingested under observation by the experimenter. Subjects were then free to leave for the day, taking three additional sets of questionnaires to fill out 1, 3 and 6 hr later. They were instructed to leave the forms blank if they did not fill them out within 15 min of the scheduled time.

Subjective Effects Questionnaires

Three different types of questionnaires were used to assess subjects' mood states. (1) Profile of Mood States (POMS). An experimental version of the POMS [18] was used consisting of 72 adjectives commonly used 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 eight clusters (scales) of items that have been separated empirically using factor analysis (Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, Elation). The value of each scale was determined by adding the numbers checked for each adjective in the cluster and dividing the total by the number of adjectives in that cluster. Two additional (unvalidated) scales (Arousal, Positive Mood) were derived from the other scales as follows: Arousal= (Anxiety + Vigor) − (Fatigue + Confusion); Positive Mood = Elation − Depression.

(2) Addiction Research Center Inventory (ARCI). The ARCI is a true-false questionnaire with empirically-derived scales that are sensitive to the effects of a variety of classes of abused drugs [16]. A short form of the inventory was used consisting of five scales with a total of 49 items [19]. The five scales were the MBG, a general measure of drug-induced euphoria; the A, a measure specific for dose-related effects of *d*-amphetamine; the BG, an amphetamine scale consisting mainly of items relating to intellectual efficiency and energy; the PCAG, a measure of sedation; and the LSD, a measure of dysphoria and somatic symptoms.

(3) Visual analog scales (VAS). This form has six horizontal 100-mm lines, each labelled with an adjective ("stimulated," "high," "anxious," "sedated," "down," and "hungry"). The left ends of the lines are labelled "NOT AT ALL" and the right ends "EXTREMELY." Subjects were instructed to place a mark on each line indicating how they felt at the moment.

Experimental Design

The study was divided into three distinct phases:

(1) Sampling/Training phase (Days 1–4). On the first and third days all subjects received Drug A, and it was identified to them as such at the time of ingestion. All subjects received Drug B on the second and fourth days, and it was also identified to them as such. For half the subjects, Drug A was placebo and Drug B was 10 mg AMP. The assignments were reversed for the other subjects.

On these four days subjects completed an additional questionnaire at hr 6. This questionnaire asked subjects to (1) label the drug they had received that day as either placebo, depressant or stimulant (based on the effects they attributed to the capsule), (2) rate their general level of activity during the day since ingesting the capsule (on a 100-mm visual analog scale, from 0="not active at all" to 100="extremely active"), and (3) rate their liking for the effects of the capsule (on a bipolar 100-mm visual analog scale, with 0="disliked a lot," 50="neutral," and 100="liked a lot").

(2) Training/Assessment phase (Days 5–11). The purpose of this phase of the study was to establish that the subjects had reliably learned the discrimination, and to provide additional exposures to the drugs for subjects who did not adequately learn the discrimination after the first four (sampling) days. On these seven (training) days, subjects received Drug A three times and Drug B four times (or vice versa), in a mixed order, with the restriction that the same drug was not scheduled more than two days in succession. The order was different for different subjects. On these days, subjects were *not* told which drug they received when they ingested the capsule. At 1, 3 and 6 hr after capsule ingestion, in addition to the questionnaires described above, subjects filled out a form on which they identified (as Drug A or Drug B) the

drug they believed they had received, and indicated on a 100-mm visual analog scale how certain they were that their identification was correct [0="NO IDEA (JUST GUESSING)"; 100="POSITIVE (ABSOLUTELY SURE)"]. Subjects were told that they were free to change their identification from hour to hour, based on what they believed at the time. There were no consequences attached to the 1- and 3-hr identifications, but the 6-hr identification was differentially reinforced as follows: After subjects filled out the final (6-hr) set of forms, they telephoned the experimenter, identified themselves, and reported their final drug identification (Drug A or Drug B). If their response was correct, they were told so and received $3.00 when they returned to the laboratory for the next session. If their response was incorrect, they were so informed and received no money at the next session. We decided that a subject had learned the discrimination if the 6-hr identification was correct either 5 days in a row or on 6 of the 7 training days. Subjects who met one of these criteria then entered the test phase. Subjects who did not were paid for their participation to that point and were debriefed. Subjects who met the criterion of 5 correct days in a row immediately started the test phase. Subjects were informed of the training criteria at the beginning of the study.

(3) Test phase (Days 12–25). The purpose of the test phase was to determine whether the discriminative stimulus properties of PPA and MAZ would substitute for those of AMP. The test phase consisted of eight "test days" intermixed with six additional training days. On test days subjects received one of the following treatments: 25 or 75 mg PPA, or 0.5 or 2.0 mg MAZ. Test days were exactly the same as training days except that subjects were not informed when they telephoned whether or not their response was correct—they were simply told that it was a "test day" and that they would receive $3.00 when they came in for the next session. Thus, on test days both responses were equally reinforced, and subjects received no feedback as to which drug they had received. Subjects were not told the purpose of test days, nor did they know when test days were scheduled until after they had reported their final (6-hr) drug identification. Each subject received each of the four test treatments in a mixed order twice, once during the first half and once during the second half of the test phase. The order of treatments varied across subjects.

The six additional training days were interspersed over the course of the test phase in order to determine whether (and attempt to ensure that) subjects maintained the discrimination. These training days were exactly like the training days during the training/assessment phase—subjects received either Drug A or Drug B, were told whether their response was correct, and were reinforced accordingly. Subjects received placebo three times and 10 mg AMP three times (in mixed order) on these training days. The training days were interspersed among the test days in an unsystematic fashion, with the restriction that no more than two test or training days occurred in succession. The order varied across subjects.

Debriefing. After completing the study, subjects returned to the laboratory for a debriefing session. After the subjects filled out several personality questionnaires the experimenter questioned the subjects about their reactions to the study, described the exact nature and purpose of the study, and answered any remaining questions.

Drugs. d-Amphetamine sulfate (Dexedrine), phenylpropanolamine hydrochloride (kindly provided by Thompson Medical) and mazindol (Sanorex) were administered in 00-sized opaque gelatin capsules. The color of the capsules varied across subjects, but each subject always received the same color capsule throughout the experiment. Drug capsules contained the drug tablets plus dextrose powder; placebo capsules contained dextrose only. Placebo and drug capsules were identical in appearance.

TABLE 1

DRUG LABELLING DURING THE SAMPLING/TRAINING PHASE

	Days 1, 2		Days 3,4	
	P	AMP	P	AMP
Placebo	5	3	7	2
Stimulant	4	8	1	10
Depressant	3	1	4	0

Each value is the number of subjects who labelled placebo (P) and 10 mg *d*-amphetamine (AMP) as indicated.

Data analysis. For each dependent variable, individual subject means were the basic unit of analysis. Univariate analysis of variance for repeated measures (BMDP P2V; [10]) was used to analyze each continuous variable. Subjective effects were analyzed with two-way ANOVA's [Drug (AMP vs. placebo) or Dose × Hour (0, 1, 3, 6)]. A drug effect was considered significant if either a main effect of Drug or a Drug × Hour interaction was obtained. Other dependent variables (e.g., certainty ratings) were analyzed in the same manner. When overall F values were significant, orthogonal polynomial trend analysis was used to characterize trends across hour or dose of PPA and MAZ (including placebo as 0 mg). F values were considered significant for $p \leq 0.05$, with adjustments of within-factors degrees of freedom (Huynh-Feldt) to protect against violations of symmetry [10].

Ratings of drug liking and general activity level were analyzed with two-way ANOVA's [Drug (AMP vs. placebo) × Day (first or second administration during the sampling/training phase)]. Certainty ratings after the test drugs (PPA or MAZ) were compared with those after the training drugs (placebo and AMP) with two-way ANOVA's [Drug (PPA or MAZ dose vs. training drugs) × Hour]. For this analysis, certainty ratings on placebo and AMP days during the test phase were pooled, since no significant difference between these ratings was obtained. Since there were no "correct" or "incorrect" drug-identification responses after PPA and MAZ all certainty ratings after placebo and AMP were used in this analysis, not only those that were made on occasions when the drug-identification response was correct.

RESULTS

Twelve of the twenty subjects met one of the training criteria, and will be referred to as discriminators. Results from the other eight subjects (nondiscriminators) will not be presented here; discriminators and nondiscriminators will be compared in a separate report.

Sampling/Training Phase

As shown in Table 1, most subjects labelled AMP as a stimulant; subjects were less successful in correctly labelling

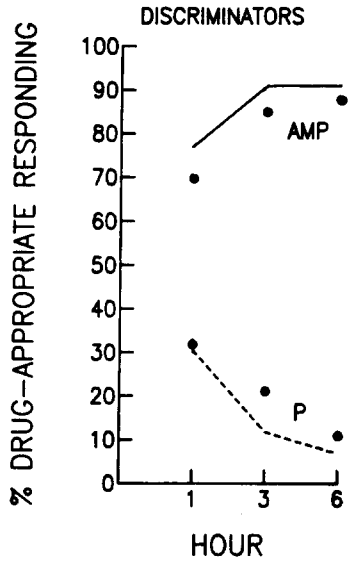

FIG. 1. Percent drug-appropriate responding as a function of hour after ingestion of placebo (P) or 10 mg *d*-amphetamine (AMP). Each point represents the group mean of individual subject mean percentages. A drug-appropriate response means that a subject made the drug identification response (Drug A or Drug B) which corresponded to AMP. The closed circles show the corresponding values obtained from the discriminators during the later test phase of the study.

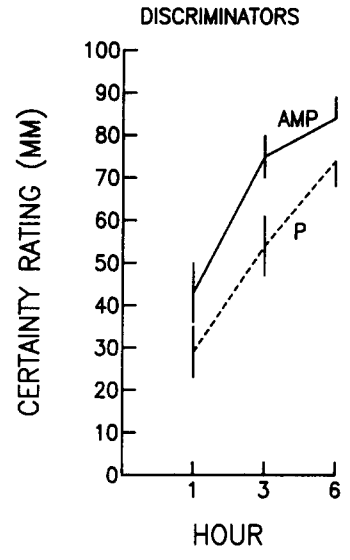

FIG. 2. Certainty ratings of discriminators as a function of hour after drug ingestion. Each point represents the group mean (±1 SE) of individual subject mean ratings.

placebo as placebo, especially on the first occasion. Ratings of drug liking increased after AMP (main Drug effect, $F(1,11)=13.89$, $p<0.005$). Mean ratings after placebo and AMP were 42.3 and 65.0, respectively. AMP also increased ratings of general activity level (Drug effect, $F(1,11)=11.50$, $p<0.01$). Mean ratings after placebo and AMP were 46.9 and 63.1, respectively.

During the sampling/training phase, AMP produced significant increases on the Vigor, Friendliness, Elation, Arousal and Positive Mood subscales of the POMS, the BG, MBG and A scales of the ARCI, and the "stimulated" and "high" visual analog scales. AMP decreased scores for Fatigue (POMS) and PCAG (ARCI).

Training/Assessment Phase

On training days discriminators made incorrect hr-6 drug identifications on 10% of occasions (Fig. 1). Subjects could discriminate AMP from placebo with about 75% accuracy by 1 hr after drug ingestion, and their discrimination accuracy increased as a function of hour. When subjects' drug identification responses were correct, their ratings of how certain they were that their responses were correct increased as a function of hour (Fig. 2) (Hour effect, $F(2,22)=48.97$, $p<0.0001$; linear component, $p<0.0001$; quadratic component, $p<0.005$). A significant Drug effect, $F(1,11)=8.76$, $p<0.02$, indicates that subjects were more certain that they were correct after AMP than after placebo.

The subjective effects of AMP during the training/assessment phase were qualitatively similar to those obtained during the sampling/training phase. On the POMS, AMP significantly increased scores for Anxiety, Vigor, Friendliness, Elation, Arousal and Positive Mood, and decreased scores for Fatigue. On the ARCI, AMP increased scores for BG, MBG and A, and decreased PCAG scores. On the VAS, AMP increased ratings of "stimulated," "high" and "anxious," and decreased ratings of "down" and "sedated." Peak effects of AMP on most scales were observed 3 hr after ingestion, and the effects began to dissipate by hr 6.

Test Phase

One subject made incorrect hr-6 drug identifications on 5 of the 6 training days during the test phase. Because this indicated that the subject had apparently lost the ability to discriminate between placebo and AMP, his drug identification and certainty ratings from the test phase were excluded from analysis. Another subject withdrew from the study before finishing the test phase. Because she had received placebo, AMP, and each dose of one of the test drugs (MAZ) before withdrawing, her data were retained.

On training days during the test phase of the study, subjects made incorrect hr-6 drug identifications on 11% of occasions (3 times after placebo and 4 times after AMP). Percent drug-appropriate responding (DAR) did not differ substantially from the corresponding values obtained during the training/assessment phase from those same subjects (closed circles in Fig. 1). Certainty ratings as a function of hour after placebo and AMP ingestion also were essentially unchanged, although ratings after AMP and placebo were not significantly different during the test phase as they were during the training/assessment phase (Fig. 2). Thus, there was little indication of tolerance to the DS effects of AMP over the course of the study.

There was also little evidence for tolerance to the subjective effects of AMP. During the test phase, AMP produced significant effects on Vigor, Fatigue, Friendliness, Elation, Arousal and Positive Mood (POMS), PCAG, BG, MBG and A (ARCI), and "stimulated," "high" and "down" (VAS) (Table 2). However, in general the peak effect of AMP (relative to placebo) on these scales was about 30% less during

TABLE 2
SIGNIFICANT SUBJECTIVE EFFECTS DURING TEST PHASE

Scale	AMP 10 mg	PPA 75 mg	MAZ 2.0 mg
POMS			
Anxiety			↑
Vigor	↑	↑	
Fatigue	↓	↓	
Friendliness	↑		
Elation	↑		
Arousal	↑	↑	
Positive Mood	↑		
ARCI			
PCAG	↓		
BG	↑		
LSD		↑	↑
MBG	↑		
A	↑	↑	
VAS			
Stimulated	↑	↑	
High	↑	↑	
Anxious		↑	↑
Down	↓		
Hungry			↓

Arrows show the overall direction of change, relative to placebo, of scores on each of the subjective effects scales significantly affected by the dose of drug shown.

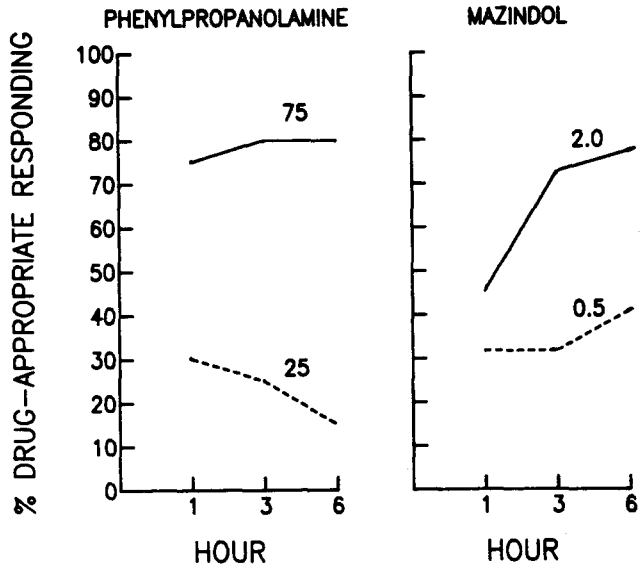

FIG. 3. Group mean percent DAR as a function of hour after ingestion of phenylpropanolamine and mazindol. Numbers refer to dose, in mg.

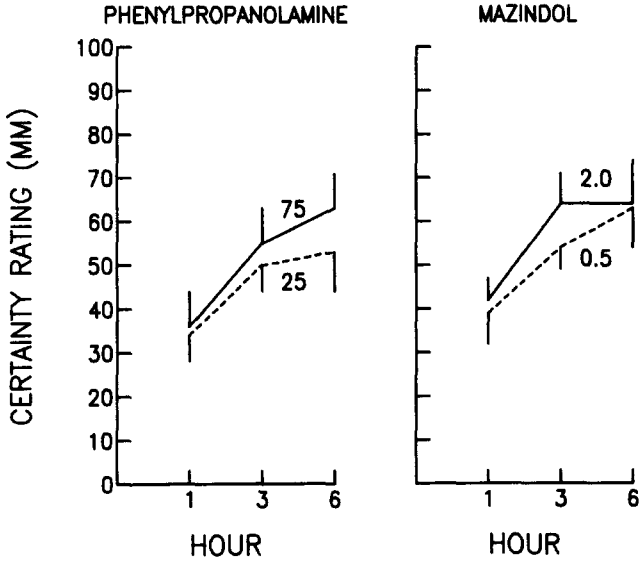

FIG. 4. Group mean (±SE) certainty ratings as a function of hour after ingestion of phenylpropanolamine and mazindol.

the test phase of the study than was obtained from the same subjects during the training/assessment phase.

Figure 3 shows mean % DAR as a function of hour after ingestion of each of the test drugs. The DS effects of both PPA and MAZ were dose-dependent, with the low dose of each drug resulting in primarily placebo-appropriate responding, and the high dose of each drug resulting in primarily drug-appropriate responding. The DS effects of PPA did not vary to any significant extent as a function of hour, but the onset of DS effects after 2.0 mg MAZ was delayed until 3 hr after ingestion.

Figure 4 shows subjects' ratings of how certain they were that their drug identifications were correct after PPA and MAZ. Certainty ratings increased as a function of hour for PPA, $F(2,16)=6.89$, $p<0.02$, and MAZ, $F(2,20)=7.97$, $p<0.01$, but did not vary significantly as a function of dose for either drug. Certainty ratings after both doses of MAZ and after 75 mg PPA did not differ significantly from ratings after the training drugs. Certainty ratings after 25 mg PPA, however, were significantly lower than those obtained after the training drugs, $F(1,8)=6.82$, $p<0.05$. Mean certainty ratings (across hour) for 25 mg PPA and the training drugs were 45.5 and 58.7, respectively.

MAZ produced significant effects on four subjective effects scales (Table 2). MAZ increased scores on the Anxiety scale of the POMS, the LSD scale of the ARCI and the "anxious" visual analog scale, and decreased ratings of "hungry." The subjective effects of MAZ were a linear function of dose. Scores reached a peak at 3 hr after ingestion and had not begun to dissipate by hr 6.

PPA produced significant subjective effects on 13 scales. Orthogonal polynomial trend analysis revealed that for most of these scales the effects of PPA were a quadratic (biphasic) function of dose. For this reason, the effects of each dose of PPA were separately compared with placebo. On the POMS, 25 mg PPA produced significant decreases, relative to placebo, for Vigor, Friendliness, Elation, Arousal and Positive Mood, and an increase for Fatigue. On the ARCI, LSD

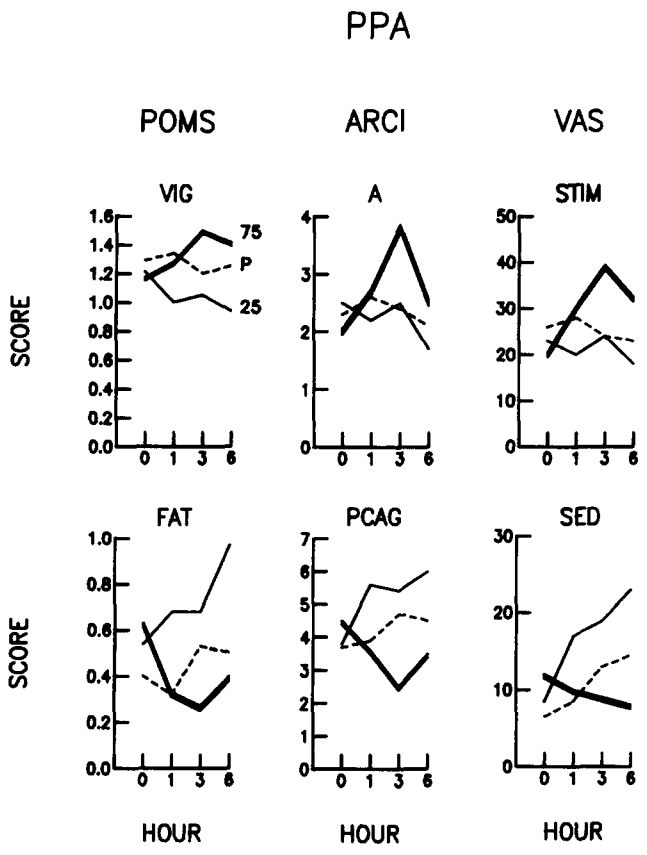

FIG. 5. Effects of phenylpropanolamine (25 and 75 mg) and placebo (P) on six subjective effects scales, as a function of hour after drug ingestion. Each point is the mean of data from 11 subjects.

scores were significantly increased by 25 mg PPA, and on the VAS, "sedated" scores were increased. The peak effect on most of these scales occurred at hr 6. In contrast, the high dose of PPA (75 mg) produced the following significant effects: increased Vigor, Arousal, LSD, A, "stimulated," "high," and "anxious" scores, and decreased Fatigue scores (Table 2). Peak subjective effects of 75 mg PPA occurred at hr 3. In summary, the high dose of PPA produced stimulant-like subjective effects whereas the low dose appeared to produce mild sedative-like effects of long duration. Figure 5 shows subjective effects after PPA from three "stimulant" scales (one from each mood questionnaire) and from three "sedative" scales (again, one from each questionnaire).

Debriefing

At the end of the study, 8 of the 12 discriminators correctly identified placebo as placebo. All of the discriminators identified AMP as a stimulant. Nine of 12 discriminators reported liking AMP more than placebo. Only two discriminators believed that they had received a drug other than "Drug A" or "Drug B" (i.e., a drug producing qualitatively different effects than A or B) during the course of the study.

The primary "cue" that subjects used to make the discrimination varied across subjects. Subjects most commonly reported stimulant effects (increased energy level, alertness, activity) (6 subjects) and decreased hunger (2 subjects) as the primary cue. Effects attributed to placebo were reported by five subjects; the most common placebo effect was increased fatigue.

DISCUSSION

The present findings are consistent with previous ones [5,6], demonstrating that only about half of the subjects studied learn to discriminate reliably between 10 mg AMP and placebo under the current procedure. Self-ratings of drug liking and general activity level, drug labelling and subjective effects after AMP were very similar to those obtained previously [5,6].

The DS effects of both PPA and MAZ were dose-dependent, with the low dose of each drug producing primarily placebo-appropriate responding and the high dose primarily drug-appropriate responding. The ability of MAZ to substitute for AMP in the present study is in agreement with findings obtained with pigeons and monkeys [24,28]. The degree of similarity between the DS effects of PPA and those of AMP remains unclear, and may be species specific. Studies from our laboratory have shown PPA to substitute for AMP in 75% of pigeons tested, but in only 50% of rhesus monkeys [24,28]. In rats, PPA was reported to produce a maximum of about 50% AMP-appropriate responding [17]. In the present study, 75 mg PPA resulted in about 80% AMP-appropriate responding. Differences among these studies in the effective training dose of AMP could also possibly account for the reported differences. It is interesting to note that certainty ratings after 25 mg PPA, which produced primarily placebo-appropriate responding, were lower than certainty ratings reported by subjects after the training drugs. This finding suggests that subjects were less certain about what they had received after 25 mg PPA, and may be due to the sedative-like effects produced by this dose of PPA.

Because of the assumed close relationship between DS effects and subjective effects (as determined with self-report mood questionnaires), we compared the subjective effects reported after 75 mg PPA and 2.0 mg MAZ (doses which substituted for AMP) with the subjective effects produced by the training dose of AMP (Table 2). For each of the three drugs there was a close relationship between the onset of DS and subjective effects. However, as Table 2 indicates, there was not a single subjective effects scale that was significantly changed by all three drugs. In fact, none of the four scales changed by MAZ were changed by AMP during the test phase. (It should be pointed out, however, that AMP did increase POMS Anxiety and VAS "anxious" scores significantly during the earlier training phase.) There were six scales (mostly indicating stimulant-like effects) that were affected by both 75 mg PPA and AMP. Thus, it is not clear from this analysis what specific subjective effects of PPA and MAZ may have served as discriminative stimuli for AMP-appropriate responding. It is possible that all three drugs might have had similar effects on a particular mood state not measured in the present study. Alternatively, it is possible that subjects based their drug identification responding on a "Drug" vs. "No Drug" discrimination. Although this latter possibility cannot be ruled out, we feel it is unlikely, since 25 mg PPA in the present study, and 10 mg diazepam in a previous study [5] produced significant subjective effects, yet did not substitute for AMP.

The profile of subjective effects obtained after PPA

(sedative-like effects after the low dose and stimulant-like effects after the high dose) was unexpected, since there is little evidence of significant subjective effects, particularly sedative-like effects, after therapeutic doses of PPA [20,25]. Nevertheless, the consistency of these subjective effects across three qualitatively different mood questionnaires would argue strongly against these effects being due to chance. The subjective effects produced by 75 mg PPA were somewhat similar to those produced by 10 mg AMP, in that both drugs increased scores on the Vigor, Arousal, "stimulated," "high" and A (amphetamine) scales, and decreased scores on the Fatigue scale. However, AMP increased scores on the Elation, Positive Mood and MBG scales (all of which indicate a euphoric effect) whereas PPA did not. These differences in the subjective effects of PPA and AMP may explain why AMP is self-administered by laboratory animals and possesses high dependence potential [13], whereas PPA is not self-administered by laboratory animals [15,28] or humans [4], and is of questionable dependence potential [2,22]. However, in view of the present findings, and the possibility that PPA may possess greater dependence potential at higher doses, or in combination with other legal stimulants [17,22], the subjective effects of PPA in humans should be more extensively examined.

The present study further demonstrates the validity and utility of conducting drug discrimination studies with human subjects. With this procedure, some drugs (phenmetrazine, mazindol, phenylpropanolamine) have reliably substituted for AMP whereas others (diazepam, fenfluramine) have not [5,6]. Thus, the procedure seems capable of demonstrating drug-class (qualitative) specificity, as do the drug discrimination procedures used with other species [21]. The present study and others have shown complex relationships among the discriminative stimulus, subjective, and reinforcing effects of drugs. Given this complexity, and the difficulties inherent in generalizing across species, it seems desirable to continue to study the behavioral effects of drugs in humans whenever feasible.

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