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Phenylpropanolamine: reinforcing and subjective effects in normal human volunteers

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Abstract. The reinforcing and subjective effects of phenylpropanolamine (PPA, 25 and 75 mg, PO) were compared with those of *d*-amphetamine (AMP, 5 mg) in a group of normal, healthy adults (eight males, nine females) with no history of drug abuse. A discrete-trial choice procedure was used in which subjects first sampled placebo and a dose of one of the drugs. Subjects were then allowed to choose between self-administration of drug or placebo on three separate occasions. The relative frequency with which active drug was chosen over placebo was used as the primary index of the drug's reinforcing efficacy. Subjective effects were measured with the Profile of Mood States, a short version of the Addiction Research Center Inventory and a series of visual analog scales. Ratings of drug liking, drug labelling, general activity level and strength of drug preference were also obtained. As expected, AMP was chosen significantly more often than expected by chance (69% of occasions). AMP also increased ratings of drug liking, preference strength, and activity level, and produced a profile of subjective effects consistent with its well-established stimulant and euphorigenic properties. The low dose of PPA was without effect on most measures. PPA 75 mg was chosen significantly less often than expected by chance (39% of occasions). This dose of PPA was most frequently labelled as a stimulant, and produced significant increases on ratings of Anxiety and "stimulated," and decreases on ratings of "sedated" and "hungry." Unlike AMP, PPA did not affect ratings of drug liking or mood scales reflecting euphoria. In sum, these results indicate that PPA does not possess AMP-like dependence potential.

Key words: Humans – Drug abuse – Self-administration – Subjective effects – Stimulants – Anorectics – Dependence potential – Phenylpropanolamine – Amphetamine – Mood

Phenylpropanolamine (PPA), a structural analog of the amphetamines, is a widely used drug, found in many prescription and over-the-counter diet aids and cold medications. Both the safety and efficacy of PPA, particularly as an anorectic, have been the subject of considerable debate in recent years (Morgan et al. 1985). One aspect of the safety issue has concerned the dependence potential of PPA. The drug is not self-administered by laboratory animals (Griffiths et al. 1978; Woolverton et al. 1986; Lamb et al. 1987) and there are very few documented reports of human abuse of PPA despite its wide availability (Griffiths et al. 1980). On the other hand, on the illicit market PPA (either alone or in combinations with caffeine and ephedrine) has been frequently misrepresented as amphetamine (Lake and Quirk 1984; Pentel 1984). PPA has also been sold through the mail as a "legal stimulant" (Pentel 1984). Thus, it is unclear to what extent PPA is abused in its own right (Blum 1981; Pentel 1984).

A previous study from this laboratory examined the subjective and reinforcing effects of PPA (12.5–50 mg) in normal volunteers (Chait et al. 1987), but few significant effects of PPA were obtained in that study. The present study was a systematic replication of that study which incorporated several methodological changes designed to produce more conclusive findings. The major changes made were 1) use of a larger number of subjects, 2) extension of the upper dose range, 3) use of a pure dosage form of PPA, rather than an over-the-counter preparation, and 4) use of a positive control (*d*-amphetamine, AMP) with which to compare the effects of PPA in the same group of subjects. The reinforcing properties of PPA and AMP were measured with a discrete trial choice procedure, which allows subjects to choose on several occasions between self-administration of active drug or placebo. Previous studies using this experimental paradigm have demonstrated that normal (non-drug-abusing) human volunteers will preferentially self-administer *d*-amphetamine and other amphetamine-like anorectics, relative to placebo (Johanson et al. 1983; Chait et al. 1987).

Materials and methods

Subjects. Subjects were 17 normal, healthy adults, aged 21–35 (eight males, nine females). They were recruited by advertisements in the local university newspaper, notices posted on campus, and word-of-mouth referrals. Prior to acceptance, subjects were interviewed to explain the nature of the study and to ascertain their medical, psychiatric and drug use histories. Subjects were accepted if they were considered normal and healthy on the basis of this interview and a subsequent physical examination. Most subjects reported some experience with psychoactive drugs but none had a history of any type of drug abuse or dependence (other than tobacco dependence).

Subjects signed a consent form prior to participation which outlined the study in detail and indicated the com-

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mon side effects of the drugs they might be given. Subjects were not told what specific drugs they would receive; they were told only that they could receive either over-the-counter or prescription tranquilizers and anorectics, or placebo, and that the doses given would be within the normal daily therapeutic range. Each subject agreed not to take other drugs, except their usual amounts of coffee or tobacco, for at least 12 h before and 6 h after taking a capsule. Except for the specific drug ingested, subjects were completely informed of all other procedural details as outlined below. Subjects were fully debriefed and paid for their participation at the end of the study.

Procedure. The study consisted of three experiments. Each experiment lasted 2 weeks (7 daily sessions). In each experiment, one dose of drug was compared to placebo. Doses tested were 25 and 75 mg PPA and 5 mg AMP. Each subject participated in all three experiments. The order in which experiments were scheduled was counterbalanced across subjects. Drug administration was double-blind.

Subjects reported to the laboratory between 9 and 10 A.M. 4 days during the 1st week and 3 days during the 2nd week of each experiment. The first 4 days of each experiment were *sampling days*. On these days, when subjects arrived, they filled out subjective effects questionnaires (see below) and received a capsule for immediate ingestion. Half of the subjects received active drug on days 1 and 3 and placebo on days 2 and 4. The order was reversed for the other subjects. For each subject, active drug and placebo were contained in capsules of a consistent and distinctive color in order to facilitate identification. Capsule colors were counterbalanced across subjects. Each subject was instructed during the initial four sessions to note the capsule colors and to try to associate each of the two colors with the effects of the substances contained therein. After ingesting the capsule under observation of the experimenter, subjects were free to leave the laboratory and resume their normal activities. They took with them five additional sets of subjective effects questionnaires which they were instructed to fill out 1, 3, 6, 9 and 12 h later. At 12 h subjects filled out an additional questionnaire, indicating their liking for the effects of the capsule (on a 100-mm bipolar visual analog scale, labelled "disliked a lot" at the left end and "liked a lot" at the right end), what type of drug they believed they received (stimulant, tranquilizer or placebo), and how active they had been during the day since taking the capsule (on a 100-mm visual analog scale, labelled "not active at all" at the left end and "extremely active" at the right end).

The last 3 days of each experiment were *choice days*. On these days the procedure was identical in every respect to that of sampling days except that subjects were presented with both colored capsules and were given a choice of which capsule to ingest. The number of times active drug was chosen over placebo (drug choice) was taken as the primary indicator of the drug's reinforcing efficacy. As an adjunct measure of reinforcing efficacy, subjects indicated how strong their preference was at that moment for the capsule they were about to choose. This measure of *preference strength* was obtained just before subjects made their choice, on a 100-mm visual analog scale labelled "I have *no* preference for this color capsule over the other one" (left end) and "I have a *very strong* preference for this color capsule over the other one" (right end).

Subjective effects questionnaires. The three subjective effects questionnaires used were an experimental version of the Profile of Mood States (POMS), a short form of the Addiction Research Center Inventory (ARCI) and a series of visual analog scales (VAS). This version of the POMS (McNair et al. 1971) consists 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 using factor analysis (Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, Elation). The value of each scale is 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 are derived from the other scales as follows: Arousal = (Anxiety + Vigor) − (Fatigue + Confusion), Positive Mood = Elation − Depression.

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 (Haertzen 1974). A short form of the inventory was used consisting of five scales with a total of 49 items (Martin et al. 1971). The five scales were the MBG, a measure of drug-induced euphoria; the A, a measure specific for dose-related effects of amphetamine; the BG, a stimulant 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.

The VAS consists of a series of 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.

Drugs. The drugs used were racemic phenylpropanolamine (*d,l*-norephedrine) hydrochloride (25 and 50 mg immediate-release tablets, kindly provided by Thompson Medical Company) and *d*-amphetamine sulfate (5 mg Dexedrine tablets). The tablets were dispensed in opaque hard gelatin capsules (size 00) which were filled with dextrose powder. Placebo capsules contained dextrose powder only.

Data analysis. Choice results were analyzed by examining the distribution of subjects across the four choice categories (0–3 drug choices) with log-linear analysis (SPSSX User's Guide 1983). A drug that served as a reinforcer would by definition shift the choice distribution to the right (i.e., there would be more 2- and 3-time drug choosers than 0- and 1-time drug choosers). Conversely, a drug that served as a punisher would shift the distribution to the left (more 0- and 1-time than 2- and 3-time choosers). To identify such shifts, two types of contrasts were employed – Helmert and reverse Helmert (SPSSX, p 548). Helmert contrasts compare the level of a factor with the average effects of *subsequent* levels of a factor. In other words, the 0-drug choice category would be contrasted with the average of the 1–3-drug choice categories, the 1-drug choice category would be contrasted with the average of the 2–3-drug choice categories, etc). Reverse Helmert contrasts compare the level of a factor with the average effect of *previous* levels of

a factor (the 1-drug choice category would be contrasted with the 0-drug choice category, the 2-drug choice category would be contrasted with the average of the 0- and 1-drug choice categories, etc.). Contrasts were considered significant for Z values with probabilities less than or equal to 0.05 (two-tailed).

Individual subject means (calculated from data obtained from all 7 days of each experiment) were the basic unit of analysis for the other dependent variables. Two-way univariate analyses of variance for repeated measures (BMDP2V; Dixon 1983) were used to analyze each of the subjective effects scales. Each choice experiment was analyzed separately. The two factors were Drug (Drug dose versus placebo) and Hour (0, 1, 3, 6, 9 and 12). Huynh-Feldt adjustments of within-factors degrees of freedom were used to protect against violations of sphericity assumptions (Dixon 1983, p 379). Student's t-tests and Pearson product-moment correlations were used to analyze other dependent variables (drug liking, preference strength, activity). Statistical significance was defined by P values less than or equal to 0.05.

Results

Drug choice

Table 1 shows the choice distributions for each of the three experiments. Overall, 25 mg PPA, 75 mg PPA and 5 mg AMP were chosen on 57, 39 and 69% of occasions, respectively. Log-linear analysis indicated that the choice distribution for 25 mg PPA did not differ from chance (i.e., there was no shift in the distribution to either the left or the right). A significant preponderance of 0-time choosers of 75 mg PPA indicated that this dose of PPA served as a punisher (i.e., was chosen less often than expected by chance) (Helmert contrast, $Z=2.17$, $P<0.05$). In contrast, 5 mg AMP served as a reinforcer, with a significant preponderance of 3-time choosers (reverse Helmert contrast, $Z=2.06$, $P<0.05$). Subjects' choice of active drug in one experiment did not predict choice of active drug in the other two experiments, as evidenced by nonsignificant correlations between the number of subjects' drug choices in the three experiments.

Drug liking

Subjects' ratings of how much they liked (scores greater than 50) or disliked (scores less than 50) the effects of the capsules were not affected by PPA, relative to placebo. Mean ratings ($\pm$SE) after placebo and PPA were 43.2 ± 3.5 and 52.5 ± 4.0, respectively, in the 25 mg PPA experiment; and 50.7 ± 3.5 and 48.4 ± 5.2, respectively, in the 75 mg PPA experiment. Drug liking ratings were significantly increased by AMP: 45.8 ± 2.1 after placebo, 55.4 ± 2.6 after AMP (paired t-test, $T=2.37$, $P<0.05$). Ratings of drug liking (drug minus placebo differences) were significantly correlated with the number of drug choices in all three experiments ($r=0.71$, $P<0.01$ for 25 mg PPA; $r=0.51$, $P<0.05$ for 75 mg PPA; $r=0.58$, $P<0.05$ for AMP).

Preference strength

On each choice occasion, ratings of preference strength were scored positively if the subject chose active drug and negatively if the subject chose placebo. Each subject's three ratings from each experiment (one from each choice day) were algebraically summed and divided by three to obtain a mean rating of preference strength for each subject for each experiment. The ratings were scored in this manner so that a measure of preference strength could be obtained from every subject for each experiment, since some subjects in each experiment never chose active drug. Obviously, when calculated in this way, preference strength ratings are highly dependent upon drug choice.

Table 1. Drug choice distributions

Experiment	Nr. of drug choices				% choice
	0	1	2	3	
PPA 25	4	4	2	7	57
PPA 75	8	3	1	5	39
AMP 5	2	3	4	8	69

Each value is the number of subjects who chose the designated drug the indicated number of times. Per cent choice is the overall percentage of occasions on which the group chose active drug, calculated from the tabulated values

Individual subject mean preference strength ratings ranged from -98 to $+95$ across the three experiments. Group mean ratings ($\pm$SE) for the three experiments were 11 ± 12, -17 ± 14 and 30 ± 9 for 25 mg PPA, 75 mg PPA and AMP, respectively. Only the value for AMP differed from zero (no preference) (t-test, $T=3.31$, $P<0.005$). The mean preference strength rating for 75 mg PPA was significantly less than that for 25 mg PPA (paired t-test, $T=2.12$, $P<0.05$) and AMP (paired t-test, $T=3.12$, $P<0.01$). Ratings of preference strength were positively correlated with ratings of drug liking (drug minus placebo differences): $r=0.84$, $P<0.01$ for 25 mg PPA; $r=0.68$, $P<0.01$ for 75 mg PPA; $r=0.58$, $P<0.05$ for AMP.

General activity level

AMP significantly increased activity ratings from a mean ($\pm$SE) of 41.5 ± 3.2 after placebo to 58.8 ± 2.2 after AMP (paired t-test, $T=4.72$, $P<0.001$). Neither dose of PPA had any effect on these ratings.

Drug labelling

Table 2 indicates how subjects labelled the capsules in each experiment. Placebo was correctly labelled as placebo by most subjects in the 75 mg PPA and AMP experiments, but was labelled about equally often as placebo, stimulant and tranquilizer in the 25 mg PPA experiment; overall, placebo was correctly labelled by 53% of subjects. The low dose of PPA was labelled equally often as placebo and stimulant, whereas the high dose was labelled most frequently as stimulant. AMP was also most often labelled as stimulant. However, AMP was labelled as placebo by five subjects, whereas 75 mg PPA was labelled as placebo by only one subject.

For both drugs, a relationship was apparent between the manner in which subjects labelled the drug and the number of times they chose the drug. Of the nine subjects who labelled AMP as a stimulant, eight chose it on all

Table 2. Drug labelling

Experiment	Capsule	Label		
		PL	ST	TR
PPA 25	PL	4	5	6
	D	7	7	3
PPA 75	PL	13	0	1
	D	1	10	3
AMP 5	PL	10	0	5
	D	5	9	0

Each value is the number of subjects who labelled placebo (PL) or drug (D) as placebo, stimulant (ST) or tranquilizer (TR). Since subjects occasionally labelled the same dose differently, the data show the label each subject gave most often to each dose of drug or placebo. Data are omitted in cases of tied scores; for example, when a subject labelled a dose equally often as placebo and tranquilizer

three occasions (the other subject chose it twice). Thus, subjects' labelling AMP as a stimulant was predictive of its being chosen. This was not the case for PPA. Of the seven subjects who labelled 25 mg PPA as a stimulant, one chose it on no occasion, and two each chose it on one, two and three occasions. Of the ten subjects who labelled 75 mg PPA as a stimulant, three each chose it on no and one occasion and four chose it on all three occasions. In other words, there was no clear relationship between subjects' labelling of PPA as a stimulant and their choice of PPA. There was such a relationship, however, among the six subjects who labelled either dose of PPA as a tranquilizer (Table 2). Among these six subjects, PPA was chosen on a total of only one occasion out of a possible 18. Labelling of PPA as a tranquilizer was thus highly predictive of its being avoided.

Subjective effects

Two-way analysis of variance (experiment order × hour) of subjective effects scale scores from placebo sessions provided no evidence of change in subjects' mood over the course of the 6-week study. Significant hour effects on ten of the scales, however, indicated that these self-report measures were sensitive to changes in mood over the course of the day in the absence of active drug.

The only significant effects of the low dose of PPA were decreases in POMS Anxiety [drug effect, $F(1,16)=5.36$, $P<0.05$] and ARCI LSD [drug effect, $F(1,16)=4.89$, $P<0.05$] scores. The high dose of PPA increased Anxiety [drug effect, $F(1,16)=8.83$, $P<0.01$] and VAS "stimulated" [drug × hour interaction, $F(5,80)=3.63$, $P<0.02$] scores, while decreasing VAS ratings of "sedated" [drug × hour, $F(5,80)=3.10$, $P<0.05$] and "hungry" [drug × hour, $F(5,80)=3.09$, $P<0.02$]. By far, the greatest number of subjective effects changes were observed after AMP; it produced significant changes on all of the 21 mood scales with the exception of POMS Anxiety and Anger, ARCI LSD, and VAS "anxious."

Figure 1 shows the magnitude and time course of subjective effects for three scales of interest from each mood questionnaire. As mentioned above, consistent changes in mood over the course of the day can be observed after placebo ingestion (dashed lines) on several scales (e.g., Anxiety, Arousal, "stimulated"). The subjective effects of AMP generally peaked at 1–3 h after ingestion, but were still evident on most scales by 6 h, and had still not dissipated by 9 and 12 h on some measures (Positive Mood, "stimulated"). There was no evidence of a dysphoric rebound in mood state ("crash") during the evening hours after

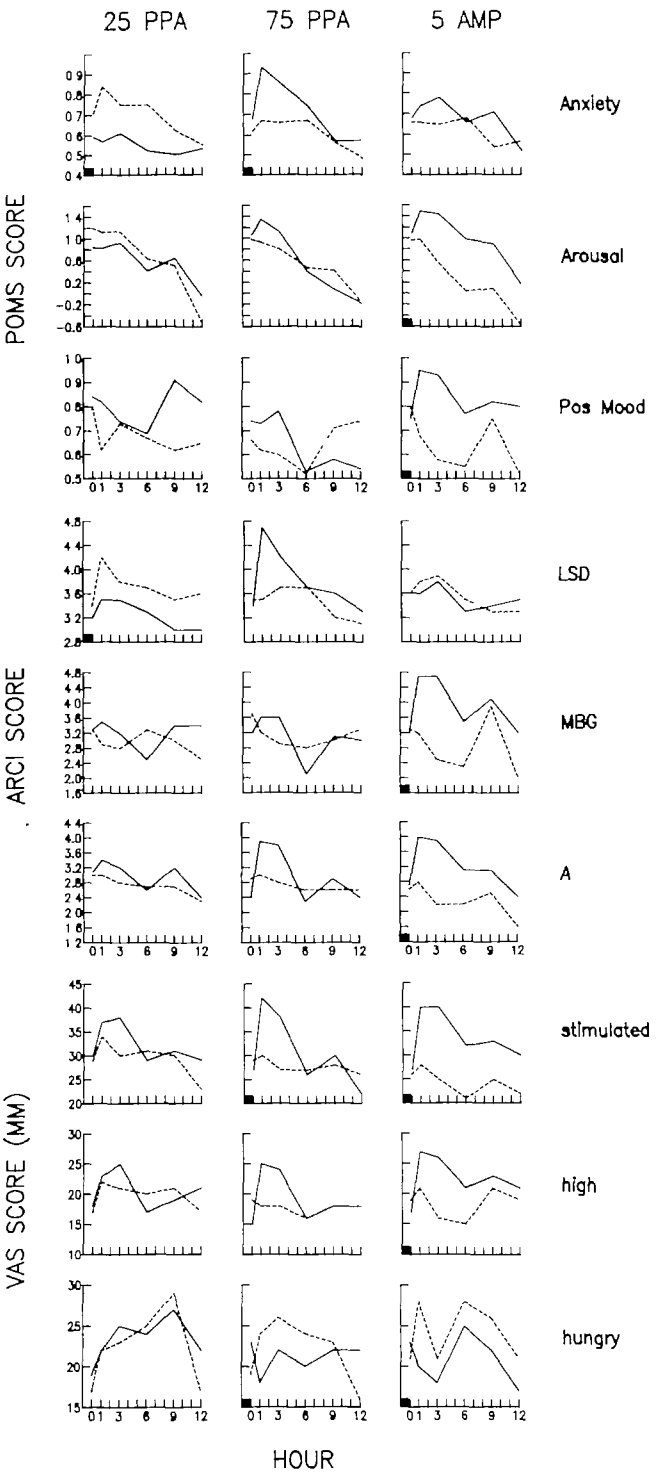

Fig. 1. Group mean subjective effects from each experiment for three scales from each of the mood questionnaires. In each panel, the *solid line* represents active drug, the *dashed line* represents placebo. *Black boxes* at the origin indicate a significant difference between drug and placebo (overall drug effect or drug × hour interaction from two-way ANOVA, $P \leq 0.05$)

AMP, perhaps because many of the acute mood effects had not yet worn off.

In contrast, most subjective effects of 75 mg PPA (Anxiety, "stimulated") were largely gone 6 h after administration. Because of concern that the inclusion of data from 9 and 12 h might have obscured significant effects on other mood scales, we reanalyzed the mood data for both doses of PPA using only hours 0–6. This new analysis yielded no significant effects of 25 mg PPA. For 75 mg PPA, the reanalysis confirmed the effects obtained previously (with the exception of ratings of "hungry") and in addition yielded significant drug × hour interactions on four additional scales: BG, LSD, A and "high" (Fig. 1).

Although 75 mg PPA and 5 mg AMP produced similar effects on some scales, the overall profile of subjective effects produced by the two drugs was clearly different (Fig. 1). For example, the two drugs produced equivalent peak effects on Arousal, A, "stimulated," and "high." However, 75 mg PPA increased ratings of Anxiety and LSD, whereas AMP was without effect on these measures. On the other hand, AMP increased ratings of Positive Mood and MBG, whereas PPA had no effect on these two scales.

The validity of these measures of mood states is further apparent when one compares the general pattern of results from scales of one instrument with those from similar scales of another instrument. For example, one would expect that the A scale of the ARCI and the "stimulated" visual analog scale would both reflect drug-induced stimulant effects; as Fig. 1 indicates, this is the case. The same is true for the MBG scale of the ARCI and the POMS Positive Mood scale, both of which can be considered measures of euphoria.

Discussion

This study provides strong evidence that PPA does not possess significant dependence potential in humans. The low dose (25 mg) produced virtually no effects on any measure, whereas the high dose (75 mg) was actually aversive, serving as a punisher. This is in sharp contrast to AMP, which did serve as a reinforcer in the present group of subjects, a finding obtained in several previous studies with equivalent subject populations (Johanson et al. 1983; de Wit et al. 1986). The present inability of PPA to serve as a reinforcer is in agreement with results from other self-administration studies in rhesus monkeys (Woolverton et al. 1986), baboons (Lamb et al. 1987) and humans (Bigelow 1985).

The low reinforcing efficacy of PPA, relative to AMP, may be related to the nature of subjective effects produced by the drug. PPA (75 mg) and AMP (5 mg) produced approximately the same level of stimulant effects in the present study, but AMP increased scores on mood scales often associated with dependence potential (ARCI MBG, POMS Elation and Positive Mood), whereas PPA did not. PPA also produced "negative" mood states (increased Anxiety and LSD scores) which were not observed after AMP. Thus, although AMP and PPA show some overlap in their subjective effects, the differences in their subjective effects profiles are apparently more closely associated with, and are intuitively consistent with, their relative reinforcing efficacies and, by inference, their relative dependence potentials.

In a previous study (Chait et al. 1986) these same two doses of PPA were tested for their ability to substitute for the discriminative stimulus effects of AMP in a group of subjects trained to discriminate between placebo and 10 mg AMP. The same mood questionnaires were used in that study as were used here. The subjective effects of 75 mg PPA in the present study agree well with those obtained in this previous study. However, a discrepancy between the two studies was found in the subjective effects observed after 25 mg PPA. In the previous study 25 mg PPA produced a profile of "negative" and sedative-like subjective effects (decreased Friendliness, Elation, Positive Mood, Vigor, Arousal; increased Fatigue, LSD, "sedated"). These effects were not replicated in the present study. The reason for the discrepancy is unclear, but may be due to the different context under which PPA was given in the previous study. In that study, 25 mg PPA was administered only twice, after all subjects had already received multiple (four to nine) doses of 10 mg AMP and placebo during discrimination training. In the present study only about half the subjects were exposed to AMP before participating in the 25 mg PPA experiment. However, further analysis failed to reveal any differences in subjective response to 25 mg PPA as a function of prior exposure to AMP. Also, in the previous study subjects were unaware that they would receive drugs other than the two they had learned to discriminate (AMP and placebo), whereas in the present study subjects were informed that they were participating in three independent choice experiments, during each one of which they could receive either placebo, anorectics or tranquilizers. Therefore, it is possible that subjects' expectations may have differed between the two studies. It is conceivable that such differential expectation effects or the differential prior exposures to AMP could have contributed to the disparate subjective effects obtained in these two studies after 25 mg PPA.

In this study we introduced an adjunct measure of reinforcing efficacy, the analog rating of preference strength. Our rationale for including this measure was our belief that it could provide a more sensitive index of the reinforcing efficacy of a drug than the single measure of number of drug choices. The limitation of drug choice in the current paradigm is that this variable can range only from 0 to 3. This measure also has little meaning for individual subjects, since a subject could choose the active drug on all three occasions simply on the basis of a capsule color preference (or on some other arbitrary basis), rather than for the drug's pharmacological properties. Number of drug choices also cannot distinguish between a subject who chooses an active drug three times, but has only a slight preference for the active drug over placebo, and a subject who chooses the same drug three times and has a very strong preference for the drug. The analog rating of preference strength, which subjects make at the very moment of their choice, has the potential for overcoming these limitations.

As calculated here, the mean preference strength rating represents a useful composite index of reinforcing efficacy (IRE), since drug choice is incorporated into the rating by assignment of a positive sign when active drug is chosen and a negative sign when placebo is chosen. According to this index, a "perfect reinforcer" would produce an IRE of +100, and a "perfect punisher" would produce an IRE of −100. A drug with no discernable effects would be expected to result in an IRE of 0, since it would theoretically be chosen on 50% of occasions. This index could provide a simple means of ranking drugs along a continuum of

reinforcing efficacy. Drugs with IRE's significantly greater than zero would be considered reinforcers, with potential for abuse. Drugs with IRE's significantly less than zero would be considered punishers, with little potential for abuse, but possible potential for clinical noncompliance.

In summary, the results of this study demonstrate that PPA does not possess amphetamine-like dependence potential. In this respect, it resembles caffeine, which is also not consistently self-administered (unpublished results), rather than diethylpropion, phenmetrazine and benzphetamine, anorectics which, like amphetamine, are reliably self-administered (Johanson and Uhlenhuth 1978; Chait et al. 1987). The possibility exists, however, that PPA could have higher dependence potential when taken in combination with other drugs (Pentel 1984) or in a particular subpopulation of drug abusers.

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